Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction

Jasper Boeddinghaus, MD[1,2,3*]; Thomas Nestelberger, MD[1,3*]; Raphael Twerenbold, MD[1,3,4]; Johannes Tobias Neumann, MD[4]; Bertil Lindahl, MD[5]; Evangelos Giannitsis, MD[6]; Nils Arne Sörensen, MD[4]; Patrick Badertscher, MD[1,3]; Janina E. Jann, MD[1,3]; Desiree Wussler, MD[1,3]; Christian Puelacher, MD[1,3]; Maria Rubini Giménez, MD[1,3]; Karin Wildi, MD[1,3]; Ivo Strebel, MSc[1,3]; Jeanne du Fay de Lavallaz, MD[1,3]; Farah Selman, MS[1]; Zaid Sabti, MD[1,3]; Nikola Kozhuharov, MD[1,3]; Eliska Potlukova, MD[1,2]; Katharina Rentsch, PhD[7]; Òscar Miró, MD[3,8]; F. Javier Martin-Sanchez, MD[3,9]; Beata Morawiec, MD[3,10]; Jiri Parenica, MD[3,11]; Jens Lohrmann, MD[1]; Wanda Kloos, MD[1]; Andreas Buser, MD[12]; Nicolas Geigy, MD[13]; Dagmar I. Keller, MD[14]; Stefan Osswald, MD[1]; Tobias Reichlin, MD[1,3]; Dirk Westermann, MD[4]; Stefan Blankenberg, MD[4] ; Christian Mueller, MD[1,3] for the APACE, BACC, and TRAPID-AMI Investigators[#]

[1]Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel; [2]Division of Internal Medicine, University Hospital Basel, University of Basel, both Switzerland; [3]GREAT network; [4]Department of General and Interventional Cardiology, Hamburg University Heart Center, Hamburg, Germany; [5]Department of Medical Sciences, Uppsala University and Uppsala Clinical Research Centre, Uppsala University, Sweden; [6]Medizinische Klinik III, University Heidelberg, Germany; [7]Laboratory Medicine, University Hospital Basel, University of Basel, Switzerland; [8]Emergency Department, Hospital Clinic, Barcelona, Catalonia, Spain; [9]Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, Spain; [10]2nd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Katowice, Poland; [11]Department of Cardiology, University Hospital Brno, Brno, Czech Republic and Medical Faculty, Masaryk University, Brno, Czech Republic; [12]Blood Transfusion Centre, Swiss Red Cross, Basel, Switzerland and Department of Hematology, University Hospital Basel, University of Basel, Switzerland; [13]Emergency Department, Kantonsspital Liestal, Switzerland. [14]Emergency Department, University Hospital Zurich, Zurich, Switzerland.

*Drs. Boeddinghaus and Nestelberger contributed equally to this manuscript and should be considered first author.

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Address for correspondence

Prof. Dr. Christian Müller, CRIB and Department of Cardiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland

Phone Number: +41 61 328 65 49; Fax number: +41 61 265 53 53

E-mail: christian.mueller@usb.ch

ABSTRACT (247 words)

Aims: We aimed to evaluate the impact of age on the performance of the European Society of Cardiology (ESC) 0/1h-algorithms and to derive and externally validate alternative cut-offs specific to older patients.

Methods and Results: We prospectively enrolled patients presenting to the emergency department with symptoms suggestive of acute myocardial infarction (AMI) in three large diagnostic studies. Final diagnoses were adjudicated by two independent cardiologists. High-sensitivity cardiac troponin (hs-cTn) T and I concentrations were measured at presentation and after 1h. Patients were stratified according to age (<55 years [young], ≥55 to <70 years [middle-age], ≥70 years [old]). Rule-out safety of the ESC hs-cTnT-0/1h-algorithm was very high in all age-strata: sensitivity 100% [95%CI, 94.9-100]) in young, 99.3% [95%CI, 96.0-99.9]) in middle-age, and 99.3% [95%CI, 97.5-99.8]) in old patients. Accuracy of rule-in decreased with age: specificity 97.0% [95%CI, 95.8-97.9]) in young, 96.1% [95%CI, 94.5-97.2]) in middle-age, and 92.7% [95%CI, 90.7-94.3]) in older patients. Triage efficacy decreased with increasing age (young 93%, middle-age 80%, old 55%, p<0.001). Similar results were found for the ESC hs-cTnI-0/1h-algorithm. Alternative, slightly higher cut-off concentrations optimized for older patients maintained very high safety of rule-out, increased specificity of rule-in (p<0.01), reduced overall efficacy for hs-cTnT (p<0.01), while maintaining efficacy for hs-cTnI. Findings were confirmed in two validation cohorts (n=2767).

