



Published in final edited form as:

Am J Cardiol. 2016 October 15; 118(8): 1105–1110. doi:10.1016/j.amjcard.2016.07.029.

Performance of the GRACE Risk Score 2.0 Simplified Algorithm for Predicting 1-year Death Following Hospitalization for an Acute Coronary Syndrome in a Contemporary Multiracial Cohort

Wei Huang, PhD^{a,*}, Gordon FitzGerald, PhD^a, Robert J. Goldberg, PhD^b, Joel Gore, MD^c, Richard H. McManus, MPP, MSW^b, Hamza Awad, MD, PhD^d, Molly E. Waring, PhD^b, Jeroan Allison, MD, MS^b, Jane S. Saczynski, PhD^e, Catarina I. Kiefe, PhD, MD^b, Keith A.A. Fox, MB, ChB^f, Frederick A. Anderson, PhD^a, David D. McManus, MD, ScM^c, and the TRACE-CORE investigators

^aCenter for Outcomes Research, Department of Surgery, University of Massachusetts Medical School, Worcester, Massachusetts

^bDepartment of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts

^cDepartment of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

^dDepartment of Community Medicine, Mercer University School of Medicine, Macon, Georgia

^eDepartment of Pharmacy and Health Systems Sciences, Northeastern University, Boston, Massachusetts

^fCenter for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom.

Abstract

The GRACE Risk Score is a well-validated tool for estimating short- and long-term risk in acute coronary syndromes (ACS). GRACE Risk Score 2.0 substitutes several variables that may be unavailable to clinicians and thus limit use of the GRACE Risk Score. GRACE Risk Score 2.0 performed well in the original GRACE cohort. We sought to validate its performance in a contemporary multiracial ACS cohort, in particular among black ACS patients. We evaluated the performance of the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality among 2,131 participants in TRACE-CORE, a multiracial cohort of patients discharged alive after an ACS in 2011–2013 from 6 hospitals in Massachusetts and Georgia. The median age of study

*Corresponding author: Tel: (+1) 508-856-1336; fax: (+1) 508-856-5058. Wei.Huang@umassmed.edu (W. Huang). Center for Outcomes Research, Department of Surgery, University of Massachusetts Medical School, 55 Lake Ave North, S3-138, Worcester, MA 01655.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

Dr. Anderson is a consultant for Takeda Pharmaceuticals and Novartis Pharmaceuticals Corporation. Professor Fox has received grants and honoraria from Bayer/Janssen, Astra Zeneca, Sanofi/Regeneron, and GlaxoSmithKline. The other authors declare that they have no conflicts of interest to disclose.

participants was 61 years, 67% were men, and 16% were black. Half (51%) of the patients experienced a non-ST-segment elevation myocardial infarction (NSTEMI) and 18% an ST-segment elevation myocardial infarction (STEMI). Eighty (3.8%) patients died within 12 months of discharge. The GRACE Risk Score 2.0 simplified algorithm demonstrated excellent model discrimination for predicting 1-year mortality following hospital discharge in the TRACE-CORE cohort (c-index = 0.77). The c-index was 0.94 among patients with STEMI, 0.78 among patients with NSTEMI, and 0.87 among black ACS patients. In conclusion, the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality exhibited excellent model discrimination across the spectrum of ACS types and racial/ethnic subgroups and thus may be a helpful tool to guide routine clinical care for ACS patients.

