# Research Letter

# Performance of the ESC 0/2h-Algorithm using High-Sensitivity Cardiac Troponin I in the Early Diagnosis of Myocardial Infarction

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**Short Title:** 0/2h-algorithm using hs-cTnI

**Word count:** 1697 words

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

**Short abstract describing the objective of the letter**

The 2020 guidelines of the European Society of Cardiology (ESC) recommend a novel ESC 0/2h-algorithm as the preferred alternative to the ESC 0/1h-algorithm in the early triage for rule-out and/or rule-in of Non-ST-segment-elevation myocardial infarction (NSTEMI). The aim was to prospectively validate the performance of the ESC 0/2h-algorithm using the high-sensitivity cardiac troponin I (hs-cTnI) assay (ARCHITECT) in an international, multicenter diagnostic study enrolling patients presenting with acute chest discomfort to the emergency department.

**Keywords:** Acute coronary syndrome, high-sensitivity cardiac troponin

Abbreviations

CI - Confidence interval

CPO – Chest pain onset

ED - Emergency Department

ESC - European Society of Cardiology

hs-cTnI – High-sensitivity cardiac troponin I

IQR – Interquartile range

NPV – Negative predictive value

NSTEMI – Non-ST-segment elevation myocardial infarction

PPV – Positive predictive value

STEMI - ST-segment elevation myocardial infarction

**Introduction**

Over the last decade, intense collaboration between academic investigators and the diagnostic industry have allowed the integration of high sensitivity cardiac troponin (hs-cTn) assays into clinical practice worldwide.[1] Hs-cTn assays, with their increased diagnostic accuracy for Non-ST-segment-elevation myocardial infarction (NSTEMI), have facilitated the maturation of early rule-out and rule-in strategies.[2–4] As one of the latest additions, the 2020 guidelines of the European Society of Cardiology (ESC) for the first time recommend a novel ESC 0/2h-algorithm, which combines the single-measurement rule-out approach with the 0/2h-algorithm. This novel ESC 0/2h-algorithm is recommended as the preferred alternative to the ESC 0/1h-algorithm in early triage towards rule-out and/or rule-in of NSTEMI.[2][3] However, the performance of this algorithm has not yet been evaluated in a prospective diagnostic study.

Therefore, our aim was to assess the performance of the novel ESC 0/2h-algorithm using the most widely used high-sensitivity cardiac troponin I (hs-cTnI) assay (ARCHITECT STAT hs-cTnI, Abbott Laboratories, IL, USA) in an international multicenter study.[5]

**Methods**

**Study design and setting**

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) was a prospective international multicenter diagnostic study including 12 centers in 5 European countries (NCT00470587) enrolling adult patients presenting to the emergency department (ED) with acute chest discomfort. [6–9] Cardiogenic shock and terminal kidney failure on chronic dialysis were exclusion criteria, The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The study was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the European Union, the University Hospital Basel, the University of Basel, Abbott, Beckman Coulter, Biomerieux, Brahms, Roche, Ortho Clinical Diagnostics, Quidel, Siemens, and Singulex. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

For this analysis, patients were excluded if they had ST-segment-elevation myocardial infarction (STEMI), missing hs-cTnI-Architect measurements at presentation or at 2h, an unknown diagnosis after final adjudication, chest pain onset (CPO) and maximum >12h before presentation, or if they had been included in the derivation of one component of the algorithm.[3]

Detailed information about the hs-cTnT assay (Roche Elecsys 2010 high-sensitivity troponin T) and the hs-cTnI-Architect assay (ARCHITECT STAT high-sensitivity troponin I, Abbott) is provided in the Online Material.

The primary diagnostic endpoint was NSTEMI at presentation to the ED. Rule-out safety of

the ESC 0/2-h algorithm was quantified by the negative predictive value (NPV) and sensitivity in the rule-out group. Accuracy of rule-in, which aims to identify patients eligible for early coronary angiography, was quantified by the positive predictive value (PPV) and specificity in the rule- in group. Efficacy of the ESC 0/2-h algorithm was quantified by the proportion of patients triaged to either rule-out or rule-in. The 95% confidence intervals (CIs) were calculated with the Wilson score method without continuity correction.