Conclusion: While safety of the ESC 0/1h-algorithms remained very high, increasing age significantly reduced overall efficacy and the accuracy of rule-in. Alternative slightly higher cut-off concentrations may be considered for older patients, particularly if using hs-cTnI.

Keywords: Age, high-sensitivitiy cardiac troponin, guidelines, 0/1h-algorithm, diagnosis of AMI.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT00470587, number NCT00470587 and NCT02355457 (BACC)

Abbreviations

APACE – Advantageous Predictors of Acute Coronary Syndromes Evaluation

BACC – Biomarkers in Acute Cardiac Care

TRAPID-AMI – High-sensitivity cardiac Troponin T assay for RAPID rule-out of AMI

ED – Emergency department

AMI – Acute myocardial infarction

NSTEMI – Non-ST-segment elevation myocardial infarction

ECG – Electrocardiography

cTn – Cardiac troponin

hs-cTn – High-sensitivity cardiac troponin

eGFR – Estimated glomerular filtration rate

NPV – Negative predictive value

PPV – Positive predictive value

IQR – Interquartile range

Introduction

In patients presenting with symptoms suggestive of acute myocardial infarction (AMI), rapid identification of AMI as a life-threatening disorder, but also rapid and accurate rule-out of AMI has enormous medical and economic value.[1–3] Recently, diagnostic strategies applying high-sensitivity cardiac troponin (hs-cTn) T or I assays, including the European Society of Cardiology (ESC) 0/1h-algorithms, have been developed and facilitate the early triage towards rule-out or rule-in of AMI.[1–11]

Beyond the presence or absence of AMI, age seems to be the most important confounder of hs-cTnT and hs-cTnI blood concentrations.[12–21] Mildly elevated hs-cTnT and hs-cTnI blood concentrations are common in elderly individuals without apparent ischemic symptoms.[2,3,12–21] Unfortunately, the impact of age on the diagnostic performance of the ESC 0/1h-algorithms is incompletely understood.

To address this major gap in knowledge, we prospectively investigated the impact of age on the performance of the ESC 0/1h-algorithms in a large multicentre diagnostic study using central adjudication. In a second step, the age-specific findings and aged-optimized alternative cut-off concentrations for older patients derived in this multicentre study were externally validated in two additional diagnostic studies.

Methods

Study design and oversight

We enrolled adult patients presenting with suspected AMI to the ED in three large prospective diagnostic studies carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees: Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE, main cohort),[5,7–10,17,22–26] Biomarkers in Acute Cardiac Care (BACC, first validation cohort)[27] and High-sensitivity cardiac Troponin T assay for RAPID rule-out of AMI (TRAPID-AMI, second validation cohort).[28] Written informed consent was obtained from all patients.

The authors designed the study, gathered, and analysed the data according to the STARD guidelines[29] for studies of diagnostic accuracy (**Supplemental Table 1**), vouched for the data and analysis, wrote the paper, and decided to publish. Routine clinical assessment and detailed methodological descriptions of all three cohorts are given in the Online Supplemental.

The ESC hs-cTnT and hs-cTnI 0/1h-algorithms

The concept of the ESC 0/1h-algorithms is described in detail in the Online Supplemental and shown in **Supplemental Figure 1**.