Keywords

myocardial infarction; angina; risk factor; mortality

Patients with an acute coronary syndrome (ACS) encompass individuals with diverse pathophysiologic underpinnings and prognoses, but ACS risk stratification relies primarily on electrocardiographic and serum cardiac biomarker data.^{1,2} National practice guidelines promote use of the Global Registry of Acute Coronary Events (GRACE) Risk Score to help clinicians estimate in-hospital and post-discharge risk for dying among ACS patients.^{1,2} The GRACE Risk Score 1.0 estimates the risk of in-hospital death and of death at 6 months post-discharge.³⁻⁵ Although accurate, a major limitation to the widespread use of the GRACE Risk Score 1.0 is the inclusion of several variables, including Killip class and creatinine values at the time of the patient's hospital presentation. GRACE Risk Score 2.0 was developed to address these limitations and to evaluate the short- and long-term risk for dying after an ACS, including up to 3 years after discharge.⁶ However, the GRACE Registry included mostly white patients of European descent. Since several studies have demonstrated that race is strongly associated with differential ACS risk and quality of medical care in United States (US),⁷⁻⁹ it is important to externally validate GRACE Risk Score 2.0 in a contemporary and multiracial ACS cohort. We evaluated the performance of the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality in the Transitions, Risks, and Actions in Coronary Events Center for Outcomes Research and Education (TRACE-CORE) cohort, a contemporary and multiracial cohort of ACS patients surviving hospitalization and followed for 1 year post-discharge in the US. Furthermore, we performed validation stratified by race and ACS subgroups.

Methods

Details of the TRACE-CORE are described elsewhere.¹⁰ In brief, TRACE-CORE was a multisite prospective cohort of adults surviving hospitalization with an ACS at 3 tertiary care and community medical centers in Worcester, Massachusetts (these centers capture most hospitalizations for ACS in central Massachusetts); 2 hospitals in Atlanta, Georgia (contracted to admit and treat members of a major health maintenance organization network); and 1 teaching hospital in Macon, Georgia (serving residents of central

Georgia).^{10,11} Participating sites served a heterogeneous patient population and were selected purposely for their sociodemographic and socioeconomic diversity.^{10,11}

Participants with an ACS were identified by trained study staff between April 2011 and May 2013 using active surveillance methods. Adults admitted to any of the participating medical centers with electrocardiographic or cardiac biomarker criteria consistent with ACS, those undergoing urgent coronary revascularization, and symptomatic participants with >70% stenosis in a coronary artery on coronary angiography were eligible. Pregnant women, patients with dementia or receiving palliative care, patients with an ACS secondary to demand ischemia, perioperative ACS cases, and patients under custody of a prison system were ineligible. Sociodemographic, body mass index, clinical, laboratory, physiologic, and treatment-related data from medical records of the index hospitalization were abstracted by trained research staff and validated by physicians. Patients were followed up to 12 months post discharge. All-cause mortality was ascertained from proxy reports and review of medical records augmented by review of local and national vital statistics records. The institutional review boards at each participating recruitment site approved the study. All participants provided written informed consent.

We examined the statistical performance of the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality after an index ACS event, since information on Killip class was not collected in TRACE-CORE. Besides substituting Killip class with diuretic use within 24 hours of presentation, the published simplified algorithm substituted serum creatinine concentration with medical history of renal insufficiency at the same time. Additional variables in the simplified model are age, initial systolic blood pressure, initial pulse, cardiac arrest on admission, positive initial biomarkers, and ST deviation.⁶

Data from TRACE-CORE participants with no missing data were used to calculate the simplified GRACE Risk Score 2.0 (validation cohort). To provide insights into differences in model performance in the validation cohort and the original GRACE cohort used to derive the GRACE risk score 2.0 simplified algorithm for predicting 1-year mortality (derivation cohort), we mapped two databases and compared the characteristics of two cohorts directly as we had access to both databases. GRACE was designed to reflect an unbiased and generalizable sample of ACS patients hospitalized from 1999 to 2007 in 94 hospitals in 14 countries. Details of the GRACE design, recruitment, and data collection are described elsewhere.^{4-6,12}

Categorical variables are reported as frequencies and percentages, and continuous variables as medians with interquartile ranges. Differences in the baseline characteristics, management, and outcomes of patients in the validation versus derivation cohorts were examined using the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Data were censored at the last contact (in survivors) up to 1 year following the index discharge. The survival rate within 1 year post discharge was estimated using the Kaplan–Meier method. The log-rank test was used to compare the survival rates between two cohorts, and among racial subgroups in the validation cohort.

