Performance of the ESC 0/1-h and 0/3-h Algorithm for the Rapid Identification of Myocardial Infarction Without ST-Elevation in Patients With Diabetes

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Diabetes Care 2020;43:460–467 | https://doi.org/10.2337/dc19-1327

OBJECTIVE

Patients with diabetes mellitus (DM) have elevated levels of high-sensitivity cardiac troponin (hs-cTn). We investigated the diagnostic performance of the European Society of Cardiology (ESC) algorithms to rule out or rule in acute myocardial infarction (AMI) without ST-elevation in patients with DM.

RESEARCH DESIGN AND METHODS

We prospectively enrolled 3,681 patients with suspected AMI and stratified those by the presence of DM. The ESC 0/1-h and 0/3-h algorithms were used to calculate negative and positive predictive values (NPV, PPV). In addition, alternative cutoffs were calculated and externally validated in 2,895 patients.

RESULTS

In total, 563 patients (15.3%) had DM, and 137 (24.3%) of these had AMI. When the ESC 0/1-h algorithm was used, the NPV was comparable in patients with and without DM (absolute difference [AD] −1.50 [95% CI −5.95, 2.96]). In contrast, the ESC 0/3-h algorithm resulted in a significantly lower NPV in patients with DM (AD −2.27 [95% CI −4.47, −0.07]). The diagnostic performance for rule-in of AMI (PPV) was comparable in both groups: 0/1-h (AD 6.59 [95% CI −19.53, 6.35]) and 0/3-h (AD 1.03 [95% CI −7.63, 9.7]). Alternative cutoffs increased the PPV in both algorithms significantly, while improvements in NPV were only subtle.

CONCLUSIONS

Application of the ESC 0/1-h algorithm revealed comparable safety to rule out AMI comparing patients with and without DM, while this was not observed with the ESC 0/3-h algorithm. Although alternative cutoffs might be helpful, patients with DM remain a high-risk population in whom identification of AMI is challenging and who require careful clinical evaluation.

The timely stratification of patients with symptoms suggestive of acute myocardial infarction (AMI) is crucial for providing fast, evidence-based treatment (1,2). During recent years, high-sensitivity cardiac troponin (hs-cTn) T and I have been implemented in different diagnostic algorithms and have facilitated the rapid triage of patients with suspected AMI (2–7). However, these assays are able to detect very modest elevations of troponins, which might be present in chronic myocardial injury. As a consequence,

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Received 5 July 2019 and accepted 9 November 2019

Clinical trial reg. nos. NCT02355457, NCT03227159, and NCT00470587, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1327/-/DC1.

the fast triage of patients with suspected AMI could be impaired in patients with chronically elevated levels of troponin (8–10). For instance, a previous study showed a significant correlation of age with levels of hs-cTn and suggested age-adjusted cutoffs to optimize the triage of elderly patients with suspected AMI without ST-elevation (10).

Previous studies have identified patients with diabetes mellitus (DM) to have significantly higher levels of troponins compared with their counterparts without DM (11–14). Importantly, patients with DM represent a growing population with an increased risk for cardiovascular events, including AMI and death (15,16). However, whether a concomitant diagnosis of DM impairs the rapid triage of patients with symptoms suggestive of AMI is unknown.

We therefore addressed this clinical need and studied the influence of DM on the diagnostic performance of the European Society of Cardiology (ESC) 0/1-h and 0/3-h algorithms using hs-cTnI in three large cohorts of prospectively enrolled patients presenting to the emergency department with symptoms suggestive of AMI without ST-elevation.

RESEARCH DESIGN AND METHODS

Study Design and Population

We combined two large prospectively enrolled cohorts of patients presenting to the emergency department with symptoms suggestive of AMI without ST-elevation: the Biomarkers in Acute Cardiac Care (BACC) (3–7,17), registered at ClinicalTrials.gov under NCT02355457, and the stenoCardia study (18), registered at ClinicalTrials.gov under NCT03227159. Both cohorts have been described previously, and a more detailed summary is provided in the Supplementary Data. For this analysis, we excluded patients with ST-elevation myocardial infarction, non–ST-elevation myocardial infarction other than type 1 or 2, patients without a known status for DM, and patients with missing serial hs-cTnI measurements. Patients were stratified according to a concomitant diagnosis of DM, which was defined as regularly taking any antidiabetic drug.

Clinical Assessment

Patients included in both studies received management in accordance with current guidelines including measurements of troponin at admission and after 3 h, recordings of an electrocardiogram (ECG) at admission, as well as laboratory parameters, imaging testing, and coronary angiography, as required. In clinical routine, conventional cTn assays (Roche Troponin T [Roche Diagnostics, Basel, Switzerland], or the Siemens Dimension RxL Troponin I [Siemens Healthcare, Erlangen, Germany]) were used for patients in the stenoCardia study and an hs-cTnT (Elecsys; Roche Diagnostics) for patients in the BACC study. The clinical management of patients was at the discretion of the physician in charge.

