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RESEARCH LETTER

External Validation of the No Objective Testing Rules in Acute Chest Pain

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Rapid high-sensitivity cardiac troponin (hs-cTn) based algorithms have substantially improved the early rule out of acute myocardial infarction (AMI) and thereby facilitated the selection of patients eligible for outpatient management.[1,2] However, it remains unclear which patients after rule out of AMI should still undergo objective anatomic or functional cardiac testing for the detection of coronary artery disease (CAD) and which not. A pilot study using a 0/2-hour rule-out protocol derived combinations of clinical variables, the so-called No Objective Testing (NOT) rules (Figure), for selection of patients who may not need objective anatomic or functional cardiac testing for CAD.[3] Hence, we aimed to externally validate the performance of the 3 NOT models in a large, prospective, international multicenter study.

The study was approved by the local ethics committees, and written informed consent was obtained from all patients. Unselected patients presenting with acute chest pain to the emergency department were prospectively enrolled between May 2006 and March 2018. The final diagnosis of acute coronary syndrome (ACS), defined as AMI or unstable angina, was centrally adjudicated by 2 independent cardiologists applying the Fourth Universal Definition of myocardial infarction for the index event, as well as during long-term follow-up. The primary end points were the safety and efficacy of the NOT rules for rule out of ACS or cardiovascular death within 30 days of follow-up, including index events. Secondary end points included 365- and 730-day events. In addition, a sensitivity analysis on the combination of the NOT rules with a previously validated 0/2-hour algorithm that triaged patients toward rule out of AMI if 0- and 2-hour blood concentrations are <6 ng/L and Δ0/2 hours <2 ng/L was performed.[4] The data and study material that support the findings of this study are available from the corresponding author on reasonable request.

Among 3500 patients eligible for this analysis (available 0- and 2-hour Abbott Architect hs-cTnI measured from tubes containing lithium heparin or serum), 2374 (68%) were eligible for the NOT rules as they were ruled out of AMI by the 0/2-hour hs-cTnI protocol (0- and 2-hour hs-cTnI uniform cutoff <26.2 ng/L and nondiagnostic ECG without the TIMI [Thrombolysis in Myocardial Infarction] score); ACS or cardiovascular death at 30 days occurred in 332 (14%) patients. All 3 rules performed well for rule out of ACS or cardiovascular death at 30 days. The first rule (weighted score, including age, sex, cardiovascular risk factors, previous myocardial infarction or known CAD, and nitrate use) had a sensitivity of 99.7% (95% CI, 98.3%–99.9%), a negative predictive value (NPV) of 99.8% (95% CI, 98.5%–99.9%), and an area under the receiver-operating characteristic curve of 0.81. The dichotomized second (aged <50 years, no previous AMI

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For Sources of Funding and Disclosures, see page 4.

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A

Patients with acute chest pain
n=3500

Rule-out of AMI with Hs-cTnI <99th centile at 0/2h and non-diagnostic ECG
n=2374

Time	1. Rule: Weighted Score ≤ 4 points	1. Rule: Weighted Score > 4 points	2. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD, no nitrate use — True	2. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD, no nitrate use — False	3. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD — True	3. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD — False
30-days	Low risk n=454 (19%)	High risk n=1920 (81%)	Low risk n=545 (23%)	High risk n=1829 (77%)	Low risk n=546 (23%)	High risk n=1828 (77%)
	Sensitivity: 99.7% NPV: 99.8% MACE: 1 (0.2%)	MACE: 331 (17%)	Sensitivity: 99.7% NPV: 99.8% MACE: 1 (0.2%)	MACE: 331 (18%)	Sensitivity: 99.7% NPV: 99.8% MACE: 1 (0.2%)	MACE: 331 (18%)
365-days	Low risk n=440 (19%)	High risk n=1885 (81%)	Low risk n=525 (23%)	High risk n=1800 (77%)	Low risk n=526 (23%)	High risk n=1799 (77%)
	Sensitivity: 98.9% NPV: 99.1% MACE: 4 (0.9%)	MACE: 362 (19%)	Sensitivity: 98.9% NPV: 99.2% MACE: 4 (0.8%)	MACE: 362 (20%)	Sensitivity: 98.9% NPV: 99.2% MACE: 4 (0.8%)	MACE: 362 (20%)
730-days	Low risk n=406 (19%)	High risk n=1764 (81%)	Low risk n=490 (23%)	High risk n=1680 (77%)	Low risk n=491 (23%)	High risk n=1679 (77%)
	Sensitivity: 99.2% NPV: 99.3% MACE: 3 (0.7%)	MACE: 375 (21%)	Sensitivity: 98.9% NPV: 99.2% MACE: 4 (0.8%)	MACE: 374 (22%)	Sensitivity: 98.9% NPV: 99.2% MACE: 4 (0.8%)	MACE: 374 (22%)