The validations were conducted in the overall TRACE-CORE validation cohort and in subgroups stratified by ACS diagnosis (STEMI, non-STEMI [NSTEMI], unstable angina) and race (black, non-black, white). To be consistent with the methods used to derive the GRACE Risk Score 2.0, Cox proportional hazards regression models were also used to validate the model. As we only intended to validate GRACE Risk Score 2.0, the proportional hazard assumption for each risk factor in TRACE-CORE was not assessed. Continuous variables in the TRACE-CORE validation were modeled using restricted cubic spline functions with the knots as defined in GRACE Risk Score 2.0, but we report categorical estimates to reflect the general shapes of these functions for presentation. In addition, the original GRACE Risk Score 2.0 paper presented a mixture of estimates for the full model variables plus the two substitute variables from the simplified algorithm.¹³ Therefore, to make comparisons equitable, we report estimates generated from a single model containing the listed factors using the derivation cohort and the validation cohort. The c-index, calculated by using the Harrell macro for Cox regression, was used to assess model discrimination.¹³ Although we intended to assess the goodness-of-fit (calibration) using the May–Hosmer method, owing to the small number of post-discharge deaths in TRACE-CORE, we could only form two risk groups based on this method.^{14,15} We did not, therefore, report model calibration. Instead, we reported the individual risk predictor estimates from the derivation and validation cohorts.

To guard against the possibility of over-fitting the GRACE model to smaller datasets, we conducted a sensitivity analysis in which we evaluated model discrimination by computing a risk score ($X\hat{\beta}$) for each TRACE-CORE patient, using GRACE-derived model estimates ($\hat{\beta}_s$). We then refit the Cox models in TRACE-CORE data using the risk score as sole covariate, and recomputed c indices. C indices thus computed ensure the model was not over-fit to TRACE-CORE data, as the score is a single degree of freedom variable whose estimates derive from a different (i.e. GRACE) data set.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and statistical significance level was prespecified as $\alpha = 0.05$ (2-sided).

Results

Of the 2,174 patients enrolled in TRACE-CORE in 2011–2013, 2,131 (98%) patients had no missing data needed to calculate the simplified GRACE Risk Score 2.0 (validation cohort). Most patients in the validation cohort were white (77%), 16% were black, and 7% were other races. A small percentage of the validation cohort (3.2%) considered themselves to be Hispanic/Latino ethnicity. The comparison on baseline characteristics of the derivation (GRACE) and validation (TRACE-CORE) cohorts are presented in Table 1.

The in-hospital death rate was 4.1% in the GRACE derivation cohort; TRACE-CORE only enrolled ACS patients who survived hospitalization. Comparing hospital survivors in both cohorts, the median 1-year survival in TRACE-CORE was 365 days, with a 96% survival rate (80 deaths, 3.8% cumulative incidence rate of death) while the median 1-year survival in GRACE was 204 days, with a 95% survival rate (1,210 deaths, 5.2% cumulative incidence rate of death) (log-rank test $p < 0.005$).

The individual risk predictor estimates generated from the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality in the derivation and validation cohorts are reported in Table 2. The simplified GRACE Risk Score 2.0 performed almost as well in our multiracial, contemporary replication cohort (c-index = 0.77) as in the original GRACE cohort (c-index = 0.82). The model performances in subgroups according to ACS diagnostic are presented in Table 3.

Although there was a lower percentage of patients with myocardial infarction among black TRACE-CORE participants (14% with STEMI, 47% with NSTEMI) compared with non-black TRACE-CORE participants (19% with STEMI, 52% with NSTEMI), the death rate among black participants was higher than among non-black participants (5.7% vs 3.4%). We therefore validated the simplified GRACE Risk Score 2.0 specifically among TRACE-CORE black participants (c-index = 0.87) (Table 3). Since black participants in TRACE-CORE were disproportionately recruited from hospitals in Georgia, we conducted a sensitivity analysis to examine whether adjustment for hospital site affected the c-index. As shown in Table 3, adjustment for hospital site did not substantially change the c-index.

