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Direct comparison of the 0/1h- and 0/3h-algorithm for early rule-out of acute myocardial infarction

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Patients with symptoms suggestive of acute myocardial infarction (AMI) account for about 10% of all emergency department (ED) presentations.(1) The majority of patients are finally found to have diagnoses other than AMI.(2) Thus, the expeditious evaluation of such patients is important as delays in ruling out AMI may interfere with the detection of other underlying diseases. The 0/1hour(h)-algorithm and the 0/3h-algorithm are both recommended by the European Society of Cardiology (ESC) with a class I recommendation for the early rule-out of AMI.(1) The 0/1h- and the 0/3h-algorithm are completely different protocols. While the 0/1h-algorithm uses high-sensitivity cardiac troponin (hs-cTn) concentrations at presentation and absolute changes within the first hour, and hence takes optimal advantage of the increased diagnostic accuracy and precision of hs-cTn assays, the 0/3h-algorithm uses a fixed threshold protocol based on the 99th percentile at presentation and 3h in conjunction with clinical criteria (Global Registry of Acute Coronary Events (GRACE) score below 140 and the need to be pain-free). It is currently unknown whether one algorithm is preferable to the other.

The aim of this study was to directly compare safety quantified by the negative predictive value (NPV) and the negative likelihood ratio (LR) for the presence of AMI, and efficacy quantified by the proportion of patients triaged towards rule-out in a large diagnostic multicenter study enrolling patients presenting with suspected AMI to the ED (NCT00470587). 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. Patients presenting with ST-Segment-Elevation MI were excluded. Triage towards rule-out by the 0/1h- or the 0/3h-algorithm was compared against the final adjudication performed by two independent cardiologists using all information including cardiac imaging and serial

hs-cTnT measurements. Analyses were performed using hs-cTnT and hs-cTnI. NPV and efficacy were compared using McNemar's test, respectively Pearson X^2 test. 95%-Confidence intervals were calculated using the Wilson score method without continuity correction.

Among 2547 patients eligible for analysis using hs-cTnT, AMI was the final adjudicated diagnosis in 387 patients (15%). The 0/1h-algorithm provided similar safety compared to the 0/3h-algorithm (NPV 99.8% (95%CI 99.4-99.9%) and negative LR 0.01 (95%CI 0.00-0.03) versus 99.7% (95%CI 99.2-99.9%) and 0.02 (95%CI 0.00-0.05)), but allowed to rule-out significantly more patients as compared to the 0/3h-algorithm (60% vs. 44%, p<0.001). Among 2197 patients eligible for analysis using hs-cTnI, AMI was the final diagnosis in 327 patients (15%). The 0/1h-algorithm provided higher safety compared to the 0/3h-algorithm (NPV 99.6% (95%CI 99.1-99.9%) and negative LR 0.02 (95%CI 0.01-0.05) vs. 97.8% (95%CI 96.7-98.5%) and 0.13 (95%CI 0.09-0.19)), and allowed to rule-out a similar portion of patients as compared to the 0/3h-algorithm (52% vs. 51%, p=0.507, Figure 1).

Overall, 711 patients (28%) presented within the first two hours from chest pain onset (CPO). Safety for the 0/1h- and 0/3h-algorithm using hs-cTnT was very high (NPV 99.6% (95%CI 98.4-99.9%) versus 100% (95%CI 98.9-100%) and comparable to late presenters (CPO>2h) with 99.9% (95%CI 99.5-100%) versus 99.6% (95%CI 98.9-99.9%), respectively. The 0/1h-algorithm allowed to rule-out more patients compared to the 0/3h-algorithm in early presenters (64% versus 49% p<0.001) and in late presenters (59% versus 42%, p<0.001). Findings were confirmed using hs-cTnI as well as using 30-days survival as an additional outcome measure for safety with survival rates of 99.9%-100% for patients triaged towards rule-out by both algorithms.

