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IMPORTANCE The Global Registry of Acute Coronary Events (GRACE) risk score, a guideline-recommended risk stratification tool for patients presenting with acute coronary syndromes (ACS), does not consider the extent of myocardial injury.

OBJECTIVE To assess the incremental predictive value of a modified GRACE score incorporating high-sensitivity cardiac troponin (hs-cTn) T at presentation, a surrogate of the extent of myocardial injury.

DESIGN, SETTING, AND PARTICIPANTS This retrospectively designed longitudinal cohort study examined 3 independent cohorts of 9803 patients with ACS enrolled from September 2009 to December 2017; 2 ACS derivation cohorts (Heidelberg ACS cohort and Newcastle STEMI cohort) and an ACS validation cohort (SPUM-ACS study). The Heidelberg ACS cohort included 2535 and the SPUM-ACS study 4288 consecutive patients presenting with a working diagnosis of ACS. The Newcastle STEMI cohort included 2980 consecutive patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Data were analyzed from March to June 2023.

EXPOSURES In-hospital, 30-day, and 1-year mortality risk estimates derived from an updated risk score that incorporates continuous hs-cTn T at presentation (modified GRACE).

MAIN OUTCOMES AND MEASURES The predictive value of continuous hs-cTn T and modified GRACE risk score compared with the original GRACE risk score. Study end points were all-cause mortality during hospitalization and at 30 days and 1 year after the index event.

RESULTS Of 9450 included patients, 7313 (77.4%) were male, and the mean (SD) age at presentation was 64.2 (12.6) years. Using continuous rather than binary hs-cTn T conferred improved discrimination and reclassification compared with the original GRACE score (in-hospital mortality: area under the receiver operating characteristic curve [AUC], 0.835 vs 0.741; continuous net reclassification improvement [NRI], 0.208; 30-day mortality: AUC, 0.828 vs 0.740; NRI, 0.312; 1-year mortality: AUC, 0.785 vs 0.778; NRI, 0.078) in the derivation cohort. These findings were confirmed in the validation cohort. In the pooled population of 9450 patients, modified GRACE risk score showed superior performance compared with the original GRACE risk score in terms of reclassification and discrimination for in-hospital mortality end point (AUC, 0.878 vs 0.780; NRI, 0.097), 30-day mortality end point (AUC, 0.858 vs 0.771; NRI, 0.08), and 1-year mortality end point (AUC, 0.813 vs 0.797; NRI, 0.056).

CONCLUSIONS AND RELEVANCE In this study, using continuous rather than binary hs-cTn T at presentation, a proxy of the extent of myocardial injury, in the GRACE risk score improved the mortality risk prediction in patients with ACS.

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Supplemental content

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Mortality after acute coronary syndromes (ACS) has declined substantially over the past 6 decades. Yet it remains high particularly in those presenting with extensive myocardial injury and thus at high risk of adverse outcomes.[1-4] Refined risk stratification to optimize decisions regarding timing of invasive treatment in non–ST-elevation (NSTE) ACS may further improve survival.[5] Additionally, improvement of postdischarge risk stratification of patients with ACS may further trigger clinical research to guide (1) short-term decisions on intensity and duration of post-percutaneous coronary intervention (PCI) antithrombotic treatment by balancing ischemic vs bleeding risk[5,6] and (2) long-term decisions on indications for novel therapies to address residual cardiovascular risk beyond the standard of care, such as low-dose anticoagulants and antiplatelets in very high-risk patients after ACS diagnosis.[5-8]

The Global Registry of Acute Coronary Events (GRACE) risk score is the most established, broadly validated, and therefore widely recommended risk stratification tool for patients presenting with ACS across international guidelines.[5-8] Informed by an array of clinical features available at the time of acute presentation, including the presence or absence of abnormal myocardial injury biomarkers, the GRACE score allows the prediction of adverse events following the index ACS.[9] In patients presenting without persistent ST-segment elevation (NSTE-ACS), short-term risk stratification with the GRACE score allows the identification of high-risk individuals who benefit from early invasive management beyond optimal pharmacological therapy.[5,7] In fact, the GRACE risk score remains foundational to international ACS guidelines to decide on timing of an interventional strategy and to estimate prognosis in patients with NSTE-ACS while allowing for proper risk assessment and adjustment of patients with ST-elevation myocardial infarction (STEMI).[6,10]

Cardiac troponin is the biomarker of choice for the evaluation of myocardial necrosis, and high-sensitivity cardiac troponin (hs-cTn) T or I assays are widely recommended for routine clinical use.[11-13] Yet neither hs-cTn T nor hs-cTn I assays were available at the time of GRACE score derivation and validation; thus, only the binary information of whether myocardial injury was present or not is currently considered.[14] Furthermore, the magnitude of cardiac troponin elevation after myocardial infarction reflects the extent of myocardial damage, with cTn T concentration as a continuous variable showing a direct association with mortality.[15] However, this is presently not part of the GRACE score, in which only the presence or absence but not the extent of myocardial necrosis is considered. As such, the GRACE score may miss important prognostic information conveyed by hs-cTn T concentration at presentation, which may be reflected in improved score performance and thus improved risk prediction both for early and long-term management of patients with ACS.

Key Points

Question Does a modified Global Registry of Acute Coronary Events (GRACE) risk score incorporating high-sensitivity cardiac troponin (hs-cTn) T at presentation as a continuous rather than a binary variable improve risk prediction in patients with acute coronary syndromes (ACS)?