Discussion

In this study, we evaluated the performance of the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality in TRACE-CORE, a multiracial and geographically diverse contemporary US cohort of patients discharged from the hospital after an ACS. We observed that, despite differences in the characteristics of the TRACE-CORE validation and GRACE derivation cohorts, the simplified GRACE Risk Score 2.0 exhibited excellent discriminatory capacity with respect to prediction of 1-year mortality risk, both in the overall sample and in analyses restricted to black TRACE-CORE participants and in patients with the different subtypes of ACS, particularly those with a myocardial infarction.

The overall performance of the simplified GRACE Risk Score 2.0 was, not surprisingly, slightly better in the GRACE derivation cohort as compared with what we observed using TRACE-CORE data (c-index 0.82 vs 0.77) as model discrimination is almost always superior in the derivation dataset when compared to independent validation datasets.¹⁶ Although the difference in model performance was trivial, one explanation for the slightly inferior performance of the simplified GRACE Risk Score 2.0 in our analyses could relate to differences in the baseline characteristics, clinical practice patterns, or post-discharge death rates between TRACE-CORE and GRACE. For example, TRACE-CORE excluded participants who died during hospitalization or were unable to sign consent due to illness, and therefore TRACE-CORE participants were at lower risk for dying overall compared with GRACE participants. Perhaps relating to the changing epidemiology of acute myocardial infarction in the US, with an increasing proportion of NSTEMI relative to STEMI observed in recent years,¹⁷ fewer participants in TRACE-CORE were diagnosed with STEMI in comparison with GRACE participants. As others and we have observed a superior model performance for GRACE Risk Score 2.0 among patients with STEMI, another explanation for the slightly poorer discriminatory ability observed in this validation cohort in relation to the derivation cohort may relate to the relative proportion of STEMI

versus NSTEMI and unstable angina participants in TRACE-CORE.¹¹ The implementation of high-sensitivity cardiac troponin assays in clinical practice has affected the clinical diagnosis of ACS (with some former unstable angina patients now being classified as having NSTEMI) and subsequent clinical management.^{18,19}

Importantly, the original description of the GRACE Risk Score 2.0 demonstrated consistent high model discrimination for predicting post-discharge death at both 1 and 3 years.⁶ The external validation of the simplified GRACE Risk Score 2.0 in FAST-MI showed excellent model discrimination (c-index 0.81 to 0.82) but included only participants with myocardial infarction.⁶ Despite the aforementioned differences between the FAST-MI and TRACE-CORE cohorts, the simplified GRACE Risk Score 2.0 performed similarly in our study, showing the same excellent model discrimination for predicting 1-year mortality among TRACE-CORE patients with any myocardial infarction (c-index = 0.81) as in the GRACE cohort. Following stratification of the TRACE-CORE cohort into STEMI, NSTEMI, and unstable angina subgroups, model discrimination improved with increasing severity of ACS category, although ST deviation was a predictor in GRACE Risk Score 2.0. This pattern was similar to the external validation results among the FAST-MI cohort, which demonstrated that model discrimination in GRACE Risk Score 2.0 was slightly better in patients with STEMI versus NSTEMI.⁶ Indeed, we observed better model discrimination among the STEMI group compared with the external validation results presented in the original manuscript (our c-index was 0.94 versus 0.82 in STEMI hospital survivors in FAST-MI). Another external validation of the GRACE Risk Score 2.0 full algorithm for predicting 1-year mortality was performed among 412 Japanese patients with STEMI who underwent a percutaneous coronary intervention, with the authors reporting a similar superior model discrimination (area under the curve = 0.92).²⁰

We observed excellent model discrimination in analyses restricted to black participants in TRACE-CORE, even after adjustment for hospital site. To our knowledge, ours is the first analysis to validate the performance of the simplified GRACE Risk Score 2.0 in a sample composed of black study participants. Our findings are notable in light of the published literature suggesting that black patients with an ACS are less likely than their white counterparts to receive evidence-based treatments and have higher rates of in-hospital complications and post-discharge mortality.⁷⁻⁹ Despite racial differences in ACS types and death rates observed in TRACE-CORE between white and black participants, the simplified GRACE Risk Score 2.0 performed well in both groups. Since it is accepted that a model with a c-index value of approximately 0.8 demonstrates discrimination adequate for genuine clinical utility,¹⁶ our findings would suggest that implementation of the simplified GRACE Risk Score 2.0 may aid in guiding therapeutic decision making for all ACS patients. Since it performs particularly well among black patients, its use might help better target black patients for evidence-based therapies and thereby reduce racial disparities in ACS care and outcomes.

