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The GRACE registry: how real-life evidence contributes to acute coronary syndrome guidelines

Freek W. Verheugt*

Heartcenter Onze Lieve Vrouwe Gasthuis (OLVG), Oosterpark 9, 1091 AC, Amsterdam, The Netherlands

The continuing burden of acute coronary syndrome: a need for risk stratification

Acute coronary syndrome (ACS) is an umbrella term for the three manifestations of unstable coronary artery disease: unstable angina (UA), ST-segment elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI). These conditions share an underlying pathophysiology involving the rupture or erosion of an atheromatous plaque, followed by varying degrees of superimposed thrombosis and distal embolisation.[1] They differ, however, with respect to clinical presentation, electrocardiographic changes, and serum concentration of cardiac enzymes and markers.[1,2]

Acute coronary syndrome poses a considerable disease burden. The annual incidence of NSTEMI is ~3 per 1000 inhabitants, although this number varies between countries.[1] Globally, ACS is the leading cause of mortality in industrialized countries,[3] and myocardial infarction (MI) accounts for almost half of all deaths related to cardiovascular disease.[4]

Even with optimal treatment—such as dual antiplatelet therapy—patients with ACS face an increased risk of MI and death in the short and long term.[1] The prognosis is generally poor but varies across the spectrum of ACS: The 30-day and 6-month mortality rates are 4.5% and 8.6%, respectively, in UA patients and 12.9% and 19.2%, respectively, in STEMI patients, based on UK registry data.[5] Because of this variability, it is recommended that ACS patients are risk-stratified on hospital admission in order to assess their risk of ischaemic and bleeding outcomes.[1]

Several ACS risk-prediction tools have been developed, of which the Global Registry of Acute Coronary Events (GRACE) risk score, discussed in detail below, is considered the most robust.[6] Also widely used is the Thrombolysis in Myocardial Infarction (TIMI) risk score, which estimates the composite of all-cause mortality, new or recurrent MI, and severe recurrent ischaemia requiring urgent revascularization within 14 days.[7] The platelet glycoprotein IIb/IIIa in Unstable Angina: receptor suppression using integrilin therapy (PURSUIT) risk score predicts 30-day mortality and the composite of mortality/MI; despite having comparable discriminative efficacy with the GRACE score, PURSUIT is rarely used in practice.[8–10] Bleeding risk assessment is also an important component of the decision-making process—major bleeding in patients with ACS is associated with a 5-fold increase in the risk of death during the first 30 days after hospitalization/randomization.[11] Available bleeding risk scores include the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE), which was developed from a cohort of 71 277 patients from the CRUSADE registry to help estimate a patient's baseline risk of in-hospital major bleeding during NSTEMI.[12] The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials produced another bleeding risk score from a pooled cohort of 17 421 patients with ACS,[13] while the Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines (ACTION Registry-GWTG) database developed an in-hospital major bleeding risk model from 72 313 patients.[14] Both of these scores were derived from STEMI and NSTEMI patients. Of all three bleeding risk scores, CRUSADE was shown to be the most accurate quantitative tool for NSTEMI and STEMI patients undergoing coronary arteriography in a study of 4500 consecutive patients with ACS.[12]

The Global Registry of Acute Coronary Events and risk score

The Global Registry of Acute Coronary Events is the largest and best-known database study in the field of ACS. Patients

* Corresponding author. Tel: +31 20 6755251, Fax: +31 84 8675789, Email: fvh@telfort.nl

are enrolled from >240 hospitals in 30 countries across Europe, North and South America, Asia, Australasia, and New Zealand using the same eligibility criteria.[15] To be eligible for inclusion, patients must be ≥18 years old with a presumptive diagnosis of ACS and a clinical history of ACS plus at least one of the following: electrocardiogram (ECG) changes consistent with ACS; serial increases in levels of biochemical markers of cardiac necrosis (e.g. troponin) and documented coronary artery disease.[16,17]

Registry data from GRACE have been used to develop a risk-prediction tool for estimating the cumulative 6-month risk of death or death/MI in patients admitted to hospital with ACS, based on eight readily available clinical variables. These are age, congestive heart failure, systolic blood pressure, Killip class, initial serum creatinine concentration, positive initial cardiac markers, cardiac arrest on admission, and number of leads with ST deviation.[18] Using Cox proportional hazards analysis, the GRACE score was highly predictive of death or death/MI within 5 years of the index admission, and those in the intermediate [hazard ratio (HR): 2.14, 95% CI 1.63–2.81] and high-risk strata (HR: 6.36, 95% CI 4.95–8.16) had a substantially higher risk of death compared with the low-risk stratum (*Figure 1*).[16] Recently