Stratification of patients according to age

We aimed to stratify patients by age into three equally large cohorts. Based on previous findings from APACE[5,8–10,22,25,31–34] we assumed that the following three age-strata should yield near-equal group-size: <55 years (young), ≥55 to <70 years (middle-age), ≥70 years (old).

Statistical analysis

Safety for rule-out was quantified by the resulting sensitivity (and negative predictive value [NPV]), accuracy for rule-in was quantified by the resulting specificity (and positive predictive value [PPV]) for NSTEMI and overall efficacy was quantified by the percentage of patients triaged either towards rule-out or rule-in by the respective strategy. Time since chest pain onset

(cpo) was determined at the time of first study blood draw. In the main cohort, subgroup analyses were performed in early presenters (cpo ≤2h), late presenters (cpo >6h) and in very old patients (age ≥80 years).

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. Statistical analyses were performed using SPSS for Windows, version 24.0 (SPSS Inc, Chicago, IL), MedCalc, version 9.6.4.0 (MedCalc Software, Ostend, Belgium), and R (Version 3.3.1, Vienna, Austria). Detailed information is given in the **Online Supplemental Methods**.

Results

Main cohort

Study cohort and characteristics of patients

From April 2006 to August 2015, 3123 patients were available for the analysis of the ESC hs-cTnT 0/1h-algorithm and 2828 patients for the analysis of the ESC hs-cTnI 0/1h-algorithm (**Supplemental Figure 2**). Older patients differed in multiple characteristics from younger and middle-aged patients, particularly a higher prevalence of pre-existing cardiovascular disorders including AMI and stroke **(Table 1, Supplemental Table 2)**.

Adjudicated final diagnosis

Among patients with complete dataset of hs-cTnT, the adjudicated final diagnosis was NSTEMI in 491/3123 patients (16%), unstable angina in 301/3123 (10%), cardiac symptoms of origin other than coronary artery disease such as tachyarrhythmia, Tako-Tsubo cardiomyopathy, heart failure or myocarditis in 476/3123 (15%), non-cardiac symptoms in 1728/3123 (55%) and unknown in 127/3123 patients (4%). The prevalence of NSTEMI increased with increasing age (young 6.4%, middle-aged 15%, old 27%, $p<0.001$). Distribution of final diagnoses was similar in patients with complete dataset of hs-cTnI (**Online Supplemental Results**).

Hs-cTn concentrations at presentation according to age and final diagnoses and interaction between age and hs-cTn

Concentrations of hs-cTnT and hs-cTnI at presentation showed a moderate-to-high correlation with age in both datasets ($\rho=0.6$ for hs-cTnT and $\rho=0.49$ for hs-cTnI, respectively, both $p<0.001$). Old patients had significantly higher hs-cTnT and hs-cTnI concentrations at presentation than young and middle-aged patients, particularly in patients with final diagnoses other than NSTEMI (**Supplemental Figure 3A+B**). The Interaction between age and hs-cTnT concentrations for NSTEMI was significant ($p<0.001$), but not for hs-cTnI ($p=0.31$). **Online Supplemental Results**, **Online Supplemental Figure 4A+B**).

Diagnostic accuracy of hs-cTnT and hs-cTnI

AUCs of hs-cTnT concentrations at presentation in young, middle-aged, and old patients were 0.96 (95%CI, 0.94-0.98), 0.93 (95%CI, 0.91-0.95), and 0.89 (95%CI, 0.87-0.91), respectively. AUCs of hs-cTnI concentrations at presentation in young, middle-aged, and old patients were 0.95 (95%CI, 0.93-0.97), 0.92 (95%CI, 0.90-0.94), and 0.87 (95%CI, 0.85-0.90), respectively (**Figure 1A)**.

Diagnostic performance of the ESC hs-cTnT 0/1h-algorithm according to age

Among 1122 (36%) young patients, 956/1122 (85% [95%CI, 83-87]) were triaged towards rule-out (sensitivity 100% [95%CI, 94.9-100], NPV 100% [95%CI, 99.6-100]), 92/1122 (8% [95%CI, 7-10]) patients were triaged towards rule-in (specificity 97.0% [95%CI, 95.8-97.9], PPV 66.3% [95%CI, 56.2-75.1]).