Findings In this cohort study composed of 3 independent cohorts of 9803 patients with ACS, the incorporation of continuous hs-cTn T at presentation conferred improved discrimination and reclassification compared with the original GRACE score for the prediction of in-hospital, 30-day, and 1-year mortality.

Meaning In this study, using continuous rather than binary hs-cTn T at presentation substantially improved GRACE risk score performance for the prediction of short-term and long-term mortality across the whole spectrum of ACS.

Methods

Patient Population and Study Design

This is a retrospectively designed longitudinal cohort study examining 3 independent ACS cohorts. All cohorts included in this study complied with the Declaration of Helsinki. This study was exempted from approval and informed consent was waived by the institutional review board of the coordinating institution (Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Alexandra Hospital). **Figure 1** depicts the flowchart of the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

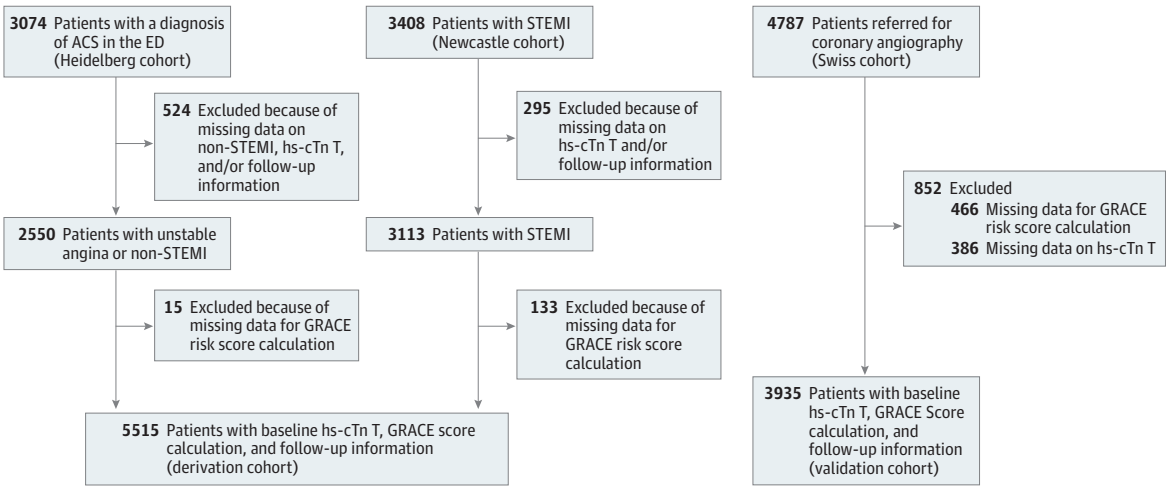
Derivation Cohort

Details on the derivation cohorts are provided in the eMethods in Supplement 1. Patients presenting to the emergency department of Heidelberg University Hospital, Heidelberg, Germany, with a working diagnosis of ACS were prospectively recruited from June 2009 to April 2014, as previously described.[16,17] Data from 3113 consecutive patients with STEMI treated with primary PCI admitted to the Freeman Hospital, Newcastle upon Tyne, UK, between June 2010 and December 2014 were collected prospectively, as previously described.[18] The research protocol did not interfere with the management of study patients. Local institutional ethics committees approved the studies, and all patients gave informed consent for the Heidelberg cohort. No informed consent was obtained for the Newcastle cohort since data were derived from a clinical audit. The 2 derivation cohorts were pooled in the analysis to include representative numbers from patients with STEMI and NSTE-ACS in a single derivation cohort because the GRACE score was originally developed and validated in mixed ACS populations, and the Heidelberg derivation cohort included only a small sample size of patients with STEMI (440 [17.4%]).[14]

External Validation Cohort

The external validation cohort was based on the SPUM-ACS study,[19] an investigator-initiated, multicenter prospective cohort study that enrolled a total of 4787 patients with ACS from December 2009 to December 2017 in Switzerland, as previously described.[20] Inclusion criteria can be found in the eMethods in Supplement 1. In the present study, 3935 patients with available GRACE score variables and continuous hs-cTn T concentrations were included. All participants gave writ-

Figure 1. Flowchart of the Study



The derivation cohort was composed of 2 cohorts: (1) patients presenting to the emergency department (ED) of Heidelberg University Hospital, Heidelberg, Germany, with a working diagnosis of acute coronary syndrome (ACS) from June 2009 to April 2014, as previously described,[16,17] and (2) consecutive patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention admitted to the Freeman Hospital, Newcastle upon Tyne, UK, between June 2010 and December 2014, as previously described.[18] The external validation cohort was based on the SPUM-ACS study,[19] an investigator-initiated, multicenter prospective cohort study that enrolled patients with ACS from December 2009 to December 2017 in Switzerland, as previously described.[20] GRACE indicates Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin.

ten informed consent, and the Ethical Committee of the Canton of Zurich approved the study.

