Letters to the Editor

Analytical sensitivity is an important determinant of the diagnostic power of cardiac troponin (cTn)\(^1\) for diagnosing myocardial infarction (MI) (1, 2). Increased cTn only partially fulfills the criteria to document acute injury, however, because a change in biomarker concentration is required (1). A recent study of a contemporary sensitive, guideline-acceptable cTn assay suggested that change criteria improved risk stratification because it improved the specificity of cTn in the study for acute coronary syndrome (ACS) (2). Data about the use of change criteria are only beginning to emerge (2). Furthermore, as assay performance improves and more diagnostic companies proceed to develop the second- and third-generation high-sensitivity (hs) assays (3), each must be validated with these criteria. Moreover, there remains no consensus on the criteria to define a changing pattern for cTn assays in clinical use, or for the new hs-cTn assays. One approach has been to use criteria for change obtained from the 2007 universal myocardial infarction (MI) definition (1). This was recently used in a comparison of a sensitive cTn assay [AccuTnI; refer to Apple (3) for assay designation] against a research third-generation hs assay (hs-cTnI) for early detection of myocardial injury (4). In the present study, we assessed if the criteria for change used in the previous study (4) also add to risk stratification with this hs-cTnI assay.

In a cohort of unique subjects (\(n = 257\)) presenting with chest pain to an emergency department at a community hospital in 1996, we obtained time of symptom onset, with heparinized plasma collected hourly until 6 h after symptom onset and then at 9, 12, 24 and 48 h, or until the patient was discharged, declined further participation, or was removed from the study by those responsible for care. Plasma was originally thawed in 2003 to measure cTnI (\(\mu g/L\)) with the AccuTnI assay. The same specimens (\(n = 1057\)) were thawed a second time in 2007 (stored at \(-80^\circ C\)) and analyzed with a research hs-cTnI assay (ng/L; Beckman Coulter) (4). Consistent with our previous analysis on identification of myocardial injury, we applied concentration change criteria from the 2007 MI definition (>3SD or >20%) (1, 4). For low concentrations (<0.10 \(\mu g/L\)), the directly observed imprecision of the assay was used to determine the 3SD value. At concentrations >0.10 \(\mu g/L\), a difference of 20% between values was considered significant. We applied these change criteria using the lowest and highest cTn concentrations in a given subject (median 4 specimens/subject) and the 2 earliest specimens (presentation and the next available, median time interval 1 h). In the event that the above change criteria failed to show significance for outcomes, we used a secondary approach using ROC analyses with logistic regression modeling to find the optimal percent difference (6), with the calculated % change in concentrations ([peak-earliest]/earliest) used only to focus on rising patterns (5). We obtained health outcomes (MI/death) via linkage to the Registered Persons Data Base for mortality outcomes and the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) for Ontario hospital discharges associated with MI over the first year after presentation. CIHI-DAD has been validated as a source for obtaining MI outcomes in Ontario hospitals and captures the hospital discharge abstracts with the diagnoses coded via the International Classification of Diseases, 9th Revision coding scheme (e.g., code for acute MI is 410). We performed Cox proportional hazard models to compare time to an event while adjusting for

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2007 Universal Myocardial Infarction Definition Change Criteria for Risk Stratification by Use of a High-Sensitivity Cardiac Troponin I Assay

To the Editor:

Analytical sensitivity is an important determinant of the diagnostic power of cardiac troponin (cTn)\(^1\) for diagnosing myocardial infarction (MI) (1, 2). Increased cTn only partially fulfills the criteria to document acute injury, however, because a change (increase/decrease) in biomarker concentration is required (1). A recent study of a contemporary sensitive, guideline-acceptable cTn assay suggested that change criteria improved risk stratification because it improved the specificity of cTn in the study for acute coronary syndrome (ACS) (2). Data about the use of change criteria are only beginning to emerge (2). Furthermore, as assay performance improves and more diagnostic companies proceed to develop the second- and third-generation high-sensitivity (hs) assays (3), each must be validated with these criteria. Moreover, there remains no consensus on the criteria to define a changing pattern for cTn assays in clinical use, or for the new hs-cTn assays. One approach has been to use criteria for change obtained from the 2007 universal myocardial infarction (MI) definition (1). This was recently used in a comparison of a sensitive cTn assay [AccuTnI; refer to Apple (3) for assay designation] against a research third-generation hs assay (hs-cTnI) for early detection of myocardial injury (4). In the present study, we assessed if the criteria for change used in the previous study (4) also add to risk stratification with this hs-cTnI assay.