Among 935 (30%) middle-aged patients, 606/935 (65% [95%CI, 62-68]) were triaged towards rule-out (sensitivity 99.3% [95%CI, 96.0-99.9], NPV 99.8% [95%CI, 99.1-100]), 141/935 (15% [95%CI, 13-17]) patients triaged towards rule-in (specificity 96.1% [95%CI, 94.5-97.2], PPV 78.0% [95%CI, 70.5-84.1]).

Among 1066 (34%) old patients, 317/1066 (30% [95%CI, 27-33]) were triaged towards rule-out (sensitivity 99.3% [95%CI, 97.5-99.8], NPV 99.4% [95%CI, 97.7-99.8]), 272/1066 (25% [95%CI, 23-28]) patients were triaged towards rule-in (specificity 92.7% [95%CI, 90.7-94.3], PPV 79.0% [95%CI, 73.8-83.5]; **Table 2A, Figure 2A**).

One middle-aged and 2 old patients with NSTEMI were missed (**Supplemental Table 3**). Detailed diagnostic performance of the ESC hs-cTnT 0/1h-algorithm in decades of age is shown in **Figure 2B.**

Diagnostic performance of the ESC hs-cTnI 0/1h-algorithm according to age

Overall, similar findings emerged when assessing the diagnostic performance of the ESC hs-cTnI 0/1h-algorithm according to age (**Figure 3, Table 3A, Supplemental Table 3).**

Derivation of alternative cut-off criteria for the ESC hs-cTnT 0/1h-algorithm

Optimal alternative cut-offs for rule-out were <8ng/L at presentation in patients presenting with a cpo >3h or <12ng/L at presentation *and* an absolute 1h-change <3ng/L. The safety was identical to the original ESC hs-cTnT 0/1h-algorithm, but the proportion of patients eligible for direct rule-out increased from 2.2% (95%CI, 1.3-3.1) to 11% (95%CI, 8.9-13). The proportion of patients ruled-out overall was identical to that of the original ESC 0/1h-algorithm. For rule-in, optimal alternative cut-offs were ≥80ng/L at presentation *or* an absolute 1h-change ≥6ng/L. These cut-offs improved specificity from 92.7% (95%CI, 90.7-94.3) to 96.8% (95%CI, 95.3-97.8, p<0.01) and PPV from 79.0% (95%CI, 73.8-83.5) to 87.8% (95%CI, 82.6-91.6, p=0.04). However, the proportion of patients ruled-in for NSTEMI decreased from 25% (95%CI, 23-28) to 21% (95%CI, 18-24) and from 18% [95%CI, 16-21] to 12% [95%CI, 10-14] for direct rule-in; **Supplemental Table 4A**). Accordingly, overall efficacy decreased from 55% to 51% (p<0.001).

Derivation of alternative cut-off criteria for the ESC hs-cTnI 0/1h-algorithm

Optimal alternative cut-offs for rule-out were <4ng/L at presentation in patients presenting with cpo >3h or <6ng/L at presentation *and* an absolute 1h-change <3ng/L. The safety was similar to the original ESC hs-cTnI 0/1h-algorithm (NPV 97.5% vs. 98.1%, p=0.67), and the proportion of patients eligible for rule-out increased from 25% (95%CI, 22-27) to 32% (95%CI, 29-35) and for direct rule-out from 1.4% (95%CI, 0.7-2.4) to 12% (95%CI, 10-14) (**Supplemental Table 4B**). For rule-in, optimal alternative cut-offs were ≥100ng/L at presentation *or* an absolute 1h-change ≥8ng/L. These cut-offs significantly improved specificity from 86.4% (95%CI, 83.7-88.7) to 90.6% (95%CI, 88.3-92.5, p=0.01), while the increase in PPV did not reach statistical significance 67.9% (95%CI, 62.4-72.9) to 74.2% (95%CI, 68.6-79.2, p=0.11). Again, the proportion of patients ruled-in for NSTEMI decreased from 31% (95%CI, 28-34) to 27% (95%CI, 24-30) and from 23% [95%CI, 20-25] to 16% [95%CI, 14-19] for direct rule-in;

Table 3A Supplemental Table 4B). Accordingly, overall efficacy increased from 56% to58% ($p<0.03$).

