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Short communication

Lower diagnostic accuracy of hs-cTnI in patients with prior coronary artery bypass grafting☆

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ABSTRACT

Background: High-sensitivity cardiac troponin T (hs-cTnT) and the ESC 0/1h-hs-cTnT-algorithm have worse performance in the early diagnosis of myocardial infarction (MI) in patients with prior coronary artery bypass grafting (CABG). It is unknown, whether this concern applies also to hs-cTnI, the most widely used analyte worldwide.

Methods: In an international multicenter diagnostic study, two cardiologists centrally adjudicated the final diagnosis in patients presenting to the emergency department with symptoms suggestive of MI according to the Third Universal Definition of MI. The objective was to compare the diagnostic accuracy of hs-cTnI assays and their performance within the ESC hs-cTnI 0/1h-algorithms in patients with versus without prior CABG. Findings were externally validated in an U.S. multicenter diagnostic study.

Results: A total of 392/5′200 patients (8%) had prior coronary artery bypass grafting (CABG). Diagnostic accuracy of hs-cTnI as quantified by the area under the receiver-operating characteristics-curve (AUC) in these patients was high, but lower versus patients without prior CABG (e.g. hs-cTnI-Architect 0.91 versus 0.95; $p = 0.016$). Sensitivity/specificity of rule-out/in by the European Society of Cardiology (ESC) 0/1h-hs-cTnI-algorithms remained very high [e.g. hs-cTnI-Architect 100% and 93.5%], but efficacy was lower (52% versus 74%, $p < 0.01$). External validation ($n = 2113$) confirmed these findings in 192 patients with prior CABG using hs-cTnI-Atellica, with 52% versus 36% ($p < 0.001$) remaining in the observe zone.

Conclusions: Diagnostic accuracy of hs-cTnI and efficacy of the ESC 0/1h-hs-cTnI-algorithms are lower in patients with prior CABG, but sensitivity/specificity remain very high.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT00470587, number NCT00470587.

Abbreviations: CABG, Coronary artery bypass grafting; CI, Confidence interval; CV, Coefficient of variation; ED, Emergency department; ESC, European Society of Cardiology; hs-cTn/I, High-sensitivity cardiac troponin/I; MI, Myocardial infarction.

☆ L.K., J.B., R.T., C.M. had full access to the data in APACE and J.M., R.N., R.C., C.D.,F.A. had full access to the data in HIGH-US. All authors have contributed substantially to the manuscript. All authors read and approved the manuscript.

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1. Introduction

In patients with prior coronary artery bypass grafting (CABG) presenting with acute chest pain, the prevalence of acute myocardial infarction (MI) was two-fold higher and that of unstable angina three-fold higher compared to patients without prior CABG. [1] Therefore, it is of major concern that recent pilot studies have suggested that all three pillars of the early diagnosis of MI, chest pain characteristics, 12-lead ECG, and high-sensitivity cardiac troponin T (hs-cTnT) may have lower diagnostic accuracy in patients with prior CABG. [1,2]

While clinical practice and clinical practice guidelines in general assume that the release of cTnI and cTnT into the circulation reflects identical pathophysiological processes,important pathophysiological differences between cTnT and cTnI, including circadian rhythm of cTnT, but not cTnI, and stronger influence of skeletal muscle disease and renal dysfunction on cTnT, as well as possible differences among different hs-cTnI assays, have been reported. [3–8] Since patients with prior CABG surgery represent a vulnerable subgroup with high age, high incidence of diabetes, atherosclerosis, possible remaining chronic myocardial ischemia, and renal insufficiency, it is unknown whether the concern of lower diagnostic accuracy applies also for hs-cTnI, the most widely used analyte. [1,2,9,10]

Therefore, the aim of this study was to assess the diagnostic accuracy of hs-cTnI and the performance of the corresponding ESC hs-cTnI 0/1h-algorithms in patients with prior CABG using four different hs-cTnI assays [3–6].

2. Material and methods

2.1. Study design and setting

This is a secondary analysis based on two large prospective multicenter diagnostic studies enrolling adult patients presenting to the emergency department (ED) with symptoms suggestive of MI: Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE), including 12 centers in 5 European countries (NCT00470587), [1,2,4,5,11] and HIGH-US, including 29 centers in the U.S. [12]

Detailed information about in- and exclusion criteria are provided in the Online Supplemental.