The strengths of the present analysis include its use of data from a contemporary, multiracial cohort recruited from a geographically diverse set of hospitals, its use of rigorous quality-control methods for in-hospital data abstraction, and ascertainment of mortality through death records. Nonetheless, our findings need to be interpreted with appropriate caution due

to a relatively small sample size of non-white ACS patients and lack of global geographic representation, though the six US sites were purposely selected to provide diversity in race/ethnicity and socioeconomic status. However, when one considers that 77% of participants in our study were white and that 78% of the US population was white according to the 2013 US Census (<https://www.census.gov/popest/data/index.html>), our cohort mirrors that of the US population.

The number of deaths was modest, especially in smaller subgroups (STEMI, black patients), limiting the precision of our estimates. However, based on our sensitivity analyses, more conservative estimates using the single degree of freedom risk score demonstrate at least modest clinical utility (c-index = 0.7), with the exception of the unstable angina subgroup (c-index = 0.67). Finally, as data on in-hospital mortality were not collected in the TRACE-CORE cohort, we could not provide a complete performance assessment of GRACE Risk Score 2.0. Analyses should therefore be duplicated in larger samples or cohorts including in-hospital mortality.

Acknowledgment

Editorial support was provided by Sophie Rushton-Smith, PhD (Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA, USA).

Grant support

TRACE-CORE is supported by a National Institutes of Health, National Heart, Lung, and Blood Institute (Washington, DC, United States) grant 1U01HL105268-01. This project is additionally supported by an award from the University of Edinburgh ACS Risk Working Group (Edinburgh, United Kingdom, Project reference no. 003). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding sponsors. Dr McManus' time was also supported by 1U01HL105268-01 and KL2RR031981. Support for Dr Waring was provided by NIH grant KL2TR000160. Dr Saczynski was supported by K01AG033643 from the National Institute on Aging.

References

1. The National Clinical Guideline Centre. Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment elevation myocardial infarction. Clinical guideline. 2010; 94
2. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation*. 2007; 116:e148–304. [PubMed: 17679616]
3. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006; 333:1091. [PubMed: 17032691]
4. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003; 163:2345–2353. [PubMed: 14581255]

5. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004; 291:2727–2733. [PubMed: 15187054]
6. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Gabriel Steg P, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open*. 2014; 4:e004425.
7. Green AR, Carney DR, Pallin DJ, Ngo LH, Raymond KL, Jezzoni LI, Banaji MR. Implicit bias among physicians and its prediction of thrombolysis decisions for black and white patients. *J Gen Intern Med*. 2007; 22:1231–1238. [PubMed: 17594129]
8. Sonel AF, Good CB, Mulgund J, Roe MT, Gibler WB, Smith SC Jr. Cohen MG, Pollack CV Jr. Ohman EM, Peterson ED. Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). *Circulation*. 2005; 111:1225–1232. [PubMed: 15769762]
9. Venkat A, Hoekstra J, Lindsell C, Prall D, Hollander JE, Pollack CV Jr. Diercks D, Kirk JD, Tiffany B, Peacock F, Storrow AB, Gibler WB. The impact of race on the acute management of chest pain. *Acad Emerg Med*. 2003; 10:1199–1208. [PubMed: 14597496]
10. Waring ME, McManus RH, Saczynski JS, Anatchkova MD, McManus DD, Devereaux RS, Goldberg RJ, Allison JJ, Kiefe CI. Transitions, Risks, and Actions in Coronary Events--Center for Outcomes Research and Education (TRACE-CORE): design and rationale. *Circ Cardiovasc Qual Outcomes*. 2012; 5:e44–50. [PubMed: 22991349]
11. Goldberg RJ, Saczynski JS, McManus DD, Waring ME, McManus R, Allison J, Parish DC, Lessard D, Person S, Gore JM, Kiefe CI, TRACE-CORE investigators. Characteristics of Contemporary Patients Discharged From the Hospital After an Acute Coronary Syndrome. *Am J Med*. 2015; 128:1087–1093. [PubMed: 26007672]
12. Alnasser SM, Huang W, Gore JM, Steg PG, Eagle KA, Anderson FA Jr. Fox KA, Gurfinkel E, Brieger D, Klein W, van de Werf F, Avezum A, Montalescot G, Gulba DC, Budaj A, Lopez-Sendon J, Granger CB, Kennelly BM, Goldberg RJ, Fleming E, Goodman SG, GRACE Investigators. Late Consequences of Acute Coronary Syndromes: Global Registry of Acute Coronary Events (GRACE) Follow-up. *Am J Med*. 2015; 128:766–775. [PubMed: 25554379]
13. Harrell FE Jr. Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA*. 1982; 247:2543–2546. [PubMed: 7069920]
14. May S, Hosmer DW. A cautionary note on the use of the Gronnesby and Borgan goodness-of-fit test for the Cox proportional hazards model. *Lifetime Data Anal*. 2004; 10:283–291. [PubMed: 15456108]
15. Hosmer Jr, DW.; Lemeshow, S.; May, S. *Applied Survival Analysis: Regression Modeling of Time to Event Data*. 2nd Edition. Wiley-Interscience; New York, NY: 2008. p. 903
16. Ohman EM, Granger CB, Harrington RA, Lee KL. Risk stratification and therapeutic decision making in acute coronary syndromes. *JAMA*. 2000; 284:876–878. [PubMed: 10938178]
17. Chen HY, Gore JM, Lapane KL, Yarzebski J, Person SD, Gurwitz JH, Kiefe CI, Goldberg RJ. A 35-Year Perspective (1975 to 2009) into the Long-Term Prognosis and Hospital Management of Patients Discharged from the Hospital After a First Acute Myocardial Infarction. *Am J Cardiol*. 2015; 116:24–29. [PubMed: 25933734]
18. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Munzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med*. 2009; 361:868–877. [PubMed: 19710485]
19. Sandoval Y, Smith SW, Apple FS. Present and Future of Cardiac Troponin in Clinical Practice: A Paradigm Shift to High-sensitivity Assays. *Am J Med*. 2015 DOI: 10.1016/j.amjmed.2015.12.005 [Epub ahead of print].

20. Fujii T, Suzuki T, Torii S, Murakami T, Nakano M, Nakazawa G, Masuda N, Shinozaki N, Matsukage T, Ogata N, Yoshimachi F, Ikari Y. Diagnostic accuracy of Global Registry of Acute Coronary Events (GRACE) risk score in ST-elevation myocardial infarction for in-hospital and 360-day mortality in Japanese patients. *Circ J.* 2014; 78:2950–2954. [PubMed: 25283791]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Baseline characteristics of the derivation (GRACE) and validation (TRACE-CORE) cohorts