Study End Points

The study end points were all-cause mortality at 30 days from the index event and at 1 year, which included both in-hospital and post-hospital discharge deaths. In-hospital all-cause mortality was used as a clinically relevant end point aligning with guideline recommendations for decisions on timing of invasive treatment.[5,10] The 1-year mortality end point was selected according to Fox et al (GRACE risk model version 2.0),[9] as recommended by the Coordinating Center for the Global Registry of Acute Coronary Events. The 30-day mortality end point was selected as an end point based on the event adjudication procedure and data availability of each cohort. Details on follow-up and outcome adjudication are provided in the eMethods in Supplement 1.

cTn Measurement

Serum samples were obtained from arterial blood collected from the radial or femoral sheath on admission to the catheterization laboratory (directly prior to the start of primary PCI) in the derivation STEMI cohort and at presentation in the derivation ACS cohort, whereas blood samples were drawn at the time of index coronary angiography in the validation cohort.[21] cTn T was quantified by using the Roche Elecsys hs-cTn T assay on the Cobas e601 module (Roche Diagnostics) in all 3 cohorts, with a lower limit of detection at 2.05 ng/L and coefficients of variation less than 10% at the 99th percentile (14 ng/L). In the validation cohort, cTn T was measured centrally in a core lab at the University Hospital Zurich.[20] Although the same assay was used in all cohorts included in this study, a variety of hs-cTn T assays are commercially available with different coefficients of variations. For this reason, fold increases in troponin concentrations relative to the upper normal limit were used to enhance generalizability of our results.

GRACE Score Calculation

We used 2 different formulas to calculate the GRACE risk score for patients presenting to the hospital with ACS. First, we used the Granger model estimates provided by the Coordinating Center for the Global Registry of Acute Coronary Events[22] and estimated the risk of in-hospital and 30-day mortality for each patient (original GRACE score).[23] Next, we used the GRACE version 2.0 model and calculated the risk of death within 1 year after the index event (original GRACE score).[9]

Albeit commonly referred to as the GRACE score, it is important to note that short-term vs 1-year mortality risk estimates derive from different regression models, depending on the end point analyzed and thus model used.[9,14] Indeed, while the GRACE score for short-term mortality risk is estimated by logistic regression (GRACE version 1.0),[14] the calculation of 1-year mortality risk estimates relies on Cox regression (GRACE version 2.0). Therefore, we followed the identical methodology used during GRACE score derivation and validation to provide data comparable with previously published evidence.

Then, we regressed ad hoc the predictors constituting the GRACE score on the odds of 30-day mortality (Granger multiple logistic regression model) and risk of 1-year mortality (GRACE version 2.0 multiple Cox regression model) and calculated new probabilities for the respective mortality end points based on updated coefficients of exposure variables (calibrated GRACE score). Calibrated GRACE scores were used

to control for statistical overoptimism due to recalculation of coefficients after fitting the multivariable model in this study's population.

Next, we repeated the above step but substituted dichotomous with continuous hs-cTn T and derived a new set of estimates. We applied these estimates and calculated the modified GRACE score for 30-day and 1-year mortality, now incorporating information on continuous hs-cTn T at presentation. Identical equations were used for both the ACS and STEMI cohorts in our study.

In a final step, we used established cutoff values[24] for probabilities of in-hospital and 30-day mortality to stratify the study population in low, intermediate, and high-risk categories separately for each version of the GRACE score (original, calibrated, and modified). The original GRACE score was calculated in 9803 of 10 450 patients from the pooled population of all study participants with a main diagnosis of ACS and available hs-cTn T concentration. Of these 9803 patients, the modified GRACE score was calculated in 9450 patients (96.4%) with complete data.

Statistical Analysis

Continuous variables are presented as mean and SDs or medians and IQRs. Nominal variables are shown as counts and percentages.

Depending on the end point studied, logistic and/or Cox regression models were used to assess the association of continuous hs-cTn T (fold hs-cTn T) at presentation or modified GRACE score with 30-day, in-hospital, and 1-year mortality independently of the original GRACE score. We further compared the predictive value of continuous hs-cTn T or the modified GRACE score with the original GRACE score by (1) assessing the difference in the area under the receiver operating characteristic curve (AUC; 30-day and in-hospital mortality)[25] or in the Harrell C indices (1-year mortality),[26] (2) evaluating the categorical (ie, event rate–based) net reclassification improvement (NRI) for all time points,[27] and (3) calculating the likelihood ratio (LR) test for logistic (30-day and in-hospital) or survival (1-year) models. LR tests are used in statistical modeling to compare the goodness-of-fit of 2, typically nested, models.[28] Under weak regularity assumptions, the LR test statistic is approximately χ^2 distributed with *df* equal to the difference of the dimensions of the unrestricted and restricted model. Hence, the higher the LR test statistic (χ^2 value), the more confident we are that the likelihoods of the tested models do differ and that the addition of a new biomarker significantly improves fit for the unrestricted/nonparsimonious model compared with the parsimonious/restricted model. AUCs and their corresponding 95% CIs were computed as suggested by DeLong et al.[25] 95% CI for NRIs were calculated using the standard normal distribution.[29] For calculating uncertainty of the LR test, we assumed that the test statistic is approximately distributed as X.[2]

We solidified our findings by repeating the main analyses in the external validation cohort composed of a mixed ACS population with or without persistent ST-elevation. Finally, we used Nelson-Aalen survival curves allowing for graphical evaluation of the modified GRACE score compared with the original GRACE score, showing the reclassification of patients with events or nonevents into true higher or lower risk categories for 30-day mortality. All tests were 2-tailed. Statistical analysis was performed with Stata version 17.1 (StataCorp). Statistical significance was deemed at $P < .05$.

Results

Patient Characteristics

Of 9450 included patients, 7313 (77.4%) were male, and the mean (SD) age at presentation was 64.2 (12.6) years. Baseline characteristics of patients included in both the pooled derivation cohort (n = 5515) and the validation cohort (n = 3935) are shown in **Table 1**. In the derivation cohort, 177 deaths (3.2%) and 362 deaths (6.6%) occurred at 30 days and 1 year, respectively. In the external validation cohort, 81 deaths (1.9%) occurred at 30 days after ACS and 177 (4.1%) at 1 year (Table 1).

