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An approach to rule-out an acute cardiovascular event or death in emergency department patients using outcome-based cutoffs for high-sensitivity cardiac troponin assays and glucose☆,☆☆

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ABSTRACT

Objectives: The application of "undetectable" high-sensitivity cardiac troponin (hs-cTn) concentrations to "rule-out" myocardial infarction is appealing, but there are analytical concerns and a lack of consensus on what concentration should be used to define the lower reportable limit; i.e., limit of detection (LoD) or limit of blank. An alternative approach is to utilize a measurable hs-cTn concentration that identifies patients at low-risk for a future cardiovascular event combined with another prognostic test, such as glucose. We assessed both of these approaches in different emergency department (ED) cohorts to rule-out an event.

Design and methods: We used cohort 1 (all-comer ED population, n = 4773; derivation cohort) to determine the most appropriate approach at presentation (i.e., Dual Panel test: hs-cTn/glucose vs. LoD vs. LoD/glucose) for an early rule-out of hospital death using the Abbott ARCHITECT hs-cTnI assay. We used cohort 2 (n = 144) and cohort 3 (n = 127), both early chest pain onset ED populations as the verification datasets (outcome: composite cardiovascular event at 72 h) with three hs-cTn assays assessed (Abbott Laboratories, Beckman Coulter, Roche Diagnostics).

Results: In cohort 1, the sensitivity was >99% for all three approaches; however the specificity (11%; 95% CI: 10–12%) was significantly higher for the Dual Panel as compared to the LoD approach (specificity = 5%; 95% CI: 4–6%). Verification of the Dual Panel in cohort 2 and cohort 3 revealed 100% sensitivity and negative predictive values for all three hs-cTn assays.

Conclusions: The combination of a "healthy" hs-cTn concentration with glucose might effectively rule-out patients for an acute cardiovascular event at ED presentation.

Introduction

The measurement of cardiac troponin I and T at low concentrations with the high-sensitivity assays (i.e., hs-cTnI and hs-cTnT) has demonstrated utility in long-term risk stratification in both healthy individuals and patients with stable cardiovascular disease [1–8] and in the early decision making process within the emergency setting [9–11]. Specifically within the emergency department (ED), studies have focused on the improved analytical sensitivity of these high-sensitivity assays and have taken the approach of assessing "undetectable" hs-cTn concentrations to effectively "rule-out" patients at presentation for acute myocardial infarction (MI) [9,11]. This approach has merit, in that the lower the cardiac troponin concentration the lower the risk in the ED setting [12]. However, there are analytical concerns when assessing hs-cTn at the limit of detection (LoD), as analytical interferences, appropriate quality control monitoring, calibration effects and calibration/reagent lot-to-lot variation may have significant impacts on the interpretation when using the LoD [13–15].

Another approach taking advantage of the improved analytical sensitivity of the hs-cTn assays for early rule-out would be to use measureable concentrations of cardiac troponin that have identified patients at low risk for future cardiovascular events and couple this information to a non-cardiac biomarker that provides additive information in this setting, in this case glucose [16]. Specifically, in patients with

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stable coronary artery disease, low measurable concentrations for hs-cTnI and hs-cTnT that identify patients at low risk can be readily obtained from the literature [1,4–6] as well as a cutoff for normal glycemia (<5.6 mmol/L) [17].

Significant research exists that suggests a link between hyperglycemia and poor outcomes in patients with acute coronary syndrome (ACS). Endothelium dependent vasodilation has been shown to be rapidly suppressed by hyperglycemia in both diabetic and non-diabetic patients, a process thought to be mediated by increased production of oxygen-derived free-radicals [18]. Timmer and colleagues have also shown that hyperglycemia is an important predictor of impaired coronary flow in patients before percutaneous coronary intervention (PCI) [19]. Other data have also indicated that hyperglycemia is associated with a prothrombotic state, to be associated with increased markers of vascular inflammation, increased generation of reactive oxygen species, higher free fatty acid concentrations, insulin resistance and impaired myocardial glucose utilization [20]. Recently, Lippi and colleagues have demonstrated in a pilot study (n = 46) that the addition of a random plasma glucose measurement to hs-cTnI markedly increased specificity and positive predictive value without affecting sensitivity and negative predictive value when predicting acute MI in patients in the ED [21].

Given these data on low hs-cTn concentrations and normoglycemia possibly identifying patients at low cardiovascular risk, the goal of the present study was to assess if the combination of hs-cTn and glucose at presentation could be used to effectively rule-out hospital death and an acute cardiovascular event in ED patients. Specifically, we assessed patients using a population-based cut-off for stable coronary artery disease [6] and the American Diabetes Association cut-off for impaired fasting glucose [17]. Using these cut-offs, we compared this approach to using the LoD alone and a combination of the LoD and glucose to determine the optimal rule-out strategy in a derivation cohort. Following this, 2 verification cohorts were used to validate the best approach using three different hs-cTn assays.