Troponin Measurements

For scientific purposes and in addition to the measurements of cTn in clinical routine, we measured hs-cTnI (ARCHITECT i1000SR; Abbott Diagnostics) at admission and 1 h (only available in BACC) and 3 h (both studies) thereafter. Results of this assay were not reported to the clinician in charge. This assay has a limit of detection of 1.9 (range, 0–50,000) ng/L, and at a concentration of 5.2 ng/L, the coefficient of variation is 10%. Coefficients of variation for intraassay and interassay testing were 4.26% and 6.29%, respectively (19).

Adjudication of the Final Diagnosis

The final diagnosis of AMI was adjudicated independently by two trained cardiologists and according to the third Universal Definition of Myocardial Infarction (20). With the exception of the hs-cTnI values measured for scientific purpose, all available clinical data were used for the adjudication of patients. This included results of the clinical examination and patient history, assessment of symptoms and severity, documented ECGs, laboratory and imaging results, and findings of coronary angiography, including the number and severity of coronary lesions and interventions, as well as potentially undertaken stress testing. Disagreements were resolved by consensus after discussion of the case with a third cardiologist.

Application of the ESC 0/1-h and 0/3-h Algorithms

Both ESC algorithms target at a rapid triage of patients with symptoms suggestive of AMI and are recommended by current guidelines (1). Both algorithms consider baseline values of troponin drawn at presentation of patients in combination with a certain change over time, which is assessed by a second troponin measurement. In brief, the ESC 0/3-h algorithm stratifies patients at presentation (0 h) according to values above or below the 99th percentile of the general population, which is 27 ng/L for the hs-cTnI assay used in the current study (21). After 3 h, the algorithm further stratifies patients based on a relative change. AMI is ruled in if there is a relative increase of $\geq$20% or $\geq$50% if the 0 h measurement is above or below the 99th percentile, respectively. If both values are below the 99th percentile, patients are ruled out of AMI. Other patients not stratified by these criteria need further workup. In contrast, the ESC 0/1-h algorithm considers hs-cTn assay-specific cutoff values that are far below the 99th percentile to rule out AMI and higher values to rule in AMI at presentation (0 h). The second troponin value is retrieved after 1 h. Now, assay-specific absolute (rather than relative) changes are considered to further triage patients toward rule-in or rule-out of AMI. Again, patients who are not stratified by these criteria need further workup and should not be discharged upfront (1,2,4,22). The application of both algorithms is described in more detail in the Supplementary Data.

Investigated Performance Measures

All outcomes were investigated separately for the ESC 0/1-h and ESC 0/3-h algorithms. The main outcomes of interest were the safety of rule-out, the accuracy of rule-in, and the overall performance of the algorithms. As the primary safety end point, we investigated the negative predictive value (NPV) for the rule-out of AMI. As the primary efficacy end point, we investigated the positive predictive value (PPV) for the rule-in of AMI. To assure high safety and accuracy, we prespecified a target of 99% for the NPV and 75% for the PPV. Performance was defined by the proportion of all correctly adjudicated patients to either rule in or rule out AMI. Also, we report the sensitivity and specificity as secondary end points.

Derivation and Validation of Alternative Cutoffs

In addition to the established ESC algorithms, we aimed to derive optimized cutoff concentrations. Our aims for such optimized cutoffs were an increase of

the NPV >99% and an increase of the PPV >75%. In addition, the derived alternative cutoffs were validated externally in the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) study cohort. APACE enrolled patients with symptoms suggestive of AMI and shares several methodological similarities with BACC and stenoCardia. An extended description is added in the Supplementary Data.

Follow-up

The primary follow-up end point was the composite of all-cause mortality, incidental myocardial infarction, revascularization, or cardiac rehospitalization. Secondary end points included the individual components of the primary end point. Trained study staff monitored patients by mail and telephone and collected data according to a prespecified questionnaire. Further information was collected by contacting the patients' general practitioners to retrieve medical records. In cases without any follow-up information, the local register of death was contacted, and all cases of death were assessed. In general, we collected data on all-cause mortality, AMI, or percutaneous coronary intervention since discharge and rehospitalization for any cardiac reason.

Statistical Analysis

Continuous variables are shown as median (25th percentile, 75th percentile), were compared with the Mann-Whitney test, and 95% CIs for the differences were calculated by bootstrapping with 4,000 replications. Binary variables are shown as absolute numbers and percentages, and *P* values and 95% CIs for the differences were produced with the χ^2 test. The assay-specific ESC 0/1-h and 0/3-h algorithms were applied with hs-cTnI, and the diagnostic performance parameters, which are the NPV and sensitivity for rule-out as well as the PPV and the specificity for rule-in, were calculated. These parameters were compared for patients with and without DM with help of the χ^2 test by calculating *P* values and 95% CIs for the differences. Survival curves with 95% CIs were produced using the Kaplan-Meier method, and the log-rank test was used to test for survival curve differences. Optimized cutoffs for the ESC 0/1-h and ESC 0/3-h algorithms were considered, and the corresponding diagnostic performance parameters and their 95% CIs were computed. Comparison

Table 1—Baseline characteristics for patients with and without AMI without ST-elevation by DM

