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External validation of the GRACE risk score 2.0 in the contemporary all-comers GLOBAL LEADERS trial

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Abstract  
Objectives: This study aimed to assess the predictive ability of the Global Registry of Acute Coronary Events (GRACE) risk score 2.0 in contemporary acute coronary syndrome (ACS) patients, and its relation to antiplatelet strategies.  
Background: The predictive value of the GRACE risk score in the contemporary ACS cohort and the appropriate antiplatelet regimen according to the risk remain unclear.  
Methods: This is a subgroup analysis of the all-comers, randomized GLOBAL LEADERS trial, comparing ticagrelor monotherapy versus conventional dual-antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). The GRACE risk score 2.0 with 1-year mortality prediction was implemented. The randomized antiplatelet effect was
assessed in predefined three GRACE risk-groups; low-risk (GRACE <109), moderate-risk (GRACE 109–140), and high-risk (GRACE >140).

**Results:** The GRACE risk score was available in 6,594 out of 7,487 ACS patients among whom 1,743, 2,823, and 2,028 patients were classified as low-risk, moderate-risk, and high-risk, respectively. At 1 year, all-cause mortality occurred in 120 patients (1.8%). The discrimination ability of the GRACE model was moderate (C-statistic = 0.742), whereas 1-year mortality risk was overestimated (mean predicted mortality rate: 3.9%; the Hosmer-Lemeshow chi-square: 21.47; p = 0.006). There were no significant interactions between the GRACE risk strata and effects of the ticagrelor monotherapy on ischemic or bleeding outcomes at 1 year compared to the reference strategy.

**Conclusion:** The GRACE risk score 2.0 is valuable in discriminating high risk ACS patients, however, the recalibration of the score is recommended for better risk stratification. There is no significant differences in efficacy and safety of ticagrelor monotherapy across the three GRACE risk strata.

**KEYWORDS**
acute coronary syndrome, dual anti-platelet therapy, GRACE risk score, percutaneous coronary intervention, ticagrelor

1 | **INTRODUCTION**

The use of the Global Registry of Acute Coronary Events (GRACE) risk score is currently endorsed by the latest clinical guidelines in risk stratification of acute coronary syndrome (ACS) patients. The original GRACE risk score was firstly developed from the GRACE registry between 1999 and 2001 to assess the risk for in-hospital mortality of ACS. In 2014, the score was updated to GRACE risk score 2.0 to predict cumulative event from early of 1 year to long-term risk of 3 years, and the score was externally validated in the French registry of Acute ST-elevation and non-ST-elevation myocardial infarction (FAST-MI-2005).

Since the last update of the GRACE score which was based on the cohort recruited in 2002–2007, devices used in percutaneous coronary intervention (PCI), adjunctive therapies, and management strategies of acute myocardial infarction have improved. The newer generation drug eluting stents (DES) have more biocompatible coating than old generation DES; during and after procedure potent anticoagulation and/or antiplatelet therapy are available; the post procedural medical management of post-infarct patients may have been improved. Therefore, the predictive performance the GRACE risk score for risk stratification in contemporary ACS cohorts still needs to be investigated.

The GLOBAL LEADERS trial was the largest contemporary all-comers randomized study to compare the novel ticagrelor monotherapy following 1-month dual-antiplatelet therapy (DAPT) with conventional antiplatelet regimens with 12-month DAPT after PCI with biolimus-A9 eluting stent implantation.

The objectives of the current study were: (1) to validate the value of GRACE risk score in ACS patients of contemporary PCI era and; (2) to assess the interaction between patient stratification according to the GRACE risk score and antiplatelet treatment strategy on ischemic and bleeding outcomes in the GLOBAL LEADERS trial.