2.2. Central adjudication

Final diagnosis was centrally adjudicated by two independent cardiologists according to the Third Universal Definition of MI (UDMI) including serial measurements of hs-cTnI-Architect in the APACE, and serial measurements of contemporary cTn in the HIGH-US study, using uniform 99th percentiles. [3,13] More information and detailed information about the characteristics of the different hs-cTnI-assays (hs-cTnI-Architect, hs-cTnI-Centaur, hs-cTnI-Access and hs-cTnI-TriageTrue) are provided in the Online Supplemental.

2.3. Statistical analysis

We constructed receiver-operating-characteristics curves and calculated corresponding areas under the curve (AUC) to assess the discriminative accuracy of hs-cTnI concentrations at presentation for the presence of MI. Performance of the ESC hs-cTnI-0/1h-algorithms was assessed by safety for rule-out (sensitivity, negative predictive value), accuracy for rule-in (specificity, positive predictive value), and overall efficacy quantified by the percentage of patients triaged towards rule-out/in. We used cross tables derived by the application of the recommended assay-specific cut-off criteria for rule-out/in of MI to calculate diagnostic performance parameters and 95% CI. CIs of proportions were calculating according to Wilson score method. All hypothesis testing was two-tailed, and *P* values of less than 0.05 were considered to indicate statistical significance without adjustments for multiple testing.

All-cause death during 30/730 days was plotted in Kaplan-Meier curves and log-rank test was used.

Statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc.,Chicago, IL), R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and MedCalc,version 9.6.4.0 (MedCalc Software,Ostend, Belgium).

3. Results

3.1. Main cohort

Among 5′200 patients, 392 patients had prior CABG (8%). These patients were significant older than patients without prior CABG, more often had prior MI, known peripheral vascular disease, and worse renal function (Online Table 2).

Patients with prior CABG more often had an adjudicated final diagnosis of MI (34% versus 16%; $p < 0.001$) versus patients without prior CABG. Concentrations of hs-cTnI at presentation were significantly higher in patients with prior CABG compared to patients without prior CABG (hs-cTnI-Architect ($n = 5119$): Median (IQR) 12.0 [5.3, 51.0] ng/L versus 4.0 [2.0, 12.8] ng/L; $p < 0.001$; hs-cTnI-Centaur ($n = 2792$): Median (IQR) 16.7 [7.1, 90.6] ng/L versus 5.6 [2.7, 18.1] ng/L; $p < 0.001$; hs-cTnI-Access ($n = 1813$): Median (IQR) 12.3 [5.6, 75.1] ng/L versus 3.7 [1.9, 10.0] ng/L; $p < 0.001$; hs-cTnI-TriageTrue ($n = 1458$): Median (IQR) 11.8 [4.8, 55.8] ng/L versus 3.2 [1.6, 8.8] ng/L; $p < 0.001$).

Diagnostic accuracy of hs-cTnI as quantified by the AUC was significantly lower in patients with prior CABG, but still high, e.g. hs-cTnI-Architect (n = 5119) 0.91 (95%CI, 0.88–0.94) versus 0.95 (95% CI, 0.94–0.95), $p = 0.016$; hs-cTnI-Centaur (n = 2792) 0.89 (95%CI, 0.85–0.94) versus 0.96 (95%CI, 0.95–0.97), $p = 0.004$, Fig. 1A/B.

Similar results were seen for hs-cTnI-Access ($n = 1813$) and hs-cTnI-TriageTrue (n = 1458) assays, Fig. 1C/D.

Among 4139 patients eligible for the analysis of the ESC hs-cTnI-Architect 0/1h-algorithm, 314 had prior CABG. While the sensitivity and specificity of the triage towards rule-out and/or rule-in by the ESC hs-cTnI-0/1h-algorithms remained very high (hs-cTnI-Architect 100% (95%CI,96.3–100) and 93.5% (95%CI, 89.4–96.1), respectively) in patients with prior CABG, efficacy was substantially lower with more patients remaining in the observe zone (48% versus 26%, $p < 0.001$; Fig. 2A) versus patients without prior CABG. These results were internally validated in patients with available 0/1 h blood concentrations of hs-cTnI-Centaur ($n = 2211$ (182 with prior CABG): 53% versus 34% in observe zone), hs-cTnI-Access ($n = 1565$ (116 with prior CABG): 53% versus 27% in observe zone) and hs-cTnI-TriageTrue ($n = 1248$ (96 with prior CABG): 44% versus 24% in observe zone), Fig. 2B-D. Cumulative 730-day all-cause mortality consistently for all hs-cTnI assays was lowest in patients triaged towards rule-out, intermediate in the observe zone, and highest in patients triaged towards rule-in (Online Figure 2A-D).