	All (N = 3,681)	DM/non-AMI (n = 426)	DM/AMI (n = 137)	DM: AD (95% CI) AMI vs. non-AMI	Non-DM/non-AMI (n = 2,622)	Non-DM/AMI (n = 498)	Non-DM: AD (95% CI) AMI vs. non-AMI
Age (years)	64.0 (52.0, 74.0)	69.0 (60.0, 76.0)	70.0 (62.0, 75.3)	1 (−2, 3)	61.0 (49.0, 72.0)	68.0 (57.0, 76.0)	7 (4.5, 8)
Male	2,364 (64.2)	288 (67.6)	103 (75.2)	7.6 (−1.4, 16.5)	1,629 (62.1)	344 (69.5)	7.4 (2.8, 12)
Hypertension	2,587 (70.4)	395 (92.7)	129 (94.9)	2.1 (−2.8, 7.1)	1,680 (64.2)	383 (77.4)	13.2 (8.9, 17.4)
Hyperlipoproteinemia	1,924 (52.3)	291 (68.3)	101 (73.7)	5.4 (−3.7, 14.5)	1,247 (47.5)	285 (57.6)	10.03 (5.2, 14.9)
History of CAD	1,282 (35.2)	242 (58.0)	89 (66.9)	8.9 (−0.9, 18.7)	779 (30.0)	172 (34.9)	4.92 (0.2, 9.6)
AMI	696 (19.1)	142 (33.9)	51 (37.8)	3.9 (−6, 13.7)	405 (15.6)	98 (19.9)	4.34 (0.4, 8.3)
Stroke	246 (6.7)	46 (10.8)	19 (13.9)	3.1 (−3.9, 10)	152 (5.8)	29 (5.8)	0.1 (−2.3, 2.4)
Former smoker	994 (27.3)	148 (35.1)	51 (39.5)	4.5 (−5.6, 14.6)	663 (25.5)	132 (26.8)	1.2 (−3.2, 5.6)
Current smoker	827 (22.6)	64 (15.1)	27 (20.3)	5.2 (−2.9, 13.4)	592 (22.7)	144 (29.1)	6.41 (2, 10.8)
Presentation <3 h	1,151 (32.3)	119 (29.0)	33 (25.2)	−3.8 (−12.9, 5.4)	837 (33.0)	162 (33.4)	0.4 (−4.3, 5.1)
Presentation between 3 and 6 h	579 (16.3)	67 (16.3)	24 (18.3)	2.0 (−6, 10)	427 (16.8)	61 (12.6)	−4.3 (−7.7, −0.8)
Presenters >6 h	1,833 (51.4)	225 (54.7)	74 (56.5)	1.7 (−8.5, 12)	1,272 (50.2)	262 (54.0)	3.9 (−1.1, 8.8)
Coronary angiography	1,188 (32.3)	142 (33.3)	114 (83.2)	49.9 (41.7, 58.1)	530 (20.2)	402 (81.2)	61.0 (57.1, 64.9)
Glucose (mg/dL)	108.5 (97.0, 128.0)	146.0 (117.0, 194.0)	189.0 (148.2, 251.3)	43 (30, 54)	105.0 (95.0, 118.0)	113.0 (101.0, 130.0)	8 (4, 9)
CKD (eGFR <60 mL/min)	787 (21.5)	140 (33.1)	64 (46.7)	13.6 (3.7, 23.6)	436 (16.7)	147 (29.8)	13.2 (8.8, 17.7)
hs-cTnI 0 h (ng/L)	6.3 (3.0, 20.1)	7.5 (4.3, 16.6)	138.5 (26.1, 956.0)	131 (71.1, 213.5)	4.6 (2.4, 9.9)	203.0 (33.4, 1,210.3)	198.4 (134.1, 272.5)
hs-cTnI 1 h (ng/L)	6.0 (2.6, 19.6)	7.6 (3.5, 17.0)	210.0 (25.0, 897.0)	202.3 (44.5, 403.7)	4.2 (2.2, 8.9)	149.3 (38.8, 820.3)	145.1 (109.4, 229)
hs-cTnI 3 h (ng/L)	7.1 (3.3, 27.3)	8.2 (4.3, 17.2)	431.6 (94.9, 1,852.5)	423.35 (267.5, 617.2)	5.2 (2.7, 11.1)	700.4 (150.8, 2,498.3)	695.2 (492, 841.4)

Continuous data are presented as the median (interquartile range) and categorical data as *n* (%). Baseline characteristics of the complete study population of the derivation cohort stratified by the diagnosis of DM and AMI without ST-elevation on the ECG. The AD within the provided characteristics is compared between patients with and without AMI stratified by the diagnosis of DM. CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

of conventional and optimized cutoffs was performed using the generalized score statistic proposed by Kosinski (23) for NPV and PPV and the McNemar test for sensitivity and specificity. In addition, best alternative values were validated in an external cohort using similar statistical approaches. All statistical analyses were performed using R version 3.5.2 software (R Foundation for Statistical Computing) (24).