2 | **METHODS**

The current study was a subgroup analysis of the GLOBAL LEADERS trial. The GLOBAL LEADERS trial was a multi-center, open-label, randomized controlled trial comparing a novel antiplatelet regimen with ticagrelor monotherapy versus conventional antiplatelet regimens in all-comers patients undergoing PCI at 130 sites in 18 countries. The design of the trial has been described previously. In brief, patients undergoing PCI with a biolimus A9-eluting stent for chronic coronary syndrome (CCS) or ACS were randomly assigned (1:1) to either 75–100 mg aspirin once daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy, or standard dual antiplatelet therapy with 75–100 mg aspirin once daily plus either 75 mg clopidogrel once daily (for patients with CCS) or 90 mg ticagrelor twice daily (for patients ACS) for 12 months, followed by aspirin monotherapy for 12 months. The institutional review board at each participating institution approved the GLOBAL LEADERS trial. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practices.

2.1 | **GRACE risk score calculation in the GLOBAL LEADERS ACS cohort**

Since the GRACE risk score is dedicated to ACS patients, patients presenting with CCS were excluded in the current analysis. In addition,
patients without available data for the GRACE risk score were also excluded. The GRACE risk score was calculated in each patient based on the clinical parameters at hospital admission. The model used eight clinical factors: age, Killip class, systolic blood pressure, ST-segment deviation (elevation or depression), cardiac arrest at presentation, serum creatinine level, elevated initial cardiac enzyme, and heart rate. The GRACE risk score 2.0 is the most updated model by employing a spline model to predict cumulative events of death or myocardial infarction at 1 year or 3 years, and death at 1 year or 3 years. The GRACE risk score was established to estimate cumulative event at 1 year and 3 years, whereas the GLOBAL LEADERS had a clinical assessment at 1 year and at the end of the study of 2 years. The all-cause mortality at 1 year in the GLOBAL LEADERS study was used to validate the GRACE Death 1-year model. ACS patients were divided into following three groups with GRACE risk score according to the current guidelines: low-risk (GRACE score < 109), moderate-risk (GRACE score 109–140), and high-risk (GRACE score > 140).

2.2 | Endpoints

The primary endpoint of the current study was all-cause mortality at 1 year from the randomization in order to assess the performance of the GRACE risk score 2.0. In addition, to assess the interaction between GRACE risk categories and antiplatelet strategy effects, we additionally evaluated the clinical endpoints of all-cause mortality, any stroke, myocardial infarction according to the third universal definition, definite stent thrombosis, and the bleeding of academic research consortium (BARC) type 3 or 5 according to Academic Research Consortium definition at 1 year. All clinical events were site-reported.

2.3 | Statistical analysis

Baseline characteristics and outcomes are reported for each classification of patients according to the GRACE risk score strata. Continuous variables are expressed as median and interquartile range (IQR) and are compared using the Kruskal-Wallis H test for multiple comparisons and the Mann–Whitney U test for pairwise comparisons. Categorical variables are presented as counts and percentages and are compared using chi-square test. Kaplan–Meier curves were used to estimate the cumulative rates of clinical events between the GRACE risk categories and the difference was assessed by the Log-rank test. Cox proportional hazards analysis was used to evaluate the proportional hazard ratios of the experimental strategy compared to the reference strategy in terms of clinical endpoints across the predefined GRACE risk categories. This involved the inclusion of interaction between the GRACE risk categories and anti-platelet regimens. The proportional hazard (PH) assumptions were assessed by using scaled Schoenfeld residual tests in terms of primary endpoints (Supplemental Appendix) across the GRACE risk strata.

The area under the receiver-operating characteristic curve, which equals the C-statistic when the outcome is binary, was estimated on the GRACE risk score for 1-year mortality.