Prediction of Mortality End Point for Original vs Modified GRACE Score

As shown in **Table 2**, continuous hs-cTn T at presentation remained an independent predictor of mortality at 30 days and at 1 year after adjustment for the original GRACE score. This association did not materially change after adjustment for the type of antiplatelet used in both the derivation (Heidelberg cohort) and validation cohort. Notably, continuous hs-cTn T provided additive prognostic value and reclassification (NRI, 0.312; 95% CI, 0.222-0.402; $P < .001$) compared with the GRACE score for the 30-day mortality end point in the derivation cohort (Table 2). In line, continuous hs-cTn T at presentation conferred incremental discriminative and reclassification value on top of the GRACE score for in-hospital mortality (NRI, 0.208; 95% CI, 0.165-0.251; $P < .001$) (Table 2). Furthermore, adding continuous hs-cTn T to the model improved the discriminative and reclassification (NRI, 0.078; 95% CI, 0.045-0.111; $P < .001$) value of the GRACE score for predicting the 1-year mortality end point (Table 2). These findings were similarly observed in the external validation cohort composed of a mixed ACS population (Table 2). In contrast, addition of peak troponin level did not improve its prognostic value compared with the GRACE score, which was consistently observed across all time points (eTable 1 in Supplement 1).

Integration of Continuous hs-cTn T in the GRACE Score

When comparing score performance of the modified GRACE score with the original GRACE score in each cohort separately, the modified GRACE score showed improved discrimination and correctly reclassified patients into risk categories for in-hospital, 30-day, and 1-year mortality end points both in the derivation and validation cohorts (**Table 3**). The modified GRACE score was more strongly associated with 1-year mortality than the original GRACE score in terms of both discrimination and reclassification in the derivation cohort compared with the validation cohort (Table 3).

Similarly, in the whole population, these results did not substantially change (Table 3). For in-hospital and 30-day mor-

Table 1. Baseline Clinical Characteristics of the Derivation and Validation Cohorts

Variable	Cohort, No. (%)	
	Derivation	Validation
Total, No.	5515	3935
Sex		
Female	1621 (29.4)	516 (13.1)
Male	3894 (70.6)	3419 (86.9)
STEMI	3420 (62.0)	2328 (58.3)
NSTE-ACS	2095 (38.0)	1960 (49.7)
Risk factors		
Current smoker	2105 (38.2)	1651 (61.5)
Hypertension	3354 (60.8)	2406 (61.1)
Diabetes	1010 (18.3)	743 (18.9)
Hypercholesterolemia	2693 (47.8)	2701 (68.6)
Medical history of CAD		
Previous MI	996 (18.1)	506 (12.8)
Previous PCI	1145 (20.8)	613 (15.6)
Previous CABG	361 (6.5)	168 (4.2)
Clinical characteristics at ACS presentation		
Age, mean (SD), y	64.8 (12.8)	63.5 (12.4)
Heart rate, median (IQR), beats per min	74 (23)	76 (20)
Systolic BP, median (IQR), mm Hg	139 (37)	128 (32)
Cardiac arrest	349 (6.3)	151 (3.5)
Killip class		
I-III	5243 (95.1)	3768 (95.7)
IV	272 (4.9)	520 (13.1)
Serum creatinine, median (IQR), mg/dL	0.92 (0.33)	0.87 (0.28)
hs-cTn T, median (IQR), ng/L	77 (323)	202 (607)
ST deviation	3845 (69.7)	3527 (87.3)
GRACE risk estimates, median (IQR)		
30-d GRACE score	3.44 (8.1)	2.37 (3.32)
30-d Modified GRACE score	0.95 (2.06)	0.83 (1.66)
1-y GRACE score	10.44 (19.99)	5.06 (6.94)
1-y Modified GRACE score	2.86 (5.5)	2.13 (4.06)
Study end points		
In-hospital mortality	145 (2.6)	55 (1.3)
30-d Mortality	177 (3.2)	81 (1.9)
1-y Mortality	362 (6.6)	177 (4.1)

Abbreviations: ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; hs-cTn, high-sensitivity cardiac troponin; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTE, non–ST-elevation; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.

tality end points, the modified GRACE score correctly reclassified patients to higher (9 of 200 [4.0%] and 4 of 258 [1.6%], respectively) and lower (1270 of 8850 [13.7%] and 885 of 8792 [9.6%]) risk groups compared with the original GRACE score. Accordingly, the modified GRACE showed improved goodness of fit compared with the original GRACE score for the prediction of both short-term (ie, in-hospital and 30-day) and 1-year mortality (Table 3). While hs-cTn T alone provided good discrimination for the prediction of 30-day mortality (AUC, 0.771; 95% CI, 0.751-0.790) and 1-year mortality (AUC, 0.797; 95% CI, 0.778-0.815), its predictive value was expectedly outperformed by the modified GRACE score, which yielded superior metrics (30-day mortality: AUC, 0.858; 95% CI, 0.835-0.880; 1-year mortality: AUC, 0.813; 95% CI, 0.795-0.831). In the whole population, among the 3473 patients with ACS classified as high risk for in-hospital death by the original GRACE score, the modified GRACE score could correctly discriminate patients who were at low to intermediate observed risk for 30-day mortality (2251; mortality incidence of 2.0% [45 deaths] compared with 14.5% [176 deaths] in the remaining 1222 patients) (**Figure 2**C). In contrast, among 3212 patient classified as being at intermediate risk by the original GRACE score, 2406 were reclassified to low risk according to the modified GRACE score with markedly lower 30-day mortality (12 deaths [0.5%]) (Figure 2B). The agreement between both scores in patients originally classified as being at low risk was relatively good as observed (Figure 2A). The modified GRACE score provided additive prognostic value compared with the original GRACE score for the prediction of 1-year mortality (18 of 539 [3.4%] correctly reclassified to higher risk and 167 of 8511 [2.0%] correctly reclassified to lower risk) (Table 3).

