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

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2 Patients with symptoms suggestive of acute myocardial infarction (AMI) account for

3 about 10% of all emergency department (ED) presentations.(1) The majority of

4 patients are finally found to have diagnoses other than AMI.(2) Thus, the expeditious

5 evaluation of such patients is important as delays in ruling out AMI may interfere with

6 the detection of other underlying diseases. The 0/1hour(h)-algorithm and the 0/3h-

7 algorithm are both recommended by the European Society of Cardiology (ESC) with

8 a class I recommendation for the early rule-out of AMI.(1) The 0/1h- and the 0/3h-

9 algorithm are completely different protocols. While the 0/1h-algorithm uses high-

10 sensitivity cardiac troponin (hs-cTn) concentrations at presentation and absolute

11 changes within the first hour, and hence takes optimal advantage of the increased

12 diagnostic accuracy and precision of hs-cTn assays, the 0/3h-algorithm uses a fixed

13 threshold protocol based on the 99th percentile at presentation and 3h in conjunction

14 with clinical criteria (Global Registry of Acute Coronary Events (GRACE) score below

15 140 and the need to be pain-free). It is currently unknown whether one algorithm is

16 preferable to the other.

17 The aim of this study was to directly compare safety quantified by the negative

18 predictive value (NPV) and the negative likelihood ratio (LR) for the presence of AMI,

19 and efficacy quantified by the proportion of patients triaged towards rule-out in a

20 large diagnostic multicenter study enrolling patients presenting with suspected AMI to

21 the ED (NCT00470587). The study was carried out according to the principles of the

22 Declaration of Helsinki and approved by the local ethics committees. Written

23 informed consent was obtained from all patients. Patients presenting with ST-

24 Segment-Elevation MI were excluded. Triage towards rule-out by the 0/1h- or the

25 0/3h-algorithm was compared against the final adjudication performed by two

26 independent cardiologists using all information including cardiac imaging and serial

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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.

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52   These findings corroborate and extend previous work on the development and

53   validation of safe and effective rule-out strategies for AMI and have important clinical

54   implications.(3–5) The excellent safety achieved with both algorithms documents the

55   suitability of most of these patients for early discharge and outpatient management.

56   Beyond the more favorable combination of safety and efficacy by the 0/1h-algorithm

57   versus the 0/3h-algorithm, the following features may help physicians and institutions

58   in the selection of their preferred triage algorithm. First, the 0/1h-algorithm has the

59   obvious and important additional advantage of allowing clinical decision-making two

60   hours earlier as compared to the 0/3h-algorithm. As most patients triaged towards

61   early rule-out are also candidates for direct discharge from the ED, it is very likely

62   that it will reduce time to discharge and treatment cost in the ED. Second, the 0/1h-

63   algorithm does not require the use of a specific risk score, which further increases its

64   feasibility. Previous studies have documented that omitting any of the three elements

65   of the 0/3h-algorithm (hs-cTn, GRACE-score, pain-free criteria) in an effort to simplify

66   the approach would worsen its safety and is therefore discouraged.(3) When putting

67   our findings into clinical perspective, it is important to highlight that the 0/1h-algorithm

68   and the 0/3h-algorithm should always be used in conjunction with all clinical

69   information available. This is of paramount importance as among patients presenting

70   with acute chest discomfort to the ED, the rule-out of AMI is related to the possibility

71   of rapid discharge and outpatient management, but not identical to it.

72   In conclusion, the 0/1h-algorithm is superior to the 0/3h-algorithm using hs-

73   cTnT as well as hs-cTnI, as it more favorably combines safety with efficacy.

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76

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

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All other authors declare that they have no conflict of interest with this study. The investigated hs-cTn assay 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.

Appendix

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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.