The calibration performance of the risk model was evaluated using calibration plots. Calibration-in-the-large (model intercept) and calibration slope were evaluated by fitting the calculated linear predictor in all patients with all-cause mortality as the outcome in the logistic regression model. Intercept of 0 and slope of 1 indicate perfect prediction. Negative and positive intercepts indicate overestimation and underestimation, respectively. The calibration performance of the GRACE risk score 2.0 was also evaluated by using the Hosmer-Lemeshow goodness-of-fit (GOF) test. The Brier score was calculated to assess the accuracy of probability in the GRACE risk score 2.0, where a Brier score of 0 reflected a perfect model, whereas a score of 0.25 suggested a non-informative model. Two-sided p values less than 0.05 were considered statistically significant. The statistical analyses were performed in SPSS Statistics, version 26 (IBM Corp., Armonk, 281 N.Y., USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with “survival”, “survminer”, “ggplot2”, “rms”, and “CalibrationCurves” statistical packages.

2.4 | Patient and public involvement

No Patients were involved in the design, or conduct, or reporting, or dissemination plans of the present study.

3 | RESULTS

3.1 | GRACE risk score in GLOBAL LEADERS trial

In the GLOBAL LEADERS trial, 15,991 patients were recruited between July 1, 2013 and November 9, 2015, and 23 patients withdrew their consent, thus a total of 15,968 patients remained in the analysis. Among these patients, 7,487 patients presented with ACS whereas 8,481 presented with CCS at entry to the trial. Out of those ACS patients, 893 patients (11.9%) were excluded from the current study due to incomplete predictor data to calculate the GRACE risk score 2.0 (868 patients with missing cardiac biomarker, nine patients with missing creatinine clearance, 16 patients with missing both cardiac biomarker and creatinine clearance); Consequently, 6,594 patients with available GRACE risk score were included in the analysis (Figure 1 and Online Table 1). According to the GRACE risk score, 1,743 (26.4%) patients, 2,823 (42.8%) patients, and 2,028 (30.8%) patients were classified as low-risk, moderate-risk, and high-risk patients, respectively.

The baseline patients’ clinical characteristics are summarized in Table 1. Female gender, older age, comorbidities of diabetes, hypertension, established peripheral vascular disease, known chronic obstructive pulmonary disease, and impaired renal function were more frequently observed in the GRACE high-risk group than in the moderate-risk or low-risk group. Of note, in the low-risk group, the prevalence of STEMI was less than 10% (9.2%), and similar prevalence were observed in unstable angina (47.4%) and NSTEMI (43.4%). In contrast, in the high-risk group, the prevalence of NSTEMI (47.5%) and STEMI (40.6%) were similar, whereas the prevalence of unstable angina was low (11.8%).
the high-risk group, left main PCI (3.4%) and multivessel PCI (28.0%) were more frequently performed compared to the patients in low-risk or moderate-risk groups. There were significant difference in Killip class among GRACE risk groups, although most patients presented with Killip class I even in the high-risk group (92.1%) as well as the low-risk or moderate-risk groups. Cardiac arrest was rarely observed in our cohort (none in low-risk, 0.1% in moderate-risk, and 2.6% in high-risk). Substantial differences were observed in the prevalence of ST-segment deviation among three risk groups (18.0% in low-risk, 56.9% in moderate-risk, and 86.1% in high-risk).

3.2 | All-cause death at 1 year in patients stratified according to the GRACE risk score

At 1 year, 120 patients (1.8%) died from any cause in the present study. Up to 1 year, the GRACE high-risk group had the highest incidence of all-cause death (3.5%) [N = 71], followed by moderate-risk (1.4%) [N = 40] and low-risk (0.5%) [N = 9] groups (log-rank p < 0.001) (Figure 2).

3.3 | Discrimination and calibration ability of the GRACE risk score on all-cause mortality

The overall discriminative ability of the GRACE risk score for death at 1-year was reflected by a C-statistics value of 0.742 (95% CI 0.697–0.787) (Figure 3). The calibration showed over estimation of the mortality risks in each quintile as indicated by the negative intercept (−0.80; 95% confidence interval: −0.99 to −0.62) and the Hosmer-Lemeshow GOF test (GOF chi-square: 21.47; p = 0.006) (Figure 3 and Online Figure 1). The Brier score of the GRACE risk score 2.0 was 0.018.