The modified GRACE score outperformed the calibrated GRACE score using updated coefficients derived from our study population for the in-hospital, 30-day, and 1-year mortality end points (Table 3; Figure 2D-F), further supporting our findings. In a landmark analysis, the modified GRACE retained its prognostic superiority compared with the original GRACE score beyond 1 year (NRI, 0.362; median [IQR] follow-up, 1172 [648-1255] days) (eTable 2 in Supplement 1). When comparing score performance of the modified GRACE score with the original and calibrated scores in patients with NSTE-ACS from the whole population, results did not substantially change for the in-hospital, 30-day, and 1-year mortality end points (eTable 3 in Supplement 1). Finally, in a sensitivity analysis including the Heidelberg and SPUM-ACS cohorts, the modified GRACE score conferred incremental discrimination and reclassification value compared with the original GRACE score for a composite ischemic end point (recurrent myocardial infarction, revascularization, and cardiac death) at 30 days (modified: AUC, 0.621; 95% CI, 0.578-0.665; original: AUC, 0.614; 95% CI, 0.570-0.658; $P = .03$; NRI, 0.226; 95% CI, 0.113-0.338; $P < .001$; LR, 48.5; $P < .001$) and 1-year mortality (modified: AUC, 0.566; 95% CI, 0.543-0.589; original: AUC, 0.508; 95% CI, 0.484-0.532; $P < .001$; NRI, 0.104; 95% CI, 0.054-0.153; $P < .001$; LR, 27.9; $P < .001$).

Prediction of Outcomes in Patients With ACS Using the Modified GRACE vs Clinical Variables

Compared with clinically used variables, the modified GRACE score outperformed coronary artery disease (CAD) extent and left ventricular ejection fraction for in-hospital mortality (AUC, 0.877 vs 0.723; NRI, 0.183), 30-day mortality (AUC, 0.855 vs 0.740; NRI, 0.236), and 1-year mortality (AUC, 0.756 vs 0.678; NRI, 0.108) (eTable 4 in Supplement 1). The independent and superior prognostication by the modified GRACE score compared with CAD extent (hazard ratio, 1.17; 95% CI, 1.03-1.32; $P = .02$; NRI, 0.07; 95% CI, 0.04-0.11; $P < .001$) was also evident in a sensitivity analysis

Table 2. Additive Reclassification and Discrimination Value of Fold Increases in High-Sensitivity Troponin Compared With the Global Registry of Acute Coronary Events (GRACE) Score for the Prediction of In-Hospital, 30-Day, and 1-Year Mortality[a]

	Reclassification, categorical NRI				Discrimination				
					C statistic			Likelihood ratio	
Comparator	Patients experiencing event, No. (%)	Patients not experiencing event, No. (%)	Overall NRI (95% CI)	*P* value	Original GRACE score, AUC (95% CI)	Original GRACE + modified GRACE score, AUC (95% CI)	*P* value	χ^2	*P* value
Derivation cohort									
In-hospital mortality	7 (4.83)	1376 (25.6)	0.208 (0.165-0.251)	<.001	0.741 (0.715-0.766)	0.835 (0.805-0.866)	<.001	171.93	<.001
30-d Mortality	66 (37.29)	326 (6.12)	0.312 (0.222-0.402)	<.001	0.740 (0.717-0.763)	0.828 (0.800-0.856)	<.001	163.14	<.001
1-y Mortality	6 (1.70)	315 (6.1)	0.078 (0.045-0.111)	<.001	0.778 (0.754-0.802)	0.785 (0.762-0.808)	.01	26.81	<.001
Validation cohort									
In-hospital mortality	20 (36.4)	151 (3.9)	0.325 (0.165-0.484)	.001	0.849 (0.830-0.867)	0.902 (0.874-0.930)	<.001	130.94	<.001
30-d Mortality	2 (2.74)	843 (21.4)	0.187 (0.146-0.227)	.001	0.814 (0.780-0.845)	0.869 (0.831-0.907)	<.001	128.98	<.001
1-y Mortality	3 (1.24)	150 (4.0)	0.027 (0.001-0.053)	.112	0.815 (0.781-0.849)	0.821 (0.788-0.853)	.01	2.73	.10

Abbreviations: AUC, area under the receiver operating characteristic curve; NRI, net reclassification improvement.

[a] NRI can be disentangled to NRI in events and nonevents. NRI in events is the net proportion of events assigned to a higher risk category, and NRI in nonevents is the net proportion of nonevents assigned to a lower risk category. For in-hospital mortality, on average, the modified GRACE score reclassified 7 and 20 patients from the derivation and validation cohorts, respectively, to a higher risk category and reclassified 1376 and 151 patients without an event to a lower risk category compared with the original GRACE score. For 30-day mortality, on average, the modified GRACE score reclassified 66 and 2 patients from the derivation and validation cohorts, respectively, to a higher risk category and reclassified 326 and 843 patients without an event to a lower risk category compared with the original GRACE score. For 1-year mortality, on average, the modified GRACE score reclassified 6 and 3 patients from the derivation and validation cohorts, respectively, to a higher risk category and reclassified 315 and 150 patients without an event to a lower risk category compared with the original GRACE score. NRIs were derived using event rate cutoffs as follows: in-hospital mortality, 2.7% in the derivation cohort and 2.0% in the validation cohort; 30-day mortality, 3.4% in the derivation cohort and 2.1% in the validation cohort; and 1-year mortality, 6.6% in the derivation cohort and 4.2% in the validation cohort.

assessing ischemic events (available in the Heidelberg and SPUM-ACS cohorts).