RESULTS

Patient Characteristics

In total, 3,681 of 4,125 patients enrolled in the BACC and stenoCardia study cohorts fulfilled our inclusion criteria; of those, 563 (15.29%) had DM. Baseline characteristics are provided in Table 1. Compared with patients without DM, those with DM were older, and cardiovascular risk factors and comorbidities were more prevalent, including hypertension, hyperlipidemia, known coronary artery disease, and chronic renal disease. Likewise, the proportion of patients with DM receiving antiplatelet therapy or antihypertensives was higher compared with patients without DM. The prevalence of AMI was significantly higher among patients with DM (24.3% [137 of 563]) compared with those without (15.9% [495 of 3,118], $P < 0.001$). A comparison of both patient cohorts showed the prevalence of AMI was very similar (17.6% and 16.8%), although we observed a difference with respect to the prevalence of DM (13.3% vs. 18.2%). Also, the rates of hypertension, hyperlipoproteinemia, a history of AMI or smoking, and the use of coronary angiography were higher in the stenoCardia cohort as well. A detailed comparison is supplied in the Supplementary Results.

Baseline Troponin Concentration

In patients without AMI, those with DM had significantly higher hs-cTnI levels compared with patients without DM at baseline (absolute difference [AD] 2.9 ng/L [95% CI 2.2, 3.9], $P < 0.001$), after 1 h (AD 3.5 ng/L [95% CI 2.3, 4.8], $P < 0.001$), and after 3 h (3 ng/L [95% CI 2.3, 4], $P < 0.001$). These differences were not observed in patients with AMI at baseline (AD −64.5 ng/L [95% CI −165.6, 48.1], $P = 0.27$), at 1 h (60.7 ng/L [95% CI −126.9, 274.6], $P = 0.56$), or at 3 h (−268.85 ng/L [95% CI −515.7, −28.6], $P = 0.072$). Absolute values are provided in Table 1.

ESC 0/1-h Algorithm

When the ESC 0/1-h algorithm is used, patients presenting to the emergency department with symptoms suggestive of AMI may be stratified rapidly within 1 h based on the likelihood of having AMI, which is derived by two serial measurements of hs-cTn. The hs-cTnI measurements at baseline and after 1 h were available for 1,923 patients of the BACC study cohort (Supplementary Table 1). When this approach was used, the safety to rule out, as quantified by the NPV, was comparable in patients with and without DM (Table 2). The proportion of patients with a rule-out of AMI was higher for patients without DM compared with patients with DM. Specificity for rule-in of AMI for patients with DM was significantly lower, with a comparable PPV (Table 2). Also, in a higher number of patients, AMI was ruled in. In summary, the ESC 0/1-h algorithm triaged 130 of 251 patients (51.8%) with DM toward rule-in or rule-out of AMI, which was lower compared with patients without DM (1,060 of 1,669 [63.5%]). Also, both targets regarding NPV and PPV were not met in patients with DM when the ESC 0/1-h algorithm was used.

ESC 0/3-h Algorithm

The ESC 0/3-h algorithm is recommended by current guidelines as an alternative diagnostic strategy. The hs-cTnI measurements at baseline and after 3 h were available for 3,425 patients of both cohorts. Sensitivity was comparable between patients with and without DM, whereas the NPV was significantly reduced in patients with DM (Table 2). Additionally, the proportion of patients ruled out was larger in patients without DM compared with patients with DM. Specificity for rule-in was significantly decreased in patients with DM, while the PPV was similar (Tables 2 and 3). Overall, in more patients with DM, AMI was ruled in compared with patients without DM. In line, also upon application of the ESC 0/3-h algorithm, the proportion of patients triaged toward rule-in or rule-out of AMI was higher in those without DM (497 of

Table 2—Performance of the ESC 0/1-h and ESC 0/3-h algorithms in patients with and without DM

	Patients without DM (n = 1,669)	Patients with DM (n = 251)	AD	P value
ESC 0/1-h algorithm				
Sensitivity for rule-out	99.3 (97.4, 99.9)	98.4 (91.3, 100.0)	−0.9 (−5.1, 3.3)	1.00
NPV for rule-out	99.7 (99.0, 100.0)	98.2 (90.4, 100.0)	−1.5 (−6.0 3.0)	0.54
Proportion of patients for rule-out	698 (41.8)	56 (22.3)		
Specificity for rule-in	91.5 (89.9, 92.9)	84.7 (78.7, 89.5)	−6.9 (−12.5, −1.2)	0.0035
PPV for rule-in	67.4 (62.3, 72.2)	60.8 (48.8, 72.0)	−6.6 (−19.5, 6.4)	0.34
Proportion of patients for rule-in	362 (21.7)	74 (29.5)		
ESC 0/3-h algorithm	(n = 2,910)	(n = 513)		
Sensitivity for rule-out	93.8 (91.2, 95.9)	89.8 (82.9, 94.6)	−4.0 (−10.4, 2.4)	0.19
NPV for rule-out	98.7 (98.2, 99.1)	96.4 (93.9, 98.2)	−2.27 (−4.47, −0.07)	0.0040
Proportion of patients for rule-out	2,190 (75.3)	338 (65.9)		
Specificity for rule-in	90.2 (89.0, 91.4)	85.8 (82.0, 89.1)	−4.4 (−8.2, 0.6)	0.01
PPV for rule-in	63.7 (60.0, 67.4)	64.8 (56.8, 72.2)	1.03 (−7.63, 9.7)	0.88
Proportion of patients for rule-in	662 (22.7)	159 (31.0)		

Data are presented as the median (interquartile range) or as n (%). The performance of both ESC algorithms to stratify patients with symptoms suggestive of acute AMI who present without ST-elevation on the ECG for either rule-in or rule-out of AMI. All patients were stratified by presence of DM at enrollment, and calculations were performed for both groups independently.