3.4 | The interaction between the GRACE risk categories and antiplatelet treatment effects

There are no evidences of violations of the PH assumptions in terms of the primary endpoint in any GRACE risk groups (Online Figure 2). There was no evidence of an interaction between treatment strategy and GRACE risk score categories throughout the strata on any outcomes up to 1 year (Figure 4).

4 | DISCUSSION

The main findings in this substudy of the GLOBAL LEADERS trial were the following: (1) The discriminative ability of the GRACE risk score to predict all-cause death at 1 year was moderate (“possibly helpful”12,13) whereas calibration showed the overestimation of the risk of death at 1 year; (2) There was no evidence of an interaction between GRACE risk stratification and effects of antiplatelet treatment on ischemic and bleeding outcomes up to 1 year.

4.1 | GRACE risk score for the risk stratification of ACS patients

The present study suggests that the GRACE risk score has a moderate performance for risk discrimination in ACS patients but the model calibration overestimated the actual risk. The GRACE risk score is thought to be unique in the sense that the model was aimed to estimate from short to long-term mortality of ACS patients among other risk models for estimating in-hospital or short-term mortality.14-16 The GRACE risk score 2.0 is the most updated model based on COX model by employing non-linear algorithms to predict cumulative event of death at 1 or 3 year. Recently, Hung et al elucidated the good discriminative ability of the GRACE risk score 2.0 in patients with type 1 myocardial infarction.17 However, the original derivation and validation cohorts of the GRACE risk score 2.0 were generated in the early 2000s.5 In the time elapsed between the development of the GRACE risk score and the current practice, there have been declines in mortality risk due to improved life expectancy, and improvement in short- and long-term outcomes in ACS patients, as well as important changes in the diagnosis of ACS with the advent of high-sensitivity troponins resulting in identification of more ACS patients.18 Shuvy et al. reported that the GRACE risk score had a substantial discriminative ability even in the contemporary ACS cohort, but the calibration ability was not reported.19 In our study, the median predicted 1-year mortality risks of the low-risk, moderate-risk, and high-risk groups were
| TABLE 1 | Baseline characteristics of the GRACE ACS cohort in GLOBAL LEADERS trial |
|----------|---------------------------------------------------------------------|
|          | GRACE <109 low risk (N = 1743) | GRACE 109–140 moderate risk (N = 2,823) | GRACE >140 high risk (N = 2,028) | P value for multiple comparisons | P value for pairwise comparisons |
|          |                                      |                                       |                                      |                                  | Low risk vs. moderate risk | Moderate risk vs. high risk | Low risk vs. high risk |
| Randomization |                                      |                                       |                                      |                                  |                           |                           |                           |
| Experimental arm | 48.1 (838/1743) | 50.3 (1,420/2823) | 50.5 (1,025/2028) | <0.001 | <0.001 | <0.001 |
| Reference arm | 51.9 (905/1743) | 49.7 (1,403/2823) | 49.5 (1,003/2028) | <0.001 | <0.001 | <0.001 |
| Age (years) | 56.0 (49.0–62.0) | 62.0 (56.0–69.0) | 71.0 (65.0–78.0) | <0.001 | <0.001 | <0.001 |
| Female | 19.3 (337/1743) | 21.7 (612/2823) | 28.1 (570/2028) | <0.001 | 0.058 | <0.001 |
| BMI (kg/m²) | 28.0 (25.5–31.3) | 27.5 (24.9–30.5) | 27.1 (24.6–30.0) | <0.001 | <0.001 | <0.001 |
| Clinical presentation |                                      |                                       |                                      |                                  |                           |                           |                           |
| Unstable angina | 47.4 (826/1743) | 25.4 (716/2823) | 11.8 (240/2028) | <0.001 | <0.001 | <0.001 |
| NSTEMI | 43.4 (756/1743) | 47.1 (1,331/2823) | 47.5 (964/2028) | 0.018 | 0.013 | 0.791 |
| STEMI | 9.2 (161/1743) | 27.5 (776/2823) | 40.6 (824/2028) | <0.001 | <0.001 | <0.001 |
| Comorbidities |                                      |                                       |                                      |                                  |                           |                           |                           |