Sex-specific cut-off criteria for the ESC 0/1h-algorithms for use in older patients

The diagnostic performance of derived and validated sex-specific cut-off combinations for use in older patients is shown in the **Online Supplemental Results** and **Online Supplemental Table 5A-C**.

Subgroup analyses in very early presenters, late presenters and very old patients

Among 3123 patients with hs-cTnT, 830/3123 patients (27%) presented **within 2h** from cpo. E.g. in old patients (n=226), 64/226 (28%) were ruled-out (sensitivity 98.5%), 62/226 (27%) ruled-in (specificity 91.1%), and the remaining 100/226 (44%) patients classified as observe (**Supplemental Figure 5A**). Similar results were obtained for hs-cTnI (**Supplemental Figure 5B**). The performance of both ESC hs-cTn 0/1h-algorithms in late presenters and very old patients (age ≥80 years) is given in the **Online Supplemental**.

Prognostic performance of the ESC hs-cTnT/I 0/1h-algorithms to predict death during follow-up

Survival of young patients triaged towards rule-out, observe and rule-in was 100% at 30-days for all age groups and 99.6%, 96.6%, and 95.1% at 2-years, respectively (all $p<0.001$). Among middle-aged patients, survival was 99.8%, 98.4%, and 100% at 30-days, and 99.1%, 93.1%, and 96.8% at 2-years, respectively (all $p<0.001$, $p=0.06$ for comparison between observe and rule-in). Among old patients, survival was 99.7%, 98.7%, and 94.5% at 30-days, and 93.6%, 82.2% and 75.4% at 2-years, respectively (all $p<0.001$; **Supplemental Figure 6A)**.

Similar findings emerged when assessing the prognostic performance of the ESC hs-cTnI 0/1h-algorithm (**Supplemental Figure 6B)** and for the prediction of MACE within 30 days (**Online Supplemental Results**).

Validation Cohorts

Overall, the characteristics of patients in validation cohort 1 and validation cohort 2 were similar to those of the main cohort (**Supplemental Table 6+7).**

Diagnostic accuracy of hs-cTnT

AUCs of hs-cTnT and hs-cTnI concentrations at presentation in young, middle-aged, and old patients in both validation cohorts were similar to AUCs in the main cohort (**Figure 1B+C**).

Diagnostic performance of the official ESC hs-cTn 0/1h-algorithms and validation of the alternative cut-off criteria in old patients

In both validation cohorts, findings for the ESC hs-cTnT 0/1h-algorithm (and for the hs-cTnI 0/1h-algorithm in the first validation cohort) were similar to the findings of the main cohort. While safety remained high in older patients, specificity among patients triaged towards rule-in and particularly overall efficacy decreased with increasing age (**Figure 4**, **Table 2B+C, Table 3B, Supplemental Figure 7-9**).

Prognostic performance of the ESC hs-cTn 0/1h-algorithms to predict death during follow-up

Prognostic performance of the ESC 0/1h-algorithms in both validation cohorts was similar to the prognostic performance in the main cohort (**Online Supplemental Results**, **Supplemental Figure 10**).

Discussion

This large multicentre study quantified the impact of age on the performance of the ESC 0/1h-algorithms. In a second step, we derived and externally validated alternative cut-off criteria optimized for the use in older patients. We report **eight** major findings:

First, increasing age was associated with a higher prevalence of pre-existing cardiovascular disorders. **Second**, while patients adjudicated to have NSTEMI had comparable hs-cTnT and hs-cTnI concentrations among the three age-strata, hs-cTnT and hs-cTnI concentrations were significantly higher in older patients with other causes of acute chest discomfort. This finding seems at least in part explained by the higher prevalence of pre-existing cardiovascular disorders and their association with chronic myocardial injury in older patients. **Third,** accordingly the overlap in hs-cTnT and hs-cTnI concentrations between NSTEMI and other causes of acute chest discomfort was larger resulting in a lower AUC with increasing age. The interaction term (hs-cTn*age) for NSTEMI was statistically significant when using hs-cTnT, but not when using hs-cTnI, possibly suggesting different effects of aging on hs-cTnT versus hs-cTnI concentrations. **Fourth,** the prevalence of NSTEMI increased substantially with increasing age and was more than four-times higher in older versus younger patients. **Fifth**, age had a major impact on the overall diagnostic performance of the ESC 0/1h-algorithm: while safety as quantified by sensitivity and NPV was very high in all age-strata, the percentage of patients assigned towards rule-out, the specificity among patients triaged towards rule-in and particularly overall efficacy decreased with increasing age. As a consequence, the percentage of old patients remaining in the observe zone and usually requiring additional diagnostic testing including a 3h-sample of hs-cTn and cardiac imaging was nearly twice as high as in middle-aged and more than four-times as high as in young patients. Due to the increase in AMI prevalence with age, PPV remained high in older patients. **Sixth**, use of individualized slightly higher cut-offs in older patients maintained very high safety of rule-out, increased specificity of rule-in, reduced overall efficacy for hs-cTnT, while maintaining

efficacy for hs-cTnI. Accordingly, the use of slightly higher cut-off concentrations may be considered, particularly if using hs-cTnI. Still, the overall improvement achieved was modest and needs to be balanced against the increased complexity created by specific cut-offs in elderly patients. Using sex-specific cut-off criteria versus modified cut-off criteria in older patients did not further increase the overall diagnostic performance of both ESC 0/1h-algorithms. Beyond age, also the time from chest pain onset, sex, and renal function have been shown to affect hs-cTnT and hs-cTnI concentrations. Although preliminary evidence suggests that the effect of these additional confounders overall is smaller as compared to that of age,[1,2,12,15,35] computerized integration of all confounders might be the most accurate approach once convenient physician-information technology interfaces become available. **Seventh**, while the vast majority of findings for the ESC 0/1h-algorithm using hs-cTnI mirrored the findings for the ESC 0/1h-algorithm using hs-cTnT, safety of rule-out and accuracy of rule-in were slightly lower for hs-cTnI as compared to hs-cTnT. At first glance, this finding is surprising as both assays seem to have comparable diagnostic accuracy for NSTEMI,[23] and hs-cTnI-Architect seems to have even higher analytical sensitivity as compared to hs-cTnT-Elecsys.[36] This finding is therefore more likely related to the inherent verification bias in favor of hs-cTnT (available among many other information for the adjudication) as compared to hs-cTnI (not available for the adjudication) and the rare, but previously described analytical discrepancies between hs-cTnI and hs-cTnT.[8,32] **Eighth**, irrespective of age, patients triaged towards rule-out had very high 30-day survival rates of 99-100%. As expected, 30-day and 1-year or 2-year survival rates were lower in older patients as compared to younger patients.

Our findings extend and corroborate data previously obtained for the diagnostic performance of the ESC 0/1h-algorithm assessed in all-comers with acute chest discomfort.[7,8,10,22,34] These findings also extend and corroborate more general observations made for the use of hs-cTn in elderly patients.[37]

The clinical utility of the ESC 0/1h-algorithms also remained high in very old patients

(≥80 years) and those presenting very early after chest pain onset. While patients presenting early to the ED were more frequently ruled-in by significant 1h-delta changes, late presenters were primarily ruled-in due to markedly elevated cardiac troponin concentrations. This can be explained by the fact that the increase in cardiac troponin concentrations is time-dependent. Due to the higher prevalence of NSTEMI, PPV in older patients was even higher (70-80%) as in younger patients, and in a range that most experts consider an acceptable likelihood to initiate invasive management in the majority of these patients. The additional use of short-term changes as criteria within the ESC 0/1h-algorithms at least in part was able to compensate for the substantially lower specificity of mild elevations in hs-cTn in older patients.[37]