3.2. External validation cohort

Among 2113 patients (prior CABG info is missing for 58 out of 2113 patients.), 192 patients had prior CABG (9%). Patients with prior CABG more often had an adjudicated final diagnosis of MI (18% versus 10%; $p = 0.002$) versus patients without prior CABG. In patients with prior CABG, the AUC for hs-cTnI-Atellica for MI was 0.92 (95%CI,0.86–0.97) versus 0.95 (95%CI,0.94–0.96) in patients without prior CABG. Again, the sensitivity and specificity of the triage towards rule-out and/or rule-in by the hs-cTnI-Atellica-0/1 h-algorithm remained very high (100% (95%CI,90–100) and 94% (95%CI,89–97), respectively) in patients with prior CABG. However, efficacy was lower with more patients remaining in the observe zone (52% versus 36%,$p < 0.001$) versus patients without prior CABG.

4. Discussion

These findings extend and corroborate previous observations for hs-cTnT and the ESC hs-cTnT 0/1h-algorithm in patients with prior CABG. [2] While the diagnostic accuracy of hs-cTnI for MI, the safety and accurafy of the ESC hs-cTnI-algorithms remained very high, the efficacy was substantially lower in patients with prior CABG. [2] About half of patients remained in the observe zone of the respective ESC hs-cTnI-algorithms, and thereby did not derive benefit from using this triage algorithm. The high percentage of patients with prior CABG remaining in the observe zone can likely be explained by their higher age and higher prevalence of preexisting cardiac disease, both associated with chronic myocardial injury resulting in mild-to-modest chronic hs-cTnI elevations. These findings have high generalizability as they were consistent for all four hs-cTnI-assays and confirmed in the external validation including 29 U.S. sites. [12]

These findings have immediate clinical consequences: detailed clinical assessment, hs-cTn re-sampling at 3 h, and often also early coronary angiography are necessary in this subgroup of patients to reliably differentiate MI from other causes of chest discomfort. The need for more extensive diagnostic work-up often including cardiac imaging in patients with prior CABG is further emphasized by the high prevalence of MI observed in this vulnerable patient subgroup. [1]

Given the difficulty of angiographically identifying the culprit lesion in patients with prior CABG, sophisticated non-invasive imaging using e.g. PET-scanning may by warranted in many patients remaining in the observe-zone. [14]

Evaluating alternative cut-off concentrations optimized for use in patients with prior CABG may be considered, but would inherently be associated with increasing complexity of the ESC hs-cTnI-0/1h-algorithms. [3] Similar studies focusing on patients with prior CABG are warranted for other well-validated triage algorithms such as the