Table 3—Summary of findings

1. Patients with DM who present with symptoms suggestive of AMI are a high-risk patient population characterized by an increased cardiovascular risk profile and a high incidence of AMI at presentation. However, even in the absence of AMI elevated hs-cTn troponin concentrations are commonly observed in patients with DM, accompanied by an associated worse clinical outcome.
2. Application of the ESC 0/1-h algorithm for the identification of AMI revealed comparable and of the 0/3-h algorithm reduced safety to rule-out AMI in patients with DM, while the rule-in of AMI was similar in both algorithms.
3. Using alternative cutoff values for patients with DM translated into subtle improvements of the performance of both algorithms.
4. Altogether, triaging patients with DM with suspected AMI is challenging, wherefore we recommend a careful evaluation of clinical signs and symptoms and routine use of diagnostic instruments in addition to troponin-based diagnostic algorithms (e.g., imaging modalities) must be considered in this high-risk patient population.

513 [96.9%] vs. 2,852 of 2,910 [98.0%]), and the targets for NPV and PPV were not met.

Follow-up Events

Classification of patients according to the ESC 0/1-h algorithm was associated with significant differences in patients with and without DM regarding all-cause mortality (Fig. 1*A* and *B*). With respect to the primary composite end point, the ESC 0/1-h algorithm did stratify patients without DM very well, although the level of significance was not reached in patients with DM (Fig. 1*C* and *D*). In summary, patients without DM and triaged toward rule-out had the best prognosis, whereas patients with DM triaged toward AMI or the "observe" zone had the overall worst prognosis. Results regarding all other investigated end points, including cardiovascular mortality, incident AMI, myocardial revascularization, and rehospitalization are provided in the Supplementary Results.

Upon stratification by the ESC 0/3-h algorithm, we found similar results regarding the investigated follow-up end points. These findings are provided in the Supplementary Data as well (Supplementary Figs. 7–12).

Derivation and Validation of Alternative Cutoffs for the ESC 0/1-h Algorithm

The best optimized cutoffs for rule-out using the ESC 0/1-h algorithm in patients with DM were <4 ng/L at presentation or <6 ng/L at baseline, with an absolute change within 1 h of <2 ng/L. Using these cutoffs, we achieved an NPV of 98.5% (sensitivity 98.4 [95% CI 91.3, 100.0]), which was significantly higher compared with the original algorithm (AD 0.25 [95% CI 0.09, 0.41], $P = 0.0026$) and increased the proportion of patients with DM and a rule-out of AMI to 25.9% (Fig. 2). Optimized cutoffs for rule-in had to be substantially higher, with a baseline value of 90 ng/L or an absolute change of 10 ng/L to achieve a PPV of 75.5% (Fig. 2), which reached the level of significance compared with the original algorithm (AD 14.66 [95% CI 5.97, 23.35], $P < 0.001$). The proportion of patients ruled in was 21.1% and, hence, lower compared with the original algorithm. Additionally, these alternative cutoffs were validated in an external cohort of 2,895 patients (518 [17.9%] with DM), with similar results for rule-out (NPV 98.3 [95% CI 95.6, 99.3], sensitivity 96.9 [95% CI 92.2, 99.1]) and rule-in of AMI (PPV 85.6 [95% CI 78.4, 90.7], specificity 95.9 [95% CI 93.4, 97.6]) (Fig. 2). The proportion of patients with a rule-out of AMI was increased from 37.6 to 44.4% in the validation cohort.

Derivation and Validation of Alternative Cutoffs for the ESC 0/3-h Algorithm

By using 5 ng/L as a cutoff and a Δ20%, the targeted NPV was achieved (NPV 99.0 [95% CI 94.6, 100.0], AD 2.55 [95% CI -0.91, 6.01], $P = 0.15$; sensitivity 99.2 [95% CI 95.4, 100.0]), and in 19.5% of patients, AMI was ruled out after 3 h. As the ESC 0/3-h algorithm uses the same cutoffs for rule-out and -in, optimization of rule-out came hand-in-hand with a severe reduction in the accuracy of rule-in (PPV 31.0% [95% CI 26.3, 36.0], specificity 35.7% [95% CI 31.0, 40.6]). Therefore, to improve rule-in and reach the targeted PPV of 75%, we tested individual cutoffs for optimization of rule-in. Hence, by increasing the baseline cutoff up to 50 ng/L with Δ20%, we also achieved a significant increase up to the targeted PPV (AD 11.03 [95% CI 5.91, 16.14], $P < 0.001$) (Fig. 2). These findings were externally validated in 2,600 patients (455 [17.5%] with DM), with similar findings for rule-out (NPV 99.0 [95% CI 94.6, 100.0], sensitivity 99.1 [95% CI 95.0, 100]) and rule-in (PPV 86.0 [95% CI 73.3, 94.2], specificity 98.0 [95% CI 96.0, 99.2]) of AMI. The proportion of patients with a rule-out of AMI was decreased from 46.2 to 22.2% in the validation cohort.