In a cohort of unique subjects (\(n = 257\)) presenting with chest pain to an emergency department at a community hospital in 1996, we obtained time of symptom onset, with heparinized plasma collected hourly until 6 h after symptom onset and then at 9, 12, 24 and 48 h, or until the patient was discharged, declined further participation, or was removed from the study by those responsible for care. Plasma was originally thawed in 2003 to measure cTnI (\(\mu g/L\)) with the AccuTnI assay. The same specimens (\(n = 1057\)) were thawed a second time in 2007 (stored at \(-80^\circ C\)) and analyzed with a research hs-cTnI assay (ng/L; Beckman Coulter) (4). Consistent with our previous analysis on identification of myocardial injury, we applied concentration change criteria from the 2007 MI definition (>3SD or >20%) (1, 4). For low concentrations (<0.10 \(\mu g/L\)), the directly observed imprecision of the assay was used to determine the 3SD value. At concentrations >0.10 \(\mu g/L\), a difference of 20% between values was considered significant. We applied these change criteria using the lowest and highest cTn concentrations in a given subject (median 4 specimens/subject) and the 2 earliest specimens (presentation and the next available, median time interval 1 h). In the event that the above change criteria failed to show significance for outcomes, we used a secondary approach using ROC analyses with logistic regression modeling to find the optimal percent difference (6), with the calculated % change in concentrations ([peak-earliest]/earliest) used only to focus on rising patterns (5). We obtained health outcomes (MI/death) via linkage to the Registered Persons Data Base for mortality outcomes and the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) for Ontario hospital discharges associated with MI over the first year after presentation. CIHI-DAD has been validated as a source for obtaining MI outcomes in Ontario hospitals and captures the hospital discharge abstracts with the diagnoses coded via the International Classification of Diseases, 9th Revision coding scheme (e.g., code for acute MI is 410). We performed Cox proportional hazard models to compare time to an event while adjusting for

1 Nonstandard abbreviations: cTn, cardiac troponin; ACS, acute coronary syndrome; hs, high-sensitivity; MI, myocardial infarction; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; HR, hazard ratio.
In the study cohort (mean age 64 years, 58% male), 17% had a diagnosis of MI in 1996 with 38% having a history of heart failure/MI. At 1 year, there were 52 outcomes (death/MI) in the cohort. cTnI change was observed in 36% of subjects with the AccuTnI assay, compared with 72% using the third-generation research hs-cTnI assay and 2007 change criteria. With the AccuTnI assay, subjects meeting these change criteria were at higher risk at 30 days, 6 months, and 1 year compared to those with no change (Table 1). With the research hs-cTnI assay, however, the same change definition applied to the earliest 2 specimens had lower hazard ratios (HRs) at all endpoints and failed to reach significance at 30 days, even when the change criteria were applied using the lowest and highest cTn concentrations. ROC analysis for MI/death at 30 days for the hs-cTnI assay (area under the curve of 0.70, 95% CI 0.58–0.82) had an optimal cutoff of 235%, with those subjects above the cutoff at significantly higher risk for MI/death than those below [30 days HR 3.5 (95% CI 1.4–8.6); P = 0.006 after adjusting for age and sex].

With the current sensitive cTnI assay (AccuTnI), the 2007 MI definition criteria for change improves risk stratification. For the prototype research third-generation hs-cTnI assay studied, however, the change criteria may need to be revisited, as the HR at 30 days was not significant when using the 2007 criteria. It may be that at very low concentrations, only increased values are needed to detect risk, although the time course for such risk may vary depending on the underlying disease process. More studies will be necessary to consider this possibility.

There are limitations in this study that need to be highlighted. First, the analysis was performed in a retrospective cohort study using a single prototype research third-generation hs-cTnI assay. Issues related to specimen storage, analytical measurement, and change criteria may be more critical with hs-cTn assays. Second, retrospective studies require prospective studies for validation, and concurrent measurement of both the assays would further clarify the role of change, by minimizing both analytical and sample handling variations. Finally, as the analytical performance continues to be improved for cTn assays, there must be ongoing studies in var-