The ESC hs-cTnI 0/2h-algorithm was applied as recommended in the current guidelines (Figure 1A).[2] In an additional analysis, we assessed the performance of a simplified version of the ESC 0/2h-hs-cTnI-algorithm which, in parallel to the recently developed 0/2h-hs-cTnI-algorithms using other novel hs-cTnI-assays, no longer includes a 2h-concentration for rapid rule-out but only uses the 0h-concentration and the 0/2h- delta <2 ng/L (Figure 1B).[3,5,10]

Subgroup analyses in early presenter (defined as time interval from CPO to “0h-study blood draw” ≤3h) and in patients with >3h after CPO were performed.

The authors designed the studies, gathered, and analysed the data according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (Online Material**)**.

**Central adjudication**

As described previously, adjudication of the final diagnosis was performed by two independent cardiologists at the core laboratory (University Hospital Basel) applying the fourth universal definition of AMI.[3,5–10]. More detailed information is provided in the Online Supplemental.

In order to address the uncommon, but previously described phenomenon of discrepant results for hs-cTnT and hs-cTnI and the corresponding underestimation of the true performance of hs-cTnI-based early algorithms using an adjudication based at least in part on serial hs-cTnT measurements [11], we performed the adjudication using serial hs-cTnT and in a secondary analysis hs-cTnI blood concentrations from study samples and report the results for each adjudication.

AMI was defined and (hs-)cTn interpreted as recommended in current guidelines.[12] In brief, myocardial infarction (MI) was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least one cTn value above the 99th percentile together with a significant rising and/or falling. More detailed information is provided in the Online Supplemental.

**Results**

Among 2227 eligible patients (median age 61 (interquartile range [IQR] 50.0-74.0) years, 33% women, 32% history of coronary artery disease, median time from CPO and chest pain maximum to first study blood draw 5h (2,13) and 2.2h (1,5), respectively, 39% with CPO≤3h), NSTEMI was the final adjudicated diagnosis in 379 patients (17%;293 patients with type 1 NSTEMI and 86 patients with type 2 NSTEMI; Table 1,Online Figure 1).

The ESC 0/2h-hs-cTnI-algorithm had a NPV of 99.7% (95%CI,99.2-99.9%) and a sensitivity of 99.2% (95%CI,97.7-99.7) for rule-out, and a PPV of 71% (95%CI,66.5-75.1) and a specificity of 93.4% (95%CI,92.2-94.4) for rule-in of NSTEMI (Figure 1A). Twenty-seven percent of patients could be directly ruled out with the initial blood draw at presentation, and the overall triage efficacy was 71%, with 29% of patients remaining in the observe zone. Similar results were observed for the simplified version with a NPV of 99.7% (95%CI,99.3-99.9) and a sensitivity of 99.2% (95%CI,97.7-99.7) for rule-out and a PPV of 71% (95%CI,66.5-75.1) and a specificity of 93.4% (95%CI,92.2-94.4) for rule-in of NSTEMI (Figures 1B).The very high NPV/sensitivity and PPV/specificity of both versions of the ESC 0/2h-hs-cTnI-algorithm were confirmed in a secondary analysis using, in addition to cardiac imaging and all other information, serial measurements of hs-cTnI (rather than hs-cTnT) for the adjudication of the final diagnoses (n=1863,Figure 1C/D).

The very high NPV/sensitivity and PPV/specificity of both versions of the ESC 0/2h-hs-cTnI-algorithm was further confirmed in subgroup analyses including only early presenter (defined as CPO ≤3h; n=857 and n=716, respectively) and patients presented >3h after CPO (n=1358 and n=1138, respectively, Online Figure 2&3).

**Discussion**

This international multicenter study evaluated the performance of the novel ESC 0/2h-algorithm using the most widely used hs-cTnI assay. We report six major findings. First, with a NPV of 99.7% and a sensitivity of 99.2% for rule-out of NSTEMI, safety of the ESC 0/2h-hs-cTnI-algorithm was very high. Second, with a PPV of 71% and a specificity of 93.4% for rule-in of NSTEMI, also the accuracy for rule-in was high. Third, overall triage efficacy was high with 71% of patients triaged based on the 0h and 2h sample only. Fourth, these findings were confirmed in a secondary analysis using serial measurements of hs-cTnI as part of the central adjudication. Fifth, similar findings emerged for a simplified version of the ESC hs-cTnI-0/2h-algoirthm based on the 0h-concentration and the 0/2h-change criteria only. Sixth, these findings were confirmed in subgroup analyses including only early presenter (defined as CPO ≤3h) and patients presented >3h after CPO.