Discussion

The GRACE risk score, a well-established tool to objectively assess risk, is endorsed by international guidelines for early risk stratification and estimating prognosis in patients with ACS.[5-8] Nonetheless, its clinical utility practice has been challenged by a recent open-label cluster randomized clinical trial examining the impact of implementing the original GRACE score in high-performing hospitals on the receipt of quality indicators of guideline-recommended care and outcomes in patients with ACS.[30] Despite early study cessation and low event rates, the original GRACE risk score–based ACS management contributed to a lower 12-month mortality rate in patients randomized to the intervention arm, highlighting the need for additional large-scale studies to prospectively assess the value of routine risk scoring in the management and outcomes of patients with ACS.[30] As we move toward precision medicine, the modified GRACE risk score, a refined risk prediction model with improved performance, provides a promising basis to probe its clinical utility in well-designed studies across the broad spectrum of ACS.

In the present study, we hypothesized that integration of absolute troponin levels at the time of acute presentation rather than using dichotomized cutoff values may improve the prognostic, reclassification, and discrimination value of the GRACE risk score. By harnessing 2 independent derivation ACS cohorts and a validation ACS cohort of 9450 patients, we report an additive value of continuous hs-cTn T at presentation, but not of peak hs-cTn T, compared with the original or calibrated GRACE risk scores. This finding may be explained by the fact that absolute troponin levels at presentation may mirror both the time elapsed between symptom onset and presentation as well as the extent of myocardial injury,[18] both being associated with future adverse events.[31,32] Finally, our data suggest that integration of continuous rather than dichotomous hs-cTn T in a modified GRACE risk score improves 30-day, in-hospital, and, to a lesser extent, long-term risk stratification of patients with ACS.

The timing of an invasive management in patients with NSTE-ACS is guided by high-risk features, including a high GRACE risk score.[5,10,33] Moreover, the GRACE score at presentation can facilitate the identification of patients with NSTE-ACS at high risk of life-threatening ventricular arrythmias during hospitalization[34] and thus may guide appropriate levels of care and monitoring during hospital stay. The finding that the modified GRACE score outperformed the original and the calibrated GRACE scores in patients with NSTE-ACS for the association with in-hospital mortality may encourage future investigations on its clinical utility to decide on the timing of an early invasive strategy.

In patients with ACS undergoing PCI, ischemic and bleeding risks must be carefully balanced to tailor antithrombotic regimens during the 12 months after ACS.[5-7,10] The use of

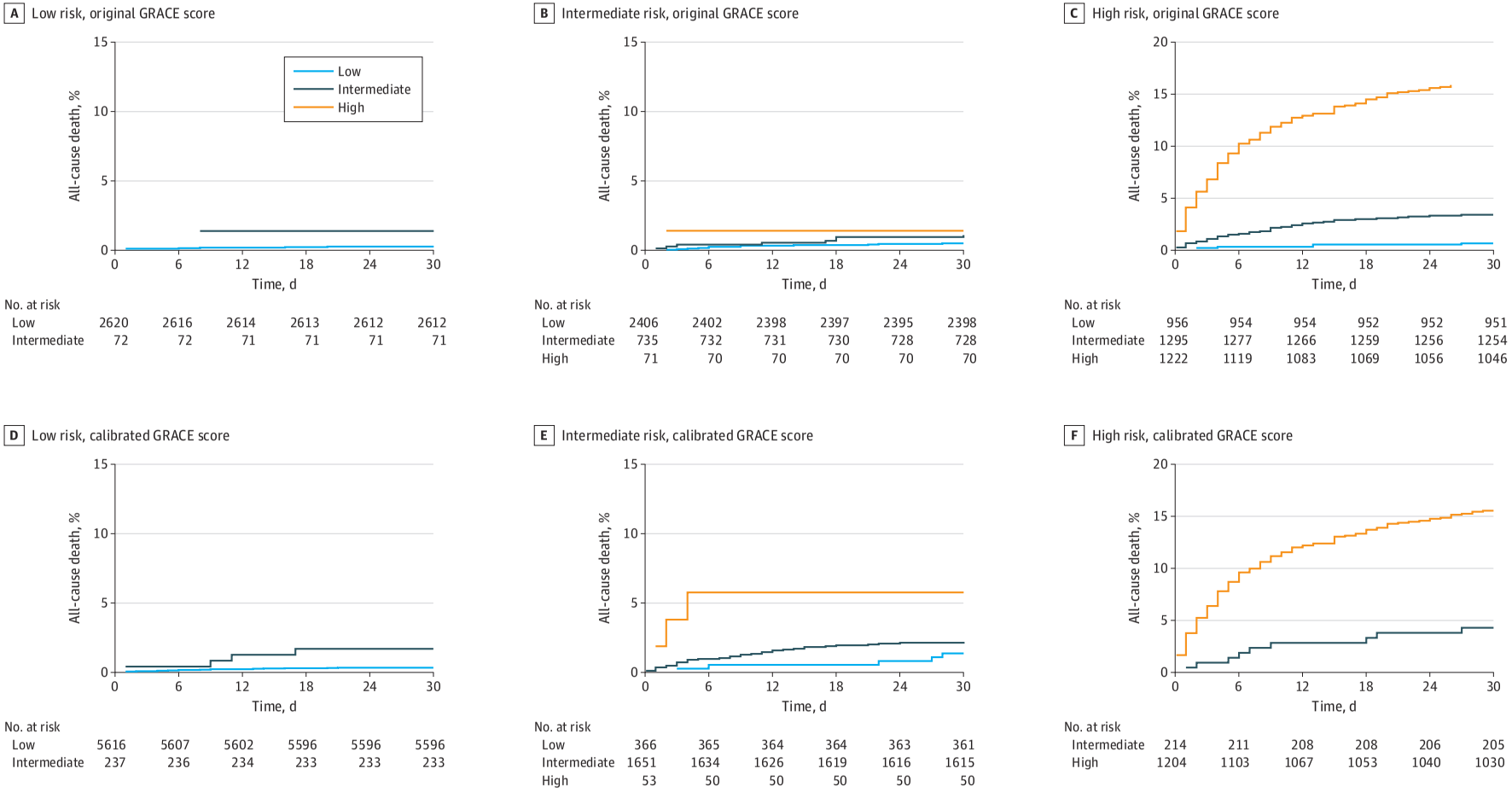
Table 3. Additive Reclassification and Discrimination Value of the Modified Global Registry of Acute Coronary Events (GRACE) Score Incorporating Fold Increases in High-Sensitivity Troponin for the Prediction of In-Hospital, 30-Day, and 1-Year Mortality[a]

