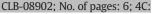
ARTICLE IN PRESS

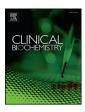
Clinical Biochemistry xxx (2014) xxx-xxx



Contents lists available at ScienceDirect

Clinical Biochemistry





journal homepage: www.elsevier.com/locate/clinbiochem

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 $\stackrel{\leftrightarrow, \leftarrow \leftrightarrow}{\xrightarrow{}}$

Colleen Shortt ^{a,b}, Kim Phan ^c, Stephen A. Hill ^{a,b}, Andrew Worster ^d, Peter A. Kavsak ^{a,b,*}

^a Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada

^b Department of Medicine, McMaster University, Hamilton, Canada

^c McGill University, Montreal, QC, Canada

^d Division of Emergency Medicine, McMaster University, Hamilton, Canada

ARTICLE INFO

Article history: Received 4 September 2014 Received in revised form 4 November 2014 Accepted 8 November 2014 Available online xxxx

Keywords: High-sensitivity cardiac troponin Glucose Acute coronary syndrome Emergency department Rule-out Health outcomes

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-cTnl 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.

© 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

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].

E-mail address: kavsakp@mcmaster.ca (P.A. Kavsak).

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

http://dx.doi.org/10.1016/j.clinbiochem.2014.11.010

0009-9120/© 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Please cite this article as: Shortt C, et al, An approach to rule-out an acute cardiovascular event or death in emergency department patients using outcome-based cutoffs for high-sensitivity cardiac troponin ..., Clin Biochem (2014), http://dx.doi.org/10.1016/j.clinbiochem.2014.11.010

 $[\]stackrel{\leftrightarrow}{\rightarrow}$ Funding: Canadian Institutes of Health Research, Abbott Laboratories and Beckman Coulter.

Disclosures: PK has received grants/honorariums/consultant/advisor fees from Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho Clinical Diagnostics, Roche Diagnostics, and the Canadian Agency for Drugs and Technologies in Health with respect to cardiac troponin testing. He is listed as an inventor on patents filed by McMaster University related to laboratory testing in acute cardiac care.

^{*} Corresponding author at: Juravinski Hospital and Cancer Centre, 711 Concession Street Hamilton, ON L8V 1C3, Canada.

2

ARTICLE IN PRESS

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 (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

Please cite this article as: Shortt C, et al, An approach to rule-out an acute cardiovascular event or death in emergency department patients using outcome-based cutoffs for high-sensitivity cardiac troponin ..., Clin Biochem (2014), http://dx.doi.org/10.1016/j.clinbiochem.2014.11.010

Download English Version:

https://daneshyari.com/en/article/8317259

Download Persian Version:

https://daneshyari.com/article/8317259

Daneshyari.com