| Diabetes mellitus | 19.0 (332/1743) | 20.8 (588/2821) | 25.0 (507/2026) | <0.001 | 0.142 | 0.001 |
| Insulin-treated | 5.4 (94/1738) | 6.0 (168/2809) | 7.3 (148/222) | <0.041 | 0.421 | 0.063 |
| Hypertension | 68.9 (1,196/1735) | 68.5 (1,924/2809) | 71.3 (1,439/2028) | 0.095 | 0.756 | 0.036 |
| Hypercholesterolemia | 66.1 (1,096/1659) | 62.7 (1,687/2690) | 57.3 (1,118/1950) | <0.001 | 0.025 | <0.001 |
| Current smoker | 41.7 (727/1743) | 36.3 (1,026/2823) | 25.0 (506/2028) | <0.001 | 0.534 | 0.175 |
| PVD | 4.7 (81/1733) | 5.1 (142/2792) | 6.0 (120/2004) | 0.174 | 0.001 | 0.021 |
| COPD | 2.7 (47/1741) | 4.7 (131/2811) | 6.2 (124/2012) | <0.001 | <0.001 | <0.001 |
| Renal impairment | 5.7 (100/1743) | 10.6 (298/2823) | 23.4 (475/2028) | <0.001 | <0.001 | <0.001 |
| Medical history |                                      |                                       |                                      |                                  |                           |                           |                           |
| Previous bleeding | 0.3 (6/1740) | 0.4 (11/2815) | 1.0 (21/2026) | 0.005 | 0.805 | 0.006 |
| Previous stroke | 1.7 (30/1740) | 2.3 (65/2819) | 3.4 (68/2025) | <0.004 | 0.182 | 0.027 |
| Previous MI | 20.6 (358/1740) | 18.0 (508/2819) | 16.9 (341/2023) | 0.011 | 0.033 | 0.293 |
| Previous PCI | 27.4 (478/1743) | 22.7 (641/2821) | 20.7 (420/2027) | <0.001 | <0.001 | 0.096 |
| Previous CABG | 2.4 (42/1743) | 4.0 (113/2823) | 4.4 (89/2027) | 0.003 | 0.004 | 0.505 |
| Procedure |                                      |                                       |                                      |                                  |                           |                           |                           |
| Number of lesion treated | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) | <0.001 | 0.001 | 0.092 |
| Categorical groups |                                      |                                       |                                      |                                  |                           |                           |                           |
| One lesion | 71.0 (1,230/1733) | 66.3 (1,863/2810) | 64.3 (1,296/2014) | <0.001 | 0.004 | 0.079 |
| Two lesions | 21.1 (366/1733) | 24.9 (699/2810) | 24.9 (502/2014) | <0.001 | 0.001 | 0.092 |
| Three or more | 7.9 (137/1733) | 8.8 (248/2810) | 10.7 (216/2014) | <0.001 | 0.001 | 0.092 |
| GRACE <109 low risk (N = 1743) | GRACE 109–140 moderate risk (N = 2,823) | GRACE >140 high risk (N = 2,028) | P value for multiple comparisons | P value for pairwise comparisons |
|-------------------------------|------------------------------------------|-----------------------------------|----------------------------------|----------------------------------|
| Low risk vs. moderate risk     | Moderate risk vs. high risk              | Low risk vs. high risk            |                                  |                                  |
| Left main PCI                 | 1.8 (31/1733)                            | 2.5 (69/2810)                     | 3.4 (69/2014)                    | 0.006                            | 0.137                           | 0.046 | 0.002 |
| RCA PCI                       | 36.7 (636/1733)                          | 39.8 (1,118/2810)                 | 39.8 (802/2014)                 | 0.076                            | 0.244                           | 0.407 | 0.068 |
| LAD PCI                       | 49.4 (856/1733)                          | 51.2 (1,438/2810)                 | 52.4 (1,055/2014)               | 0.187                            | 0.441                           | 0.293 | 0.828 |
| LCX PCI                       | 33.5 (581/1733)                          | 32.4 (911/2810)                   | 33.9 (682/2014)                 | 0.536                            | 0.038                           | 0.981 | 0.050 |
| Bypass graft PCI              | 0.8 (13/1733)                            | 1.2 (35/2810)                     | 1.8 (36/2014)                   | 0.019                            | 0.113                           | 0.123 | 0.005 |
| Multivessel PCI               | 20.7 (359/1733)                          | 24.9 (700/2810)                   | 28.0 (563/2014)                 | <0.001                           | 0.001                           | 0.018 | <0.001 |