The lower efficacy observed in older patients is not unique to the ESC 0/1h-algorithms, but seems to be a universal phenomenon of all currently available diagnostic algorithms.[2,3,38] The higher prevalence of cardiovascular comorbidities in older patients invariably reduces the diagnostic performance of clinical assessment, the ECG, hs-cTn, and cardiac imaging.[2,3,38]

The exact pathophysiological mechanisms resulting in cardiomyocyte injury in the aging heart are incompletely understood, but seem to include the effect of pre-existing cardiovascular disorders such as previous AMI, hypertensive heart disease, as well as myocardial fibrosis.[2,3,39]

It is important to highlight that irrespective of the use of the uniform or individualized cut-offs in older patients, the ESC 0/1h-algorithms should always be used in conjunction with full clinical assessment and the ECG. Accordingly, the final sensitivity achieved by the combination of both ESC 0/1h-algorithms with clinical assessment and the ECG will be even slightly higher as that reported for the ESC 0/1h-algorithms only. Vice-versa, efficacy will be slightly lower as the clinician will overrule the triage recommendation provided by the algorithm in some patients.

Some limitations merit consideration when interpreting these findings. **First**, our study was conducted in ED patients with symptoms suggestive of AMI. Further studies are required

to quantify the utility of the ESC 0/1h-algorithms in patients with either a higher pre-test probability (e.g., in a coronary care unit setting) or in patients with a lower pre-test probability (e.g., in a general practitioner setting) for AMI. **Second**, no specific sample size calculation was performed. Although this secondary analysis from an ongoing multicenter study is one of the largest ever performed, it still may have been underpowered for some comparisons. **Third**, not all patients with acute chest pain had a second set of laboratory measurements at 1h. The most common reasons for missing blood samples were logistic issues in the ED that precluded blood draw around the 1h-window. However, it is unlikely that the absence of these patients significantly influenced our results. **Fourth**, although we used the most stringent methodology to adjudicate the presence or absence of AMI including central adjudication by experienced cardiologists and serial measurements of hs-cTn, we still may have misclassified a small number of patients.[30] **Fifth**, our findings are specific to the two hs-cTn assays currently available for routine clinical care. Once other hs-cTn assays will become available for clinical care, additional studies will need to derive and validate a 0/1h-algorithm and examine whether our findings can be generalized to them. Finally, we cannot generalize our findings to patients with terminal kidney failure requiring dialysis, since they were excluded from this study.

Conclusion

While the safety of the ESC 0/1h-algorithms remained very high, increasing age significantly reduced overall efficacy and the accuracy of rule-in. Alternative slightly higher cut-off concentrations may be considered for older patients, particularly if using hs-cTnI.

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Conflict of interest

The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. Drs. Boeddinghaus, Nestelberger, Twerenbold, Badertscher, Rubini Gimenéz, Wildi, Puelacher, Reichlin 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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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.

[#]APACE and TRAPID-AMI Investigators who also contributed to this manuscript:

Samyut Shrestha, MD[1,3]; Dayana Flores, MD[1,3]; Michael Freese, SN[1,3]; Claudia Stelzig, MS[1]; Caroline Kulangara, PhD[1]; Kathrin Meissner, RN[1]; Nicolas Schaerli, MD[1,2,3]; Deborah Mueller, MD[1,3]; Lorraine Sazgary, MD[1,2,3]; Stella Marbot, MD[1,3]; Beatriz López, MD[3,4]; Sofia Calderón, MD[3,4]; Esther Rodriguez Adrada, MD[5]; Damian Kawecki, MD[6]; Ewa Nowalany-Kozielska, MD, PhD[6]; Eva Ganovská, MD[3,7]; Arnold von Eckardstein, MD[8]; Isabel Campodarve, MD[9]; Michael Christ, MD[10]; Jorge Ordóñez-Llanos, MD[11]; Christopher R. de Filippi, MD[12]; James McCord, MD[13]; Richard Body, MD[14]; Mauro Panteghini, MD[15]; Thomas Jernberg, MD[16]; Mario Plebani, MD[17]; Franck Verschuren, MD[18]; John K. French, MD[19]; Robert Christenson, MD, PhD[20]; Silvia Weiser, PhD[21]; Garnet Bendig, PhD[21]; Peter Dilba, PhD[21].