CONCLUSIONS

In this analysis based on three large prospectively enrolled, multicenter diagnostic cohorts of patients with suspected AMI without ST-elevation, we report that the application of the ESC 0/1-h and 0/3-h algorithms in patients with DM overall provides safety and accuracy to rule out and rule in AMI. Additionally, we derived and validated optimized cutoffs for both algorithms, which might improve the diagnostic accuracy. Our study revealed the following major findings:

In line with previous reports, we were able to confirm increased concentrations of hs-cTnI comparing patients with and without DM in those without AMI at presentation. While there are different hypotheses why patients with DM have elevated troponin levels, the reasons might be multifactorial. On one hand, several factors that share an association with elevated troponin, older age, reduced renal function, metabolic syndrome, or microvascular dysfunction, among others, are more prevalent in patients with DM (8–10,25,26). In this regard, patients with DM in our study were older and renal dysfunction was more prevalent as well. On the other hand, elevated levels of troponin have been noted even in patients with a very short duration of DM or in those without evident macrovascular dysfunction, suggesting a direct pathophysiological mechanism that occurs already before the clinical manifestation of diabetic sequela (27–29). Also, the association of chronic hyperglycemia and elevated troponin holds after adjusting for patient characteristics and comorbidities (14). Hence, apart from classical cardiovascular risk factors, other factors might play an important role as well; that is, a previous

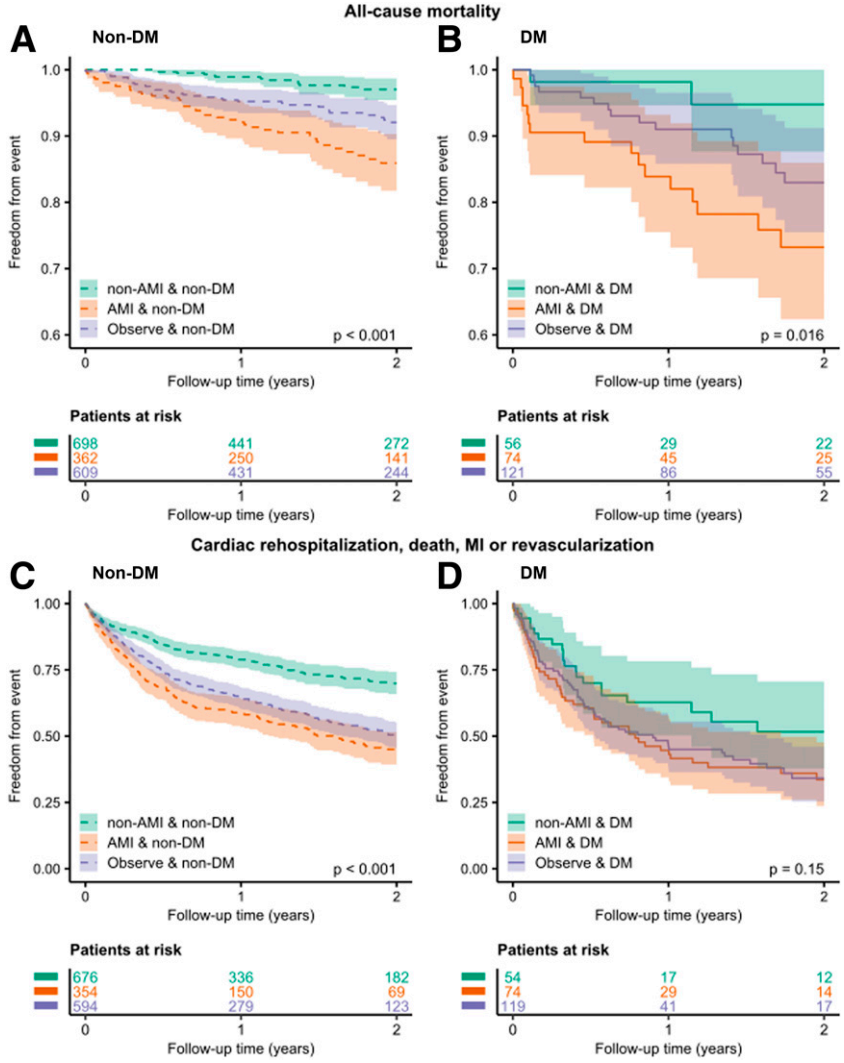

Figure 1—Kaplan-Meier-curves provide crude event rates after stratification by the ESC 0/1-h algorithm for all-cause mortality for patients without (*A*) and with (*B*) DM. Also, we provide event rates for the composite end point of all-cause mortality, percutaneous coronary intervention, incidental myocardial infarction (MI), or cardiac rehospitalization for patients without (*C*) and with (*D*) DM after stratification by the ESC 0/1-h algorithm. Comparison between groups was done by the log-rank test.

study revealed an association of arterial stiffness measured by pulse wave velocity with troponin elevation in patients with DM without established macrovascular disease (27), and cardiac dysfunction was already detected in asymptomatic patients with DM as well (29).