These findings extend and corroborate prior studies establishing the optimal assay-specific cut-offs for the two components of the ESC 0/2h-hs-cTnI-algorithm: the single measurement rule-out approach and the 0/2h-algorithm.[3,10]They clearly support the class I recommendation provided in the 2020 ESC-guidelines for the ESC 0/2h-hs-cTnI-algorithm as it balanced safety and efficacy very well.[2] The overall performance of the ESC 0/2h-hs-cTnI-algorithm was comparable to the ESC 0/1h-hs-cTnI/T-algorithms. E.g. in four recent validation studies of the ESC 0/1h-hs-cTnI/T-algorithms, the NPV were 99.7-100%, the sensitivity 98.9-100%, the PPV 62.3-76.8%, the specificity 89.6-95.9%, and the overall triage efficacy 67%-75%. [6–9]

Furthermore, a simplified version of the ESC 0/2h-hs-cTnI-algorithm which, in parallel to the recently developed 0/2h-hs-cTnI-algorithms using other novel hs-cTnI-assays, no longer includes a 2h-concentration for rapid rule-out but only uses the 0h-concentration and the 0/2h- delta <2 ng/L provided very high safety for rule-out and high accuracy for rule-in of acute MI with an even slightly higher efficacy and less patients remaining in the observe zone.[3,5,10]

Similar to the ESC 0/1h-algorithm, it provides detailed guidance for rule-out AND rule-in, and therefore, may be particularly helpful for institutions introducing hs-cTn assays with the associated challenge of managing an increased number of patients with mild hs-cTn elevations.[2]The ESC 0/2h-algorithm also may have higher feasibility as the ESC 0/1h-algorithm, as more time (2h versus 1h) is allowed between the two early blood draws in the ED.

Some limitations merit consideration when interpreting these findings. 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, no specific sample size calculation was performed. Although this secondary analysis is one of the largest studies on 0/2h-algorithms ever performed, it still may have been underpowered for some comparisons.

Important strengths of this study include central adjudication by two independent cardiologists and secondary analysis including serial hs-cTnT versus hs-cTnI measurements with the primary and the secondary analysis providing highly consistent findings. Despite the excellent performance of the ESC 0/2h-hs-cTnI-algorithm, it is important to highlight that this hs-cTnI-only algorithm should always be used in conjunction with all other clinical information including detailed clinical assessment and a 12-lead electrocardiogram, and that despite rule-out of NSTEMI, some patients will still require work-ups for other life-threatening diseases such as acute aortic syndromes and pulmonary embolism.[2] Also, population differences may change the percentage of patients triaged to each of the three sectors of the algorithm. While this cohort included also a high number of early presenters (n=857), of which 138 had NSTEMI, the number of patients presenting very early (e.g. within 1h) from CPO was only modest. Therefore, clinicians need to apply special attention in these patients. Additional studies in patients presenting very early are warranted. In conclusion, the ESC 0/2h-hs-cTnI-algorithm provides very high safety and efficacy in the triage towards rule-out and/or rule-in of NSTEMI in the ED. Also, the simplified version showed very high safety.