### Presentation

| Killip class                  | <0.001 | 0.001 | <0.001 | <0.001 |
|-------------------------------|--------|-------|--------|--------|
| Class I                       | 99.8 (1739/1743) | 98.8 (2,788/2823) | 92.1 (1867/2028) |                     |
| Class II                      | 0.2 (4/1743)    | 1.2 (34/2823)     | 6.0 (121/2028)    |                     |
| Class III                     | 0.0 (0/1743)    | 0.0 (1/2823)      | 1.7 (34/2028)     |                     |
| Class IV                      | 0.0 (0/1743)    | 0.0 (0/2823)      | 0.3 (6/2028)      |                     |
| Abnormal cardiac enzymes     | 49.9 (870/1743) | 74.9 (2,114/2823) | 91.6 (1858/2028)  | <0.001                           |
| Cardiac arrest at presentation| 0.0 (0/1743)    | 0.1 (3/2823)      | 2.6 (52/2028)     | <0.001                           |
| ST-segment deviation          | 180 (313/1743)  | 56.9 (1,606/2823) | 86.1 (1,746/2028)  | <0.001                           |
| Systolic blood pressure       | 140 (130–160)   | 135 (120–150)     | 128 (112–140)     | <0.001                           |
| Heart rate                    | 68 (60–75)      | 70 (61–79)        | 72 (64–82)        | <0.001                           |
| Serum creatinine level        | 0.89 (0.77–1.02) | 0.92 (0.79–1.06) | 0.97 (0.82–1.15)  | <0.001                           |
| GRACE risk score 2.0          | 96.2 (87.4–103.4) | 124.9 (117.4–132.1) | 154.2 (146.5–165.4) | <0.001                           |
| Predicted in-hospital mortality (%) | 0.5 (0.4–0.7) | 1.3 (1.0–1.6) | 3.3 (2.6–4.7) | <0.001                           |
| Predicted 1-year mortality (%) | 1.6 (1.2–1.9) | 2.8 (2.3–3.6) | 5.9 (4.4–8.1) | <0.001                           |

**Abbreviations:** ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; GRACE: Global Registry of Acute Coronary Events; NSTEMI, non ST segment elevation myocardial infarction; PVD, peripheral vascular disease; STEMI, ST segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery.
1.6%, 2.8%, and 5.9%, respectively (Table 1), whereas observed mortality were only 0.5%, 1.4%, and 3.5% in the low-risk, moderate-risk, and high-risk groups, respectively, all of which were less than 50% of the corresponding predicted mortality rates according to the GRACE risk score 2.0 (Figure 3). In fact, the calibration plot in the present analysis suggested that the majority of patients had a low-risk profile, and thus the number of high-risk patients might be insufficient to evaluate the predictability of the GRACE risk score in those high-risk population.