| Table 1. HRs for myocardial infarction/death for subjects with changing cTn concentrations. AccuTnI (top section, listed as cTnI), research hs-cTnI assay (bottom section). |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | HR change*      | 95% CI          | P               | HR change vs earliest 2 specimensb | 95% CI          | P               |
| AccuTnI         |                 |                 |                 |                              |                 |                 |
| Crude           |                 |                 |                 |                              |                 |                 |
| 30 days         | 12.3            | 3.6–41.7        | <0.001          | 4.5                          | 1.9–10.6        | <0.001          |
| 6 months        | 4.5             | 2.3–8.8         | <0.001          | 3.6                          | 2.0–6.6         | <0.001          |
| 1 year          | 4.1             | 2.3–7.2         | <0.001          | 3.0                          | 1.7–5.2         | <0.001          |
| Model 1c        |                 |                 |                 |                              |                 |                 |
| 30 days         | 12.7            | 3.8–43.0        | <0.001          | 4.4                          | 1.9–10.4        | <0.001          |
| 6 months        | 4.6             | 2.4–8.9         | <0.001          | 3.5                          | 1.9–6.5         | <0.001          |
| 1 year          | 3.9             | 2.2–7.0         | <0.001          | 2.9                          | 1.7–5.1         | <0.001          |
| Research hs-cTnI|                 |                 |                 |                              |                 |                 |
| Crude           |                 |                 |                 |                              |                 |                 |
| 30 days         | 4.1             | 1.0–17.7        | 0.055           | 1.7                          | 0.7–4.2         | 0.232           |
| 6 months        | 4.0             | 1.4–11.3        | 0.008           | 1.8                          | 0.9–3.4         | 0.088           |
| 1 year          | 3.4             | 1.4–7.9         | 0.005           | 1.7                          | 1.0–3.1         | 0.070           |
| Model 1c        |                 |                 |                 |                              |                 |                 |
| 30 days         | 4.0             | 0.9–17.3        | 0.060           | 1.6                          | 0.7–3.9         | 0.302           |
| 6 months        | 3.9             | 1.4–10.9        | 0.010           | 1.7                          | 0.9–3.2         | 0.130           |
| 1 year          | 3.2             | 1.3–7.4         | 0.008           | 1.6                          | 0.9–2.8         | 0.123           |

* Change in cTnI (AccuTnI) or hs-cTnI (research hs-cTnI) relative to no cTnI or hs-cTnI change.

b Change in cTnI (AccuTnI) or hs-cTnI (research hs-cTnI) relative to no cTnI or hs-cTnI change in earliest 2 specimens.

* Model 1 was adjusted for age and sex.
ious acute and nonacute populations to assess both the diagnostic and prognostic value of these new tests.

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References


Influence of Blood Sampling Site on Intact Parathyroid Hormone Concentrations in Hemodialysis Patients

To the Editor:

Parathyroid hormone (PTH) concentrations must be determined repeatedly in hemodialysis (HD) patients to evaluate secondary hyperparathyroidism (SHPT) and adjust the dosage of PTH-lowering compounds (vitamin D or cinacalcet). Available PTH assays provide variable PTH results (1, 2) and may create uncertainty in therapeutic decision-making. Thus, there is a need to standardize PTH measurements as well as preanalytical conditions. To the best of our knowledge, the impact of the blood-sampling site on PTH determination for HD patients has not been investigated. We compared intact parathyroid hormone (iPTH) concentrations simultaneously measured in central (iPTH-c) and peripheral (iPTH-p) blood samples from CVC-bearing HD patients.

We enrolled 30 HD patients [14 women, mean age 64 (SD 14) years, 16 men, mean age 77 (6) years] after receipt of informed consent. The local ethics committee approved the study. All patients had a central venous catheter (CVC), and none had an arteriovenous fistula. All CVCs were maintained open with 3.8% sodium citrate. Approximately 10 mL blood was simultaneously collected by 2 different nurses in Vacutte Serum Tubes with separator gel, the first from a tunneled CVC placed in the superior vena cava passing through the jugular vein, and the second from a peripheral (forearm) vein, before being connected to the extracorporeal circuit for HD. All samples were left to clot, transported on ice to the central laboratory, centrifuged at 2500g, and analyzed within 30 min. We measured baseline urea, creatinine, phosphorus, calcium, magnesium, and alkaline phosphatase activity using an Olympus AU2700 analyzer. We measured serum iPTH concentrations (10–65 pg/mL) using an immunochromeluminometric assay on a Roche Modular E 170 analyzer.

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1 Nonstandard abbreviations: PTH, parathyroid hormone; HD, hemodialysis; SHPT, secondary hyperparathyroidism; iPTH, intact PTH; iPTH-c, iPTH measured from central blood sample; iPTH-p, iPTH measured from peripheral blood sample; CVC, central venous catheter; PHPT, primary hyperparathyroidism.