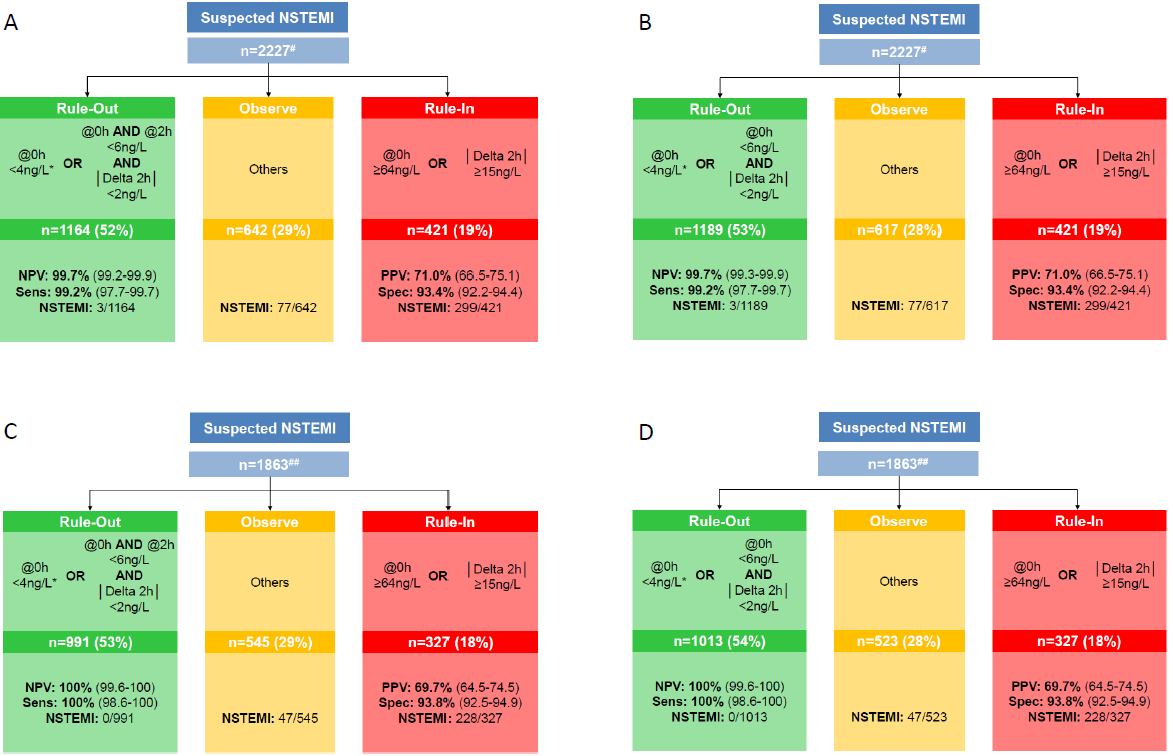
**Tables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 1 | Baseline Characteristics | | | |
|  | All patients  (n=2227) | No NSTEMI  (n=1848) | NSTEMI  (n=379) | P-Value |
| Age – years | 61.0 [50.0, 74.0] | 59.0 [47.0, 72.0] | 69.0 [59.0, 80.0] | <0.001 |
| Female gender – no. (%) | 728 (33) | 620 (34) | 108 (28) | 0.064 |
| Median time from CPO to first study blood draw– hours | 5.0 [2.0, 13.0] | 5.0 [2.0, 14.0] | 5.5 [2.0, 10.5] | 0.994 |
| Median time from chest pain maximum to first study blood draw– hours | 2.2 [1.0, 5.0] | 2.0 [1.0, 5.0] | 3.0 [1.5, 6.0] | 0.001 |
| Early presenter (CPO ≤3h) | 857 (39) | 719 (39) | 138 (37) | 0.393 |
| Vital signs, median (IQR) |  |  |  |  |
| Heart rate – beats/minute | 76.0 [67.0, 88.0] | 76.0 [66.0, 88.0] | 78.0 [68.0, 90.0] | 0.068 |
| Systolic blood pressure – mmHg | 139.0 [125.0, 154.0] | 138.0 [125.0, 154.0] | 140.0 [124.2, 159.8] | 0.243 |
| Diastolic blood pressure – mmHg | 80.0 [71.0, 90.0] | 80.0 [71.0, 90.0] | 80.0 [69.0, 90.0] | 0.288 |
| Oxygen saturation – % | 98.0 [96.0, 99.0] | 98.0 [96.0, 100.0] | 98.0 [96.0, 99.0] | <0.001 |
| Risk factors – no. (%) |  |  |  |  |
| Hypertension | 1339 (60) | 1063 (58) | 276 (73) | <0.001 |
| Hypercholesterolemia | 1055 (47) | 831 (45) | 224 (59) | <0.001 |
| Diabetes | 394 (18) | 285 (15) | 109 (29) | <0.001 |
| Current smoking | 543 (24) | 444 (24) | 99 (26) | 0.424 |
| History – no. (%) |  |  |  |  |
| Coronary artery disease | 715 (32) | 567 (31) | 148 (39) | 0.001 |
| Previous myocardial infarction | 517 (23) | 407 (22) | 110 (29) | 0.003 |
| Previous PCI | 565 (25) | 456 (25) | 109 (29) | 0.085 |
| Previous stroke | 131 (6) | 96 (5) | 35 (9) | 0.006 |
| Previous pulmonary embolism | 46 (2) | 36 (2) | 10 (3) | 0.508 |
| Peripheral artery disease | 101 (5) | 64 (3) | 37 (10) | <0.001 |
| Positive family history | 819 (37) | 691 (38) | 128 (34) | 0.254 |
| Body mass index – kg/m2 | 26.6 [23.9, 29.7] | 26.6 [23.8, 29.7] | 26.7 [24.3, 29.8] | 0.549 |
| Estimated glomerular filtration rate | 82.9 [67.7, 98.4] | 84.3 [69.6, 99.2] | 75.9 [60.4, 94.7] | <0.001 |

p-value for the comparison of patients with Non-ST-segment elevation myocardial infarction (NSTEMI) versus patients without NSTEMI.