	Reclassification, categorical NRI			Discrimination			
				C statistic		Likelihood ratio	
Comparator	Patients experiencing event, No. (%)	Patients not experiencing event, No. (%)	Overall NRI (95% CI)	Original GRACE score, AUC (95% CI)	Original GRACE + modified GRACE score, AUC (95% CI)	χ^2	*P* value
Derivation cohort							
In-hospital mortality							
Modified vs original GRACE	3 (2.1)	1918 (35.7)	0.337 (0.302-0.371)	0.741 (0.715-0.766)	0.8705 (0.843-0.898)	185.86	<.001
Modified vs calibrated GRACE	1 (0.7)	215 (4.0)	0.47 (0.016-0.078)	0.857 (0.831-0.882)	0.873 (0.848-0.898)	29.84	<.001
30-d Mortality							
Modified vs original GRACE	27 (−15.3)	2367 (44.4)	0.291 (0.223-0.359)	0.740 (0.717-0.763)	0.851 (0.825-0.877)	171.68	<.001
Modified vs calibrated GRACE	1 (0.6)	224 (4.2)	0.048 (0.017-0.078)	0.830 (0.805-0.856)	0.848 (0.823-0.873)	34.14	<.001
1-y Mortality							
Modified vs original GRACE	13 (3.7)	98 (1.9)	0.056 (0.029-0.083)	0.778 (0.754-0.802)	0.785 (0.762-0.809)	16.82	<.001
Modified vs calibrated GRACE	2 (0.6)	25 (0.5)	0.011 (0.002-0.019)	0.822 (0.800-0.843)	0.833 (0.813-0.852)	16.82	<.001
Validation cohort							
In-hospital mortality							
Modified vs original GRACE	27 (−49.1)	275 (7.1)	0.562 (0.339-0.784)	0.849 (0.830-0.867)	0.916 (0.889-0.942)	88.71	<.001
Modified vs calibrated GRACE	0	23 (0.6)	0.006 (0.003-0.009)	0.856 (0.801- 0.911)	0.873 (0.822-0.924)	37.09	<.001
30-d Mortality							
Modified vs original GRACE	2 (−1.4)	346 (6.5)	0.051 (0.023-0.079)	0.814 (0.780-0.849)	0.878 (0.837-0.918)	132.41	<.001
Modified vs calibrated GRACE	0	85 (1.6)	0.016 (0.011-0.020)	0.866 (0.822-0.909)	0.869 (0.825-0.913)	63.94	<.001
1-y Mortality							
Modified vs original GRACE	2 (1.2)	22 (0.6)	0.018 (0.001-0.036)	0.815 (0.781-0.849)	0.820 (0.789-0.853)	1.24	.27
Modified vs calibrated GRACE	48 (−27.3)	2378 (63.3)	0.36 (0.202-0.517)	0.806 (0.773-0.839)	0.835 (0.805-0.865)	1.24	.27
Whole population							
In-hospital mortality							
Modified vs original GRACE	8 (−4.0)	1270 (13.7)	0.097 (0.069-0.126)	0.780 (0.760-0.799)	0.878 (0.855-0.901)	265.77	<.001
Modified vs calibrated GRACE	0	278 (3.0)	0.030 (0.009-0.050)	0.853 (0.827-0.879)	0.869 (0.844-0.893)	443.23	<.001
30-d Mortality							
Modified vs original GRACE	4 (−1.6)	883 (9.6)	0.079 (0.059-0.100)	0.771 (0.751-0.790)	0.858 (0.835-0.880)	302.21	<.001
Modified vs calibrated GRACE	2 (−0.8)	277 (3.0)	0.022 (0.001-0.045)	0.845 (0.822-0.867)	0.856 (0.833-0.878)	498.88	<.001
1-y Mortality							
Modified vs original GRACE	18 (3.4)	167 (1.9)	0.056 (0.029-0.083)	0.797 (0.778-0.815)	0.813 (0.795-0.831)	627.57	<.001
Modified vs calibrated GRACE	3 (0.6)	44 (0.5)	0.011 (0.002-0.019)	0.827 (0.810-0.844)	0.831 (0.814-0.847)	733.19	<.001

Abbreviations: AUC, area under the receiver operating characteristic curve; NRI, net reclassification improvement.