Irrespective of these subtle elevations in hs-cTnI, the strong rise in hs-cTnI upon ongoing myocardial ischemia (as also evident in the current study) still facilitates its use in the diagnosis of AMI. Nevertheless, the current study also reveals some challenges upon application in patients with DM that should be considered. In this regard, the ESC 0/1-h algorithm revealed very high safety for the rule-out of AMI without ST-elevation in patients with DM by achieving a comparable NPV compared with patients without DM. However, a smaller proportion of patients with DM was triaged toward rule-out of AMI. Even though we observed a small improvement of rule-out upon the application of our optimized cutoffs, our NPV target of 99.0% was not achieved in the derivation or the validation cohort, and the absolute improvement in NPV was very small. Still, our alternative cutoffs led to an increased proportion of patients with safe rule-out of AMI. In contrast, the safety of the conventional ESC 0/3-h algorithm was significantly reduced in patients with DM, and by application of the alternative cutoffs, an NPV of 99% was feasible.

We revealed comparable PPVs for rule-in of AMI comparing patients with and without DM in both algorithms. However, our predefined target of a PPV of 75.0% was solely achieved by applying substantially increased hs-cTnI cutoffs. In this regard, the need for this dramatic increase could only in part be explained by the higher baseline values of hs-cTnI. However, on the basis of the extended cardiovascular risk profile that is associated with DM, these patients may be prone to other ways of myocardial injury, mimicking AMI, as well. Hence, the differentiation of patients with AMI from those with other reasons of (acute) myocardial injury (and therefore elevated and/or dynamic changes in troponin) may only be possible upon the application of such high cutoffs.

The overall performance of the ESC 0/1-h algorithm in patients with DM was highly reduced, ending up with a large proportion of patients with DM triaged toward "observe." Undoubtedly, this corroborates the diagnostic complexity of patients with DM as well as their need for further diagnostic assessment with respect to potential differential diagnoses. Findings were similar for the ESC 0/3-h algorithm; however, the application of alternative cutoffs separately for rule-in and rule-out of AMI was necessary to gain a substantial improvement.

Taken together, clinicians should merit the observed constraints upon application of the algorithms in patients with DM. In contrast to the ESC 0/3-h algorithm, alternative cutoffs only partly increased the diagnostic performance of the ESC 0/1-h algorithm. Considering the high pretest probability of AMI in patients with DM and their generally increased risk for poor outcome, the triage of patients with DM with suspected AMI requires careful evaluation, and additional instruments for AMI identification (including clinical presentation, ECG, and other imaging modalities) should be taken into account.

With respect to clinical end points during follow-up, both algorithms did stratify patients very well. We observed the highest risk in patients with DM triaged toward rule-in of AMI. Furthermore, in patients classified as "observe" by the algorithm, the diagnosis of DM was associated with poorer outcome. Even though most of these patients have not been adjudicated to have AMI, the elevated troponin levels that led to the triage toward the "observe"

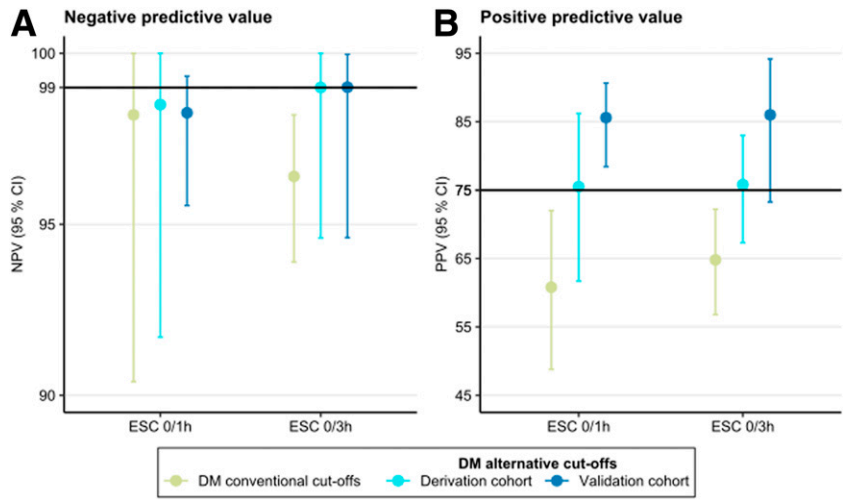

Figure 2—Comparison of the diagnostic performance of the ESC 0/1-h and ESC 0/3-h algorithms for the diagnosis of AMI without ST-elevation in patients with DM using conventional cutoffs and the proposed alternative cutoffs in the derivation and validation cohorts, respectively. We targeted an NPV for the rule-out of AMI of 99% (*A*) and PPV for the rule-in of AMI of 75% (*B*).

group per se were associated with very poor outcome previously (12,13), which is in line with the high event rate during follow-up in the current study. In fact, this underpins the utmost importance for further diagnostic and, at the best, therapeutic actions in this heterogenous group of high-risk patients.