Numbers are presented as median [IQR] or numbers (%)

PCI - Percutaneous coronary intervention



**Figure Legend**

Figure 1: Diagnostic performance of the ESC 0/2h-hs-cTnI-algorithm (A) and a simplified version (B) with adjudicated final diagnoses based on all information including serial measurements of hs-cTnT-Elecsys (n=2227) or hs-cTnI-Architect (n=1863, C&D).

#2227 patients with final adjudicated diagnoses based on serial hs-cTnT measurements

## 1863 patients with final adjudicated diagnoses based on serial hs-cTnI measurements

\* if chest pain onset >3h

Hs-cTnI- High-sensitivity cardiac troponin; NPV-Negative predictive value; Sens-Sensitivity; NSTEMI- Non-ST-segment elevation myocardial infarction; PPV-Positive predictive value; Spec-Specificity

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**Conflict of interest statement**

This work was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the European Union, the University Hospital Basel, the University of Basel, Abbott, Beckman Coulter, Biomerieux, Brahms, Quidel, Roche, Ortho Clinical Diagnostics, Siemens, and Singulex.

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, Rubini Gimenez, Wildi, 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.

We disclose that Dr. Koechlin received a research grant from the University of Basel, the Swiss Academy of Medical Sciences and the Gottfried and Julia Bangerter-Rhyner Foundation, as well as the “Freiwillige Akademische Gesellschaft Basel”. Dr. Boeddinghaus received research grants from the University Hospital of Basel, the Division of Internal Medicine, the University of Basel, the Swiss Academy of Medical Sciences and the Gottfried and Julia Bangerter-Rhyner Foundation, as well as speaker/consulting honoraria from Siemens, Roche Diagnostics, Ortho Clinical Diagnostics, and Quidel Cooperation, outside of the submitted work. Dr. Nestelberger has received research support from the Swiss National Science Foundation (P400PM\_191037/1), the Prof. Dr. Max Cloëtta Foundation, the Margarete und Walter Lichtenstein-Stiftung (3MS1038), and the University Hospital Basel as well as speaker honoraria/consulting honoraria from B.Braun, Siemens, Beckman Coulter, Bayer, Ortho Clinical Diagnostics and Orion Pharma, outside the submitted work. Dr. Wildi has received research funding from the FAG Basel (Freiwillige Akademische Gesellschaft), the Julia und Gottfried Bangerter-Rhyner-Stiftung, the Prince Charles Hospital Foundation, The Wesley Medical Research Foundation and the CRE Action fund (NHMRC). Additionnally, she received a PhD scholarship from the University of Queensland. Dr. Rubini Gimenez has received research grants from the Swiss Heart Foundation and Swiss National Science Foundation (P400PM\_180828) as well as speakers/consulting honoraria from Abbott, Ortho Clinical Diagnostics, Roche, and Siemens, outside the submitted work. Dr Gualandro received consulting honoraria from Roche, outside the submitted work. Dr. Twerenbold reports research support from the Swiss National Science Foundation (Grant No P300PB\_167803), the Swiss Heart Foundation, the Swiss Society of Cardiology, the Cardiovascular Research Foundation Basel, the University of Basel and the University Hospital Basel and speaker honoraria/consulting honoraria from Abbott, Amgen, Astra Zeneca, Roche, Siemens, Singulex and Thermo Scientific BRAHMS, Dr. Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the University Hospital Basel, the University of Basel, Abbott, Beckman Coulter, Idorsia, Ortho Clinical Diagnostics, Novartis, Quidel, Roche, Siemens, Singulex, Sphingotec, and as well as speaker honoraria/consulting honoraria from Amgen, Astra Zeneca, Boehringer Ingelheim, BMS, Idorsia, Osler, Novartis, Roche, and Sanofi.

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.

**Acknowledgments**

We are indebted to the patients who participated in the study and to the emergency department staff as well as the laboratory technicians of all the participating sites for their most valuable efforts.

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