Design and methods

hs-cTn assays and study populations

This analysis included three ED study populations, all of which received research ethics board approval with the analytical performance of the hs-cTn assays all previously reported. Briefly, the LoD for these assays is as follows: Abbott hs-cTnI; LoD = 1 ng/L, Beckman hs-cTnI LoD = 3 ng/L, Roche hs-cTnT LoD = 5 ng/L with the precision for these assays during this study listed as follows: cohort 1, CV = 4.8% for the Abbott hs-cTnI patient QC pool (n = 147; mean = 43.2 ng/L) at the Juravinski Hospital ci8200 analyzer; 5.4% (n = 103; mean = 40.8 ng/L) at the Hamilton General Hospital ci16200#1 analyzer; and 4.7% (n = 117; mean = 41.0 ng/L) at the Hamilton General Hospital ci16200#2 analyzer; with cohort 2 and 3 analyses being performed on research designated analyzers also using low concentration patient pool material to determine the imprecision (CV = 15% at 5.8 ng/L for the Abbott hs-cTnI assay (i1000; n = 43)), CV = 9.6% at 13.7 ng/L for the Beckman Coulter research hs-cTnI assay (Access 2; n = 17) and CV = 14% at 12.5 ng/L for the Roche hs-cTnT assay (Elecsys 2010; n = 19) [22–24].

Briefly, cohort 1 (an all-comer population) consisted of all consecutive ED patients from two EDs over a period of 3 months [24] who had both glucose and cTnI (including Abbott ARCHITECT hs-cTnI measurements on the clinical analyzers; blinded to the treating physicians) available at presentation. The outcome for this prospective observational study was hospital death.

Cohort 2 (from the RING study for Reducing the time Interval for identifying New Guideline defined MI in patients with suspected ACS in the ED) [23] consisted of adult patients who presented with chest pain within 6 hours of pain onset who were clinically managed with the 4th-generation cTnT assay and in whom hs-cTnI (Abbott ARCHITECT i1000 and Beckman Access 2), and hs-cTnT (Roche Elecsys 2010) were retrospectively measured in the presentation EDTA samples from these patients. Samples underwent one freeze thaw (storage at −70 °C) for the measurement of hs-cTnI (Beckman) and hs-cTnT (Roche) and a subsequent freeze–thaw cycle for the measurement of hs-cTnI (Abbott). The stability of cardiac troponin measured with these assays under these conditions has previously been demonstrated [25–27]. Patients were adjudicated for the composite outcome (PCI, coronary artery bypass graft surgery, and hospital admissions for arrhythmia, refractory ischemic cardiac pain, heart failure, MI, stroke, non-fatal cardiac arrest, or death) at 72 h from presentation.

Cohort 3 (an early chest pain onset ED population in 2003) [28] consisted of adult patients who presented with chest pain also within 6 h of onset who were clinically managed with a standard cTnI assay and in which hs-cTnI (Abbott ARCHITECT i1000 and Beckman Access 2) and hs-cTnT (Roche Elecsys 2010) were retrospectively measured in the presentation serum samples. Samples for the Beckman hs-cTnI and Roche hs-cTnT measurements underwent one freeze–thaw cycle (storage at −70 °C) with the Abbott hs-cTnI measurements performed on samples that underwent a second freeze–thaw cycle. All patients were adjudicated for the composite outcome (death, MI, heart failure, serious arrhythmia, refractory ischemic cardiac pain) at 72 h [22,28] (see Fig. 1).

Biomarker cutoff selection

Cutoffs for the analytes were selected based on several different literature sources. The American Diabetes Association (ADA) impaired glucose cutoff (<5.6 mmol/L) was used to define a normal glucose concentration [17]. For hs-cTn concentrations, the cutoffs were chosen based on the lowest risk group for future cardiovascular events in patients with stable coronary artery disease as these patients are at high-risk for future myocardial infarction [29]. Specifically, the PEACE study was used to select the lowest cutoff for the Abbott ARCHITECT hs-cTnI assay (<4 ng/L) [6] while the HOPE study was the source for both the Beckman Access hs-cTnI research assay cutoff (<6 ng/L) [4] and for the Roche hs-cTnT assay cutoff (<8 ng/L) [5]. The reported LoDs for the hs-cTn assays (Abbott hs-cTnI LoD <1 ng/L; Beckman hs-cTnI LoD <3 ng/L; Roche hs-cTnT LoD <5 ng/L) were also used as cutoffs [30].

Algorithm and statistical analysis

Cohort 1 was defined as the derivation cohort and was used to determine the most appropriate approach for early rule-out (i.e. Dual Panel [hs-cTn and glucose] vs. hs-cTn LoD vs. LoD Dual [LoD and glucose] testing). The best combination in cohort 1 was chosen based on the highest reported sensitivity and specificity for the algorithm (differences between algorithms were assessed via McNemar's test). Specifically, Dual Panel testing was defined as Abbott hs-cTnI <4 ng/L and glucose <5.6 mmol/L to yield a negative panel result, with either hs-cTnI or glucose concentration above these cutoffs yielding a positive result. Also, the LoD was defined as <1 ng/L for a negative result and LoD Dual testing was defined as hs-cTnI <1 ng/L and glucose <5.6 mmol/L for a negative result. Sensitivity, specificity, positive and negative predictive values and likelihood ratios (with 95% confidence intervals) were calculated for each approach with the best combination being employed in cohorts 2 and 3 (i.e., the verification datasets). Briefly, the Dual Panel testing criteria for other hs-cTn assays were defined as Beckman hs-cTnI <6 ng/L and glucose <5.6 mmol/L and Roche hs-cTnT <8 ng/L and glucose <5.6 mmol/L, yielding negative panel results, respectively. Non-parametric and categorical analyses (e.g., Mann–Whitney, Spearman rank correlation, Kruskal–Wallis, McNemar and chi-squared tests) were performed using Graphpad

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