Strengths and Limitations

Our findings regarding the ESC 0/1-h algorithm are derived from the BACC study cohort only, however, still including 1,922 patients. In addition, our proposed alternative cutoffs for both ESC algorithms have been validated in an external cohort, strengthening our findings. Even though we cannot totally exclude a small number of misclassifications with respect to the final classification of AMI, the final adjudication was performed centrally by two independent cardiology specialists in all study cohorts. As we only evaluated hs-cTnI, our findings are specific for the investigated assay, and we cannot guarantee that our findings will be reflected by other hs-cTn assays to the same extent. As we stratified all patients by the fact of taking any antidiabetic medication, we potentially misclassified some patients with unknown DM and also those with known DM but without treatment. Also, accounting for the disease duration was not possible.

Conclusion

Application of the ESC 0/1-h algorithm revealed comparable safety to rule out AMI comparing patients with and without DM. In contrast, safety was significantly reduced in patients with DM upon application of the ESC 0/3-h algorithm. As the application of alternative cutoffs only partly improved the diagnostic accuracy, additional diagnostic assessments are of utmost importance in this high-risk population. This highlights the need of special care when triaging patients with DM and suspected AMI.

Funding. The BACC study was supported by German Centre for Cardiovascular Research (DZHK). The stenoCardia study was supported by the University Medical Center of the Johannes Gutenberg University of Mainz. J.B. received research grants from the University of Basel, the University Hospital of Basel and the Division of Internal Medicine, the Swiss Academy of Medical Sciences, and the Gottfried and Julia Bangerter-Rhyner-Foundation. J.T.N. was supported by a grant from the German Heart Foundation/German Foundation of Heart Research and the Else Kröner Fresenius Stiftung. R.T. received research support from the Swiss National Science Foundation (P300PB_167803), the Swiss Heart Foundation, the Swiss Society of Cardiology, the University Hospital of Basel, the University of Basel, and the Cardiovascular Research Foundation Basel. C.M. has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, Kommission für Technologie und Innovation (KTI), the Stiftung für kardiovaskuläre Forschung Basel, and the University of Basel.

Duality of Interest. The BACC study was supported by an unrestricted grant from Abbott Diagnostics, Prevencio, and Singulex. The stenoCardio study was supported by an unrestricted grant from BRAHMS Aktiengesellschaft. P.M.H. reports travel grants from Bayer, Daiichi Sankyo, Boehringer Ingelheim, and Menarini and speaker honoraria from Beckman Coulter. J.B. received speaker honoraria/consulting honoraria from Siemens, Roche Diagnostics, Ortho Clinical Diagnostics, and Ortho Corporation, outside of the submitted work. J.T.N. has received honoraria from Abbott Diagnostics and Siemens. T.N. received speaker honoraria/consulting honoraria from Beckman Coulter, outside of the submitted work. R.T. received speaker honoraria/consulting honoraria from Abbott, Amgen, Brahms, Roche, Singulex, and Siemens, outside of the submitted work. S.B. has received honoraria from Abbott Diagnostics, Siemens, Thermo Fisher, and Roche Diagnostics and is a consultant for Thermo Fisher. C.M. has received research support from Abbott, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Ortho Clinical Diagnostics, Roche, Siemens, Singulex, Sphingotec, and the University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Amgen, AstraZeneca, Biomerieux, Boehringer Ingelheim, Bristol-Myers Squibb, Brahms, Cardiorentis, Novartis, Roche, Sanofi, Siemens, and Singulex, outside of the submitted work. D.W. reports personal fees from Bayer, Boehringer Ingelheim, Berlin Chemie, AstraZeneca, Biotronik, and Novartis. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.M.H., J.T.N., and N.A.S. substantially contributed to the conception and design of the work, the acquisition, analysis, and interpretation of data, drafted the manuscript, and revised the manuscript critically for important intellectual content. J.B. substantially contributed to the acquisition, analysis, and interpretation of data for the work and revised the manuscript critically for important intellectual content. T.S.H., J.L., T.K., and T.Z. substantially contributed to the acquisition and interpretation of data and revised the manuscript critically for important intellectual content. A.G. substantially contributed to the analysis and interpretation of data and revised the manuscript critically for important intellectual content. T.N. and R.T. substantially contributed to the acquisition and interpretation of data for the work and revised the manuscript critically for important intellectual content. S.B., C.M., and D.W. substantially contributed to the conception and design of the work, the acquisition, analysis and interpretation of data, and revised the manuscript critically for important intellectual content. J.T.N. and D.W. are the guarantors of this work and, as such, 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.

Prior Presentation. Parts of this study were presented as an oral presentation at the European Society of Cardiology Congress, Paris, France, 31 August–4 September 2019.

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