More recently, the Australian Grace Risk score Intervention study (AGRIS) showed that a strategy of risk stratification and implementation of evidence-based therapies using the GRACE risk score did not improve the primary endpoint of the clinical performance score compared to routine clinical care among patients presenting with ACS, although the strategy using the GRACE risk score increased an early invasive strategy.20 For better risk stratification in the contemporary ACS population, recalibration or a novel dedicated risk score might be required.21,22 Among patients presenting with STEMI, the prewiring MI-SYNTAX score may be more useful for the risk stratification, suggested by another subgroup analysis of the GLOBAL LEADERS trial.23

4.2 | GRACE risk score and antiplatelet therapy

Recent trials suggested that the novel P2Y12 inhibitor monotherapy could improve the outcomes in terms of reduction of bleeding events, even in high-ischemic risk population (e.g., ACS, multivessel disease, complex PCI).24-29 ACS patients are prone to thrombotic event, thus intense anti-thrombotic therapy is needed among ACS patients especially in acute phase.30 In the ACS cohort of the GLOBAL LEADERS trial (N = 7,487), ticagrelor monotherapy yielded a 48% reduction of BARC type 3 or 5 bleedings at 1 year compared to DAPT with ticagrelor on top of aspirin (HR: 0.52; 95% CI: 0.33–0.81; p = 0.004) without an increase in ischemic events.26 In the current analysis, the effects of ticagrelor monotherapy on BARC type 3 or 5 bleedings or ischemic endpoints did not significantly differ among three risk-groups (p value for interaction = 0.708). Of course, the GRACE risk score does not aim to make a decision for the antiplatelet strategy, however, the results may suggest that the ticagrelor monotherapy would be applicable for potential reduction of bleeding events in the entire stratification of the GRACE risk score.
4.3 Limitations

The present study has several limitations. First, although the GLOBAL LEADERS trial applied an “all-comers” design with minimum exclusion criteria, patients who were not able to provide informed consent did not partake in the trial, which could affect the overall mortality risk especially for those with very high-risk (e.g., cardiac arrest at presentation). However, even if those super high-risk patients were excluded in the current analysis, that should not be the excuse of the overestimation (especially for low- or moderate-risk patients) because the score should be able to predict a patient’s mortality risk on an individual basis based on the patient’s risk factors, irrespective of inclusion or exclusion criteria of a study. Therefore, if the patients enrolled in the GLOBAL LEADERS trial had relatively lower risk factors than other studies, then the score should predict the low mortality risk. Second, 893 patients were excluded from the ACS cohort of the GLOBAL LEADERS trial in the current analysis due to the lack of data, where some discrepancies in baseline characteristics (e.g., prevalence of STEMI or medical history of prior stroke) were observed between the included and excluded population of the current analysis (Online Table 1), which might have impacted some of the results. Third, the GRACE risk score still provided us with a moderate discrimination ability for patients stratification in death risk, but additional factors may contribute to the further refinement of the model, although this goal was beyond the scope of this study. Finally, in this trial all endpoints were site-reported without a central adjudication by an independent committee for serious adverse events. However, the primary endpoint of all-cause mortality does not need for adjudication. In addition, the GLASSY study, which is a prespecified ancillary study of the GLOBAL LEADERS trial with event adjudication by an independent clinical event committee, has reported results consistent with those of site-reported.

5 CONCLUSIONS

The GRACE risk score is able to discriminate current ACS patients at high risk after PCI, albeit the mortality risk at 1 year was overestimated. There was no evidence of heterogeneity across different categories of the GRACE risk score in the effects of ticagrelor monotherapy compared to the reference antiplatelet strategy within different levels on any ischemic or bleeding endpoints at 1 year.
CONFLICT OF INTEREST
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DATA AVAILABILITY STATEMENT
GLOBAL LEADERS trial is an investigator-initiated trial. Internal investigators, who actively participated in the study, and who provide a methodologically sound study proposal will be granted priority access to the study data for 60 months. After 60 months, this option might be extended to external investigators not affiliated to the trial, whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.