B

Patients with acute chest pain
n=3500

Rule-out of AMI with a validated 0/2h Hs-cTnI algorithm
n=2076

Time	1. Rule: Weighted Score ≤ 4 points	1. Rule: Weighted Score > 4 points	2. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD, no nitrate use — True	2. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD, no nitrate use — False	3. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD — True	3. Rule: Age < 50y, Risk factors < 3, no previous MI or known CAD — False
30-days	Low risk n=474 (23%)	High risk n=1602 (77%)	Low risk n=570 (27%)	High risk n=1506 (73%)	Low risk n=571 (28%)	High risk n=1505 (74%)
	Sensitivity: 99.5% NPV: 99.8% MACE: 1 (0.2%)	MACE: 208 (13%)	Sensitivity: 99.0% NPV: 99.7% MACE: 2 (0.4%)	MACE: 207 (14%)	Sensitivity: 99.0% NPV: 99.7% MACE: 2 (0.4%)	MACE: 207 (13%)
365-days	Low risk n=457 (23%)	High risk n=1570 (77%)	Low risk n=544 (27%)	High risk n=1483 (73%)	Low risk n=545 (27%)	High risk n=1482 (73%)
	Sensitivity: 98.3% NPV: 99.1% MACE: 4 (0.9%)	MACE: 232 (15%)	Sensitivity: 97.9% NPV: 99.1% MACE: 5 (0.9%)	MACE: 231 (16%)	Sensitivity: 97.9% NPV: 99.1% MACE: 5 (0.9%)	MACE: 231 (16%)
730-days	Low risk n=422 (22%)	High risk n=1480 (78%)	Low risk n=506 (26%)	High risk n=1396 (74%)	Low risk n=507 (27%)	High risk n=1395 (73%)
	Sensitivity: 98.8% NPV: 99.3% MACE: 3 (0.7%)	MACE: 239 (16%)	Sensitivity: 97.9% NPV: 99.0% MACE: 5 (1.0%)	MACE: 237 (17%)	Sensitivity: 97.9% NPV: 99.0% MACE: 5 (1.0%)	MACE: 237 (17%)

or known CAD, <3 risk factors, and no nitrate use) and even simpler third (nitrate use was omitted) rule best balanced safety and efficacy. Both identified 23% of patients at low risk with a sensitivity of 99.7% (95% CI, 98.3%–99.9%) and an NPV of 99.8% (95% CI, 98.7%–99.9%). All 3 rules missed one patient with unstable angina. Sensitivity of 98.9% (95% CI, 97.2%–99.7%) and NPV of 99.2% (95% CI, 98.0%–99.7%) of the second

Figure. External validation of the NOT rules and application with a well-validated 0/2-hour algorithm.
A, Validation of the performance of NOT rules for rule out of MACEs at 30 days, including index events. **B**, Performance of NOT rules for rule out of MACEs at 30 days, including index events after rule out of AMI with a well-validated 0/2-hour algorithm.[4] The second and third rules best balance safety and efficacy for the rule out of ACS or cardiovascular death. They safely classify nearly one fourth of patients at low risk who may not need objective cardiac testing. Groups and MACEs (ACS or cardiovascular death) are presented as numbers and percentages. NPV and sensitivity are presented as percentages. Risk factors include hypertension, dyslipidemia, current or previous smoking, diabetes mellitus, and family history of coronary artery disease. CAD indicates coronary artery disease; Hs-cTnI, Abbott Architect high-sensitivity cardiac troponin I; and MI, myocardial infarction. ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; MACE, major adverse cardiovascular event; NOT, No Objective Testing; and NPV, negative predictive value.

and third rule were also high for ACS or cardiovascular death at 365 days, as well as at 730 days (sensitivity, 98.9% [95% CI, 97.3%–99.7%]; and NPV, 99.2% [95% CI, 97.9%–99.7%]), respectively (Figure [A]). Similar findings were observed in the additional sensitivity analysis with the well-validated 0/2-hour algorithm (Figure [B]).[4] In addition, an excellent safety of all 3 rules was documented in the subgroup of patients presenting early to the emergency department (chest pain onset ≤3 hours), which made up 39.8% of all patients, and in patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2; sensitivity, 100.0% [95% CI, 94.6%–100.0%]; NPV, 100.0% [95% CI, not calculable]). On the other side, the rate of ACS or cardiovascular death was 18% at 30 days, 20% at 365 days, and 22% at 730 days in patients not meeting all criteria.

These findings extend and corroborate previous work aiming to better target objective anatomic or functional testing for CAD after the rule out of AMI using rapid hs-cTnI/T-based protocols.[1–3,5] In the pilot study deriving the NOT rules, after AMI rule out of 31.4% of patients was classified as low risk by the NOT rule. Sensitivity was 97.6%, and NPV was 99.6%. Similarly, in a single-center study of 282 patients, 27.7% of patients were classified as low risk by the NOT rule, and sensitivity was 100%.[3]

It is important to highlight that the NOT rules, as any other clinical decision rule, should be overruled whenever clinical assessment (eg, attributable to typical symptoms) still suggests a high likelihood for an ACS.

In conclusion, 4 simple clinical criteria (third NOT rule: aged <50 years, no previous AMI or known CAD, and <3 risk factors) identify a relevant proportion of patients (about 25%) at low risk of ACS or cardiovascular death up to 730 days. Accordingly, objective cardiac testing does not seem necessary in most of them.

APPENDIX

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Author contributions: The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the article, and decided to publish. Drs Ratmann, Boeddinghaus, 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 article. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the article. The article 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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