Variable	GRACE* (derivation cohort) (n = 33,890)	TRACE-CORE (validation cohort) (n = 2,131)	p value
ACS diagnosis			<0.001
STEMI	12,334 (36.4%)	378 (17.7%)	
NSTEMI	12,564 (37.1%)	1,085 (50.9%)	
Unstable angina pectoris	8,992 (26.5%)	668 (31.4%)	
Demographics			
Men	22,782 (67.5%)	1,421 (66.7%)	0.44
Age (years)	66 (56–76)	61 (53–69)	<0.001
Body mass index (kg/m ²)	27.0 (24.3–30.3)	29.4 (26.2–33.9)	<0.001
Medical history (6 months before index event)			
Angina pectoris	15,163 (44.8%)	880 (41.3%)	0.002
Myocardial infarction	10,167 (30.1%)	578 (27.1%)	0.004
Heart failure	3,389 (10.1%)	300 (14.1%)	<0.001
Percutaneous coronary intervention	6,490 (19.2%)	611 (28.7%)	<0.001
Coronary artery bypass graft	4,220 (12.5%)	367 (17.2%)	<0.001
Hypertension	21,703 (64.3%)	1,616 (75.8%)	<0.001
Hyperlipidemia	17,177 (50.9%)	1,468 (68.9%)	<0.001
Atrial fibrillation	2,580 (7.6%)	174 (8.2%)	0.38
TIA/stroke	2,834 (8.4%)	193 (9.1%)	0.29
Peripheral artery disease	3,017 (8.9%)	216 (10.1%)	0.06
Prosthetic valve replacement [†]	309 (0.9%)	24 (1.1%)	0.33
Smoker (former or current)	19,194 (56.8%)	1,348 (63.3%)	<0.001
Diabetes mellitus	8,628 (25.5%)	802 (37.6%)	<0.001
Renal insufficiency [‡]	2,537 (7.5%)	237 (11.1%)	<0.001
Major surgery [§]	2,434 (7.2%)	18 (0.8%)	<0.001
Major bleeding	367 (1.1%)	36 (1.7%)	0.010
Venous thromboembolism	609 (1.8%)	61 (2.9%)	0.001
Family history of CAD	9,475 (28.2%)	1,123 (52.7%)	<0.001
Presentation characteristics			
Transfer-in patients	4,330 (12.8%)	814 (38.2%)	<0.001
Pulse (beats/min)	76 (65–90)	75 (65–88)	0.002
Systolic blood pressure (mmHg)	140 (120–160)	140 (124–157)	0.24
Diastolic blood pressure (mmHg)	80 (70–90)	79 (69–90)	0.95
Cardiac arrest	641 (1.9%)	18 (0.8%)	0.001
Initial cardiac biomarker positive	17,293 (51.0%)	1,414 (66.4%)	<0.001
ST deviation on presentation	17,856 (52.7%)	459 (21.5%)	<0.001
Initial serum creatinine (mg/dL)	1.0 (0.9–1.3)	0.98 (0.8–1.2)	<0.001
In-hospital procedures			

Variable	GRACE* (derivation cohort) (n = 33,890)	TRACE-CORE (validation cohort) (n = 2,131)	p value
Cardiac catheterization	22,052 (65.4%)	2,008 (94.3%)	<0.001
Percutaneous coronary intervention	14,290 (42.3%)	1,429 (67.3%)	<0.001
Coronary artery bypass grafting	1,524 (4.8%)	279 (13.1%)	<0.001
Thrombolytics	3,544 (10.6%)	30 (1.4%)	<0.001
In-hospital events			
CHF/pulmonary edema	3,787 (11.2%)	41 (1.9%)	<0.001
Cardiogenic shock	1,195 (3.5%)	20 (0.9%)	<0.001
Cardiac arrest/ventricular fibrillation	1,374 (4.1%)	21 (1.0%)	<0.001
Atrial fibrillation/flutter	2,420 (7.2%)	166 (7.8%)	0.28
Sustained ventricular tachycardia	819 (2.4%)	84 (3.9%)	<0.001
Thrombocytopenia	74 (0.2%)	6 (0.3%)	0.56
Venous thromboembolism	97 (0.3%)	5 (0.2%)	0.65
Acute renal failure	1,289 (3.8%)	118 (5.5%)	<0.001
Myocardial infarction >24 hours after arrival/reinfarction	785 (2.3%)	5 (0.2%)	<0.001
Stroke	203 (0.6%)	9 (0.4%)	0.29
Major bleeding	749 (2.2%)	29 (1.4%)	0.007
Discharge status among hospital survivors			
Home	26,617 (76.9%)	2,049 (96.2%)	<0.001
Transfer to another acute facility	4,055 (11.7%)	5 (0.2%)	
AMA/self-discharge	254 (0.8%)	3 (0.1%)	
Other	1,545 (4.8%)	74 (3.5%)	
Length of hospital stay (days)	5 (3–8)	3 (2–5)	<0.001

Data are number (%) or median (interquartile range).