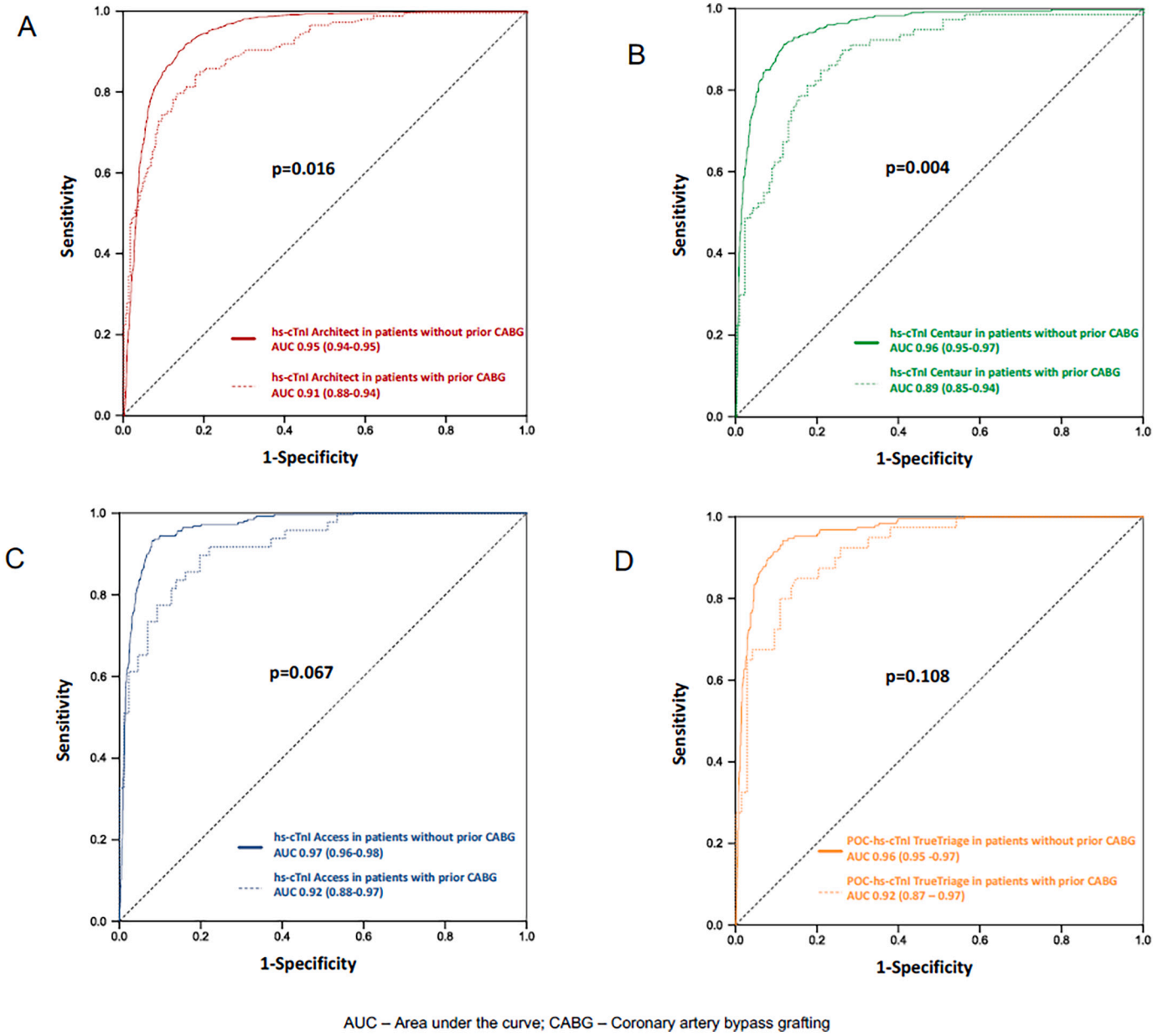

Fig. 1. Diagnostic accuracy of the four different high-sensitivity cardiac troponin assays.
AUC – Area under the curve.
CABG – Coronary artery bypass grafting.