These findings corroborate and extend previous work on the development and validation of safe and effective rule-out strategies for AMI and have important clinical implications.(3–5) The excellent safety achieved with both algorithms documents the suitability of most of these patients for early discharge and outpatient management. Beyond the more favorable combination of safety and efficacy by the 0/1h-algorithm versus the 0/3h-algorithm, the following features may help physicians and institutions in the selection of their preferred triage algorithm. First, the 0/1h-algorithm has the obvious and important additional advantage of allowing clinical decision-making two hours earlier as compared to the 0/3h-algorithm. As most patients triaged towards early rule-out are also candidates for direct discharge from the ED, it is very likely that it will reduce time to discharge and treatment cost in the ED. Second, the 0/1h-algorithm does not require the use of a specific risk score, which further increases its feasibility. Previous studies have documented that omitting any of the three elements of the 0/3h-algorithm (hs-cTn, GRACE-score, pain-free criteria) in an effort to simplify the approach would worsen its safety and is therefore discouraged.(3) When putting our findings into clinical perspective, it is important to highlight that the 0/1h-algorithm and the 0/3h-algorithm should always be used in conjunction with all clinical information available. This is of paramount importance as among patients presenting with acute chest discomfort to the ED, the rule-out of AMI is related to the possibility of rapid discharge and outpatient management, but not identical to it.

In conclusion, the 0/1h-algorithm is superior to the 0/3h-algorithm using hs-cTnT as well as hs-cTnI, as it more favorably combines safety with efficacy.

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Conflict of interests

The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. Drs. Badertscher, Boeddinghaus, 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 contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers.

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Appendix

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References

1. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016;37:267–315.
2. Nestelberger T, Wildi K, Boeddinghaus J, Twerenbold R, Reichlin T, Giménez MR, Puelacher C, Jaeger C, Grimm K, Sabti Z, Hillinger P, Kozhuharov N, du Fay de Lavallaz J, Pinck F, Lopez B, Salgado E, Miró Ò, Bingisser R, Lohrmann J, Osswald S, Mueller C. Characterization of the observe zone of the ESC 2015 high-sensitivity cardiac troponin 0h/1h-algorithm for the early diagnosis of acute myocardial infarction. Int J Cardiol. 2016;207:238–45.
3. Chapman AR, Anand A, Boeddinghaus J, Ferry A V., Sandeman D, Adamson PD, Andrews J, Tan S, Cheng SF, D'Souza M, Orme K, Strachan FE, Nestelberger T, Twerenbold R, Badertscher P, Reichlin T, Gray A, Shah ASV, Mueller C, Newby DE, Mills NL. Comparison of the Efficacy and Safety of Early Rule-Out Pathways for Acute Myocardial Infarction. Circulation. 2017;135:1586-1596.
4. Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Cupa J, Bürge T, Mächler P, Corbière S, Grimm K, Giménez MR, Puelacher C, Shrestha S, Flores Widmer D, Fuhrmann J, Hillinger P, Sabti Z, Honegger U, Schaerli N, Kozhuharov N, Rentsch K, Miró Ò, López B, Martin-Sanchez FJ, Rodriguez-Adrada E, Morawiec B, Kawecki D, Ganovská E, Parenica J, Lohrmann J, Kloos W, Buser A, Geigy N, Keller DI, Osswald S, Reichlin T, Mueller C. Direct Comparison of 4 Very Early Rule-Out Strategies for Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin IClinical Perspective. Circulation. 2017;135:1597-1611.
5. Wildi K, Cullen L, Twerenbold R, Greenslade JH, Parsonage W, Boeddinghaus J, Nestelberger T, Sabti Z, Rubini-Giménez M, Puelacher C, Cupa J, Schumacher L, Badertscher P, Grimm K, Kozhuharov N, Stelzig C, Freese M, Rentsch K, Lohrmann J, Kloos W, Buser A, Reichlin T, Pickering JW, Than M, Mueller C. Direct comparison of 2 rule-out strategies for acute myocardial infarction: 2-h accelerated diagnostic protocol vs 2-h algorithm. Clin Chem. 2017;63:1227–36.

Figure 1 **Direct comparison of the 0/1h- and 0/3h-algorithm for early rule-out of AMI using hs-cTnT (A) and hs-cTnI (B)**

The figure is illustrating both co-primary endpoints: safety, as quantified by the negative predictive value (%), and efficacy (proportion of patients assigned to ruled-out, %). Bars represent 95% confidence intervals, hs-cTn = high sensitivity cardiac troponin. AMI = acute myocardial infarction.