ACS = acute coronary syndromes; AMA = discharge against medical advice; CAD = coronary artery disease; GRACE = Global Registry of Acute Coronary Events; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; TRACE-CORE = Transitions, Risks, and Actions in Coronary Events Center for Outcomes Research and Education.

* Estimates generated from GRACE cohort used to derive the GRACE Risk Score 2.0 simplified algorithms (n = 33,890).

† Aortic, tricuspid, or mitral replacement with a bioprosthetic valve.

‡ Any documented history of renal compromise.

§ Major surgery or trauma within 2 weeks of index event.

// Documented history of significant blood loss from any site (not related to trauma) and requiring medical treatment.

Table 2

The individual risk factor estimates generated from the GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality in the derivation (GRACE) and validation (TRACE-CORE) cohorts

Risk factor	GRACE* (derivation cohort)*		TRACE-CORE (validation cohort)	
	HR (95% CI)	χ^2	HR (95% CI)	χ^2
Age per 10-year increment				
If <67, unit increment	1.6 (1.5–1.8)	1,303	2.0 (1.2–3.1)	19
If ≥67, unit increment	1.9 (1.8–2.0)		1.2 (0.8–1.8)	
Systolic blood pressure per –20 mmHg increment		503		23
If ≥139, unit increment	1.1 (1.0–1.2)		1.0 (0.7–1.3)	
If <139, unit increment	1.5 (1.4–1.6)		1.9 (1.5–2.4)	
Pulse per 30 beats/min increment		206		7
If <51, unit increment	1.2 (1.0–1.4)		3.5 (0.4–34.5)	
If 51–83, unit increment	1.6 (1.5–1.8)		2.8 (0.9–8.3)	
If 84–118, unit increment	1.4 (1.3–1.5)		0.9 (0.5–1.5)	
If >118, unit increment	0.9 (0.9–1.0)		0.5 (0.2–1.5)	
Cardiac arrest at admission	3.3 (2.8–3.9)	192	Not estimable [†]	
Positive initial biomarkers	1.5 (1.4–1.6)	84	1.1 (0.7–1.8)	0.2
ST deviation	1.6 (1.5–1.7)	123	0.9 (0.5–1.6)	0.1
Renal insufficiency	1.6 (1.4–1.7)	72	3.1 (1.9–5.0)	22
Use of diuretics in first 24 hours after presentation	2.0 (1.8–2.1)	266	2.1 (1.3–3.2)	10
c-index	0.82		0.77	

CI = confidence interval; GRACE = Global Registry of Acute Coronary Events; HR = hazard ratio; TRACE-CORE = Transitions, Risks, and Actions in Coronary Events Center for Outcomes Research and Education.

* Estimates generated from the original GRACE cohort used to derive the GRACE Risk Score 2.0 simplified algorithms (n = 33,890), not all of which were presented in the original paper.

[†] No deaths in TRACE-CORE patients with cardiac arrest at admission.

Table 3

Model performance of GRACE Risk Score 2.0 simplified algorithm for predicting 1-year mortality in a contemporary multiracial cohort of adults discharged alive following ACS (TRACE-CORE)

	n deaths / n participants	c-index	c-index adjusted for hospital site	c-index*
Total sample	80 / 2,131	0.77	0.79	0.73
Acute coronary syndrome type				
STEMI	8 / 378	0.94	0.93	0.88
NSTEMI	49 / 1,085	0.78	0.79	0.76
Unstable angina	23 / 668	0.73	0.77	0.67
Any myocardial infarction (STEMI or NSTEMI)	57 / 1,463	0.81	0.81	0.77
Race				
Black	19 / 339	0.87	0.89	0.78
Non-black	61 / 1,792	0.75	0.77	0.72
White	58 / 1,633	0.75	0.76	0.72

ACS = acute coronary syndromes; GRACE = Global Registry of Acute Coronary Events; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TRACE-CORE = Transitions, Risks, and Actions in Coronary Events Center for Outcomes Research and Education.

* From model whose sole covariate is the risk score ($X\hat{\beta}$) calculated from GRACE model estimates as applied to TRACE-CORE patient data.