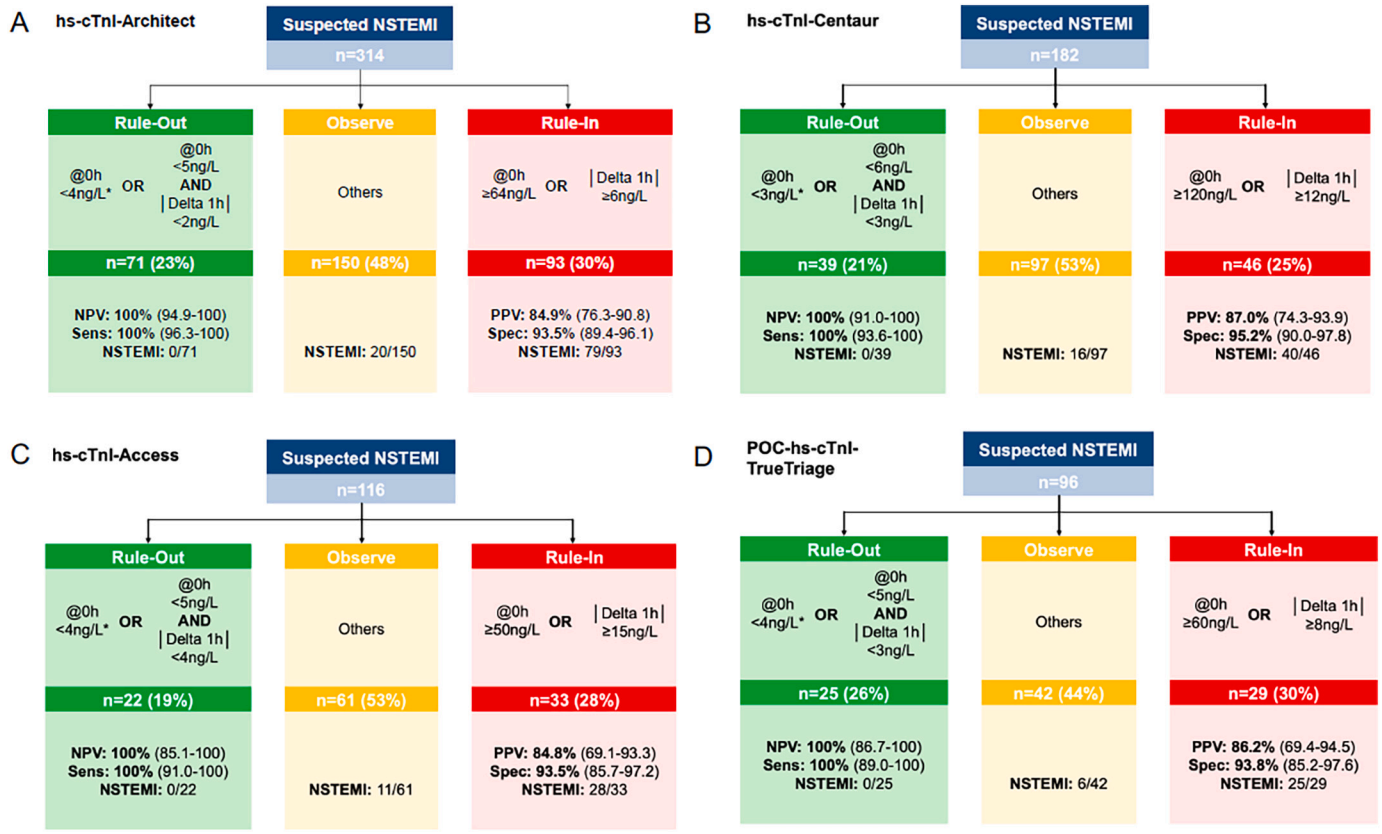

Fig. 2. Diagnostic performance of the 0/1 h-algorithms using four different high-sensitivity cardiac troponin I assays in patients with prior CABG.
* if chest pain onset >3 h.
hs-cTnI – High-sensitivity cardiac troponin I.
NPV – Negative predictive value.
NSTEMI – Non-ST-segment elevation myocardial infarction.
PPV – Positive predictive value.
Sens. – Sensitivity.
Spec. – Specificity.

High-STEACS-algorithm. [15,16]

Furthermore, future studies need to define rapid biochemical and/or imaging strategies targeted to the characteristics of patients remaining in the observe zone.

Some limitations merit consideration. First, although we used a very stringent methodology to adjudicate the presence or absence of MI including central adjudication by experienced cardiologists, we still may have misclassified a small number of patients. Second, we cannot generalize our findings to patients with terminal kidney failure requiring dialysis. Third, the low prevalence of women in both cohorts was comparable to previous studies enrolling unselected patients presenting with suspected AMI. [15,17,18] Therefore, additional studies in women are warranted. Fourth, no specific sample size calculation was performed. Although this secondary analysis is the largest diagnostic study ever performed in patients with prior CABG, it still may have been underpowered for some comparisons, especially regarding direct comparison of the various assays and long-term safety. Given the relevant long-term mortality, optimal secondary preventive measures must be applied to all patients with prior CABG presenting with acute chest pain irrespective of acute triage decision. Fifth, the external validation cohort had only one hs-cTnI assay. Therefore, additional validation studies are warranted with the other hs-cTnI assays.

5. Conclusions

In patients with prior CABG, hs-cTnI has high diagnostic accuracy, albeit lower compared to patients without prior CABG. While sensitivity/specificity of the triage towards rule-out/in by the ESC hs-cTnI-0/1h-algorithms remained very high, efficacy was significantly lower in patients with prior CABG.

Author statement

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The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. Drs. Koechlin, Boeddinghaus, Nestelberger, Twerenbold and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its content have not been published previously and are not being considered for publication elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers.

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All other authors declare that they have no conflict of interest with this study. The hs-cTn assays investigated were donated by the manufacturers, who had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

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Declaration of Competing Interest

None.

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Appendix A. APACE and High-US investigators

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.02.025.

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