[1]Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel; [2]Division of Internal Medicine, University Hospital Basel, University of Basel, both Switzerland; [3]GREAT network; [4]Emergency Department, Hospital Clinic, Barcelona, Catalonia, Spain; [5]Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, Spain; [6]2nd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Katowice, Poland; [7]Department of Cardiology, University Hospital Brno, Brno, Czech Republic and Medical Faculty, Masaryk University, Brno, Czech Republic; [8]Department of Laboratory Medicine, University Hospital Zurich, Zurich, Switzerland; [9]Emergency Department, Hospital del Mar, Barcelona, Spain; [10]Department of Emergency Medicine, Luzerner Kantonsspital, Lucerne, Switzerland; [11]Department of Clinical Biochemistry, Institut d'Investigacions Biomèdiques Sant Pau, Barcelona, Spain; [12]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD; [13]Henry Ford Heart and Vascular Institute, Henry Ford Health System, Detroit, MI; [14]Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; [15]Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan Medical School, Milan, Italy; [16]Department of Medicine, Karolinska Institutet, Huddinge, Sweden; [17]Department of Laboratory Medicine, University Hospital of Padova, Padua, Italy; [18]Department of Acute Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium; [19]Liverpool Hospital and University of New South Wales, Liverpool, NSW, Australia; [20]Department of Pathology, University of Maryland School of Medicine, Baltimore, MD; [21]Roche Diagnostics Germany, Penzberg, Germany.

References online only

Figure Legends

Figure 1	**Diagnostic accuracy of hs-cTnT and hs-cTnI concentrations at presentation to the emergency department for the diagnosis of NSTEMI in patients stratified according to age**

Receiver operating characteristics curve and corresponding areas under the curves indicating diagnostic accuracy of hs-cTnT (blue) and hs-cTnI (orange) concentrations at presentation for the diagnosis of acute myocardial infarction in patients stratified according to age into young (<55 years), middle-age (≥55 to <70 years), and old (≥70 years) in (A) main cohort, (B) first validation cohort, and (C) second validation cohort. Hs-cTnT = high sensitivity cardiac troponin T; hs-cTnI = high-sensitivity cardiac troponin I.

Figure 2	**Diagnostic performance of the ESC hs-cTnT 0/1h-algorithm according to age in the main cohort**

Diagnostic performance of the ESC hs-cTnT 0/1h-algorithm in patients stratified according to age into (A) young, middle-age, old, and (B) decades. (*) if chest pain onset >3h; Delta = unsigned change within the first hour; NSTEMI = non-ST-segment elevation myocardial infarction. Sens. = sensitivity; NPV = negative predictive value; Prev. = prevalence; Spec. = specificity; PPV = positive predictive value. hs-cTnT = high sensitivity cardiac troponin T.

Figure 3	**Diagnostic performance of the ESC hs-cTnI 0/1h-algorithm according to age in the main cohort**

Diagnostic performance of the ESC hs-cTnI 0/1h-algorithm in patients stratified according to age into (A) young, middle-age, old, and (B) decades. (*) if chest pain onset >3h; Delta = unsigned change within the first hour; NSTEMI = non-ST-segment elevation myocardial

infarction. Sens. = sensitivity; NPV = negative predictive value; Prev. = prevalence; Spec. = specificity; PPV = positive predictive value. hs-cTnI = high sensitivity cardiac troponin I.

Figure 4	**Diagnostic performance of modified cut-off criteria for use in older patients (≥70 years) in all three study cohorts**

Diagnostic performance of the (A) ESC hs-cTnT 0/1h-algorithm and (B) ESC hs-cTnI 0/1h-algorithm using modified cut-off criteria for use in older patients (≥70 years). Red numbers indicate modified cut-off values that differ from the official cut-off criteria.