[a] NRI can be disentangled to NRI in events and nonevents. NRI in events is the net proportion of events assigned to a higher risk category, and NRI in nonevents is the net proportion of nonevents assigned to a lower risk category. NRIs were derived using event rate cutoffs as follows: in-hospital mortality, 2.7% in the derivation cohort, 1.5% in the validation cohort, and 2.2% for the whole population; 30-day mortality, 4.5% in the derivation cohort, 2.1% in the validation cohort, and 2.8% for the whole population; 1-year mortality, 8.0% in the derivation cohort, 5.3% in the validation cohort, and 6.8% for the whole population. For in-hospital mortality, on average, the modified GRACE score reclassified 3, 27, and 8 patients from the derivation cohorts, validation cohort, and whole population, respectively, to a higher risk category and reclassified 1918, 275, and 1270 patients without an event to a lower risk category compared with the original GRACE score. For 30-day mortality, on average, the modified GRACE score reclassified 27, 2, and 4 patients from the derivation cohorts, validation cohort, and whole population, respectively, to a higher risk category and reclassified 2367, 346, and 883 patients without an event to a lower risk category compared with the original GRACE score. For 1-year mortality, on average, the modified GRACE score reclassified 13, 2, and 18 patients from the derivation cohorts, validation cohort, and whole population, respectively, to a higher risk category and reclassified 98, 22, and 167 patients without an event to a lower risk category compared with the original GRACE score.

Figure 2. Discrimination Value of the Modified Global Registry of Acute Coronary Events (GRACE) Risk Score Compared With the Original and Calibrated GRACE Risk Scores for 30-Day Mortality



Nelson-Aalen plots for low-risk, intermediate-risk, and high-risk patients for 30-day mortality as classified by the original and calibrated GRACE risk scores. Note that lines show discrimination of low-risk, intermediate-risk, and high-risk patients by the calibrated GRACE score using prognostic (ie, continuous) instead of diagnostic (ie, less than or greater than 14 ng/L) high-sensitivity cardiac troponin T concentrations at acute coronary syndrome (ACS) presentation. A, A total of 72 of 2692 patients with ACS classified as low risk by the original GRACE score presented with higher observed risk by the modified GRACE score. B, A total of 2406 of 3212 patients with ACS classified as intermediate risk by the original GRACE score presented at lower observed risk and 71 at higher observed risk by the modified GRACE score. C, A total of 2251 of 3473 patients with ACS originally classified as high risk presented at lower observed risk by the modified GRACE score. D, A total of 237 of 5853 patients with ACS classified as low risk by the calibrated GRACE score presented with observed higher risk by the modified GRACE score. E, A total of 366 of 2070 patients with ACS classified as intermediate risk by the calibrated GRACE score presented at lower observed risk and 53 at higher observed risk by the modified GRACE score. F, A total of 214 of 1418 patients with ACS classified by the calibrated GRACE score as high risk presented at lower observed risk by the modified GRACE score.

objective scores assessing ischemic risk, such as the GRACE score together with CAD complexity, may facilitate clinical decision-making regarding optimal antithrombotic treatment duration and intensity.[5] Importantly, although bleeding events were not available in this study, our analyses revealed that the modified GRACE score outperformed CAD extent in the association with a composite end point of ischemic events, setting the ground for further clinical research on the value of the modified GRACE score for risk stratification regarding ischemic events during the first year after ACS.

Finally, the modified GRACE score improved the performance of the original or calibrated GRACE scores for 1-year mortality, albeit to a lesser extent relative to the in-hospital or 30-day mortality end points, partly because continuous hs-cTn T may also convey information on CAD extent and subsequent systolic dysfunction following ACS. Indeed, the modified GRACE score is associated with mortality across all time points analyzed, compared with left ventricular systolic dysfunction and the extent of CAD, as confirmed by angiography.

Limitations

This study has limitations. First, the included cohorts differed in baseline characteristics and individual components of the GRACE risk score. Nonetheless, the modified GRACE score consistently provided superior performance across all cohorts, supporting its potential applicability in different patient populations and suggesting high external validity. Second, as recruitment periods of both the derivation and validation cohorts largely overlapped, bias from secular treatment trends could have affected findings. However, this effect appears to be marginal. Indeed, the association of continuous hs-cTn T at presentation with short-term mortality was independent of the type of antiplatelet therapy used in both the derivation and validation cohorts.

Conclusions

In conclusion, the modified GRACE score incorporating continuous hs-cTn T at presentation showed improved performance compared with the original GRACE score and other well-established prognostic markers, including left ventricular systolic dysfunction and extent of CAD, both of which are mostly unavailable in the initial hospitalization phase. Moreover, in patients with NSTE-ACS, the modified GRACE score outperformed the original GRACE score, a setting in which objective risk assessment represents standard of care to decide on the timing of an invasive strategy.[5,10,33] Collectively, we herein provide an improved version of the GRACE risk score, the clinical utility of which needs to be probed in prospectively designed studies. At present, this has not been shown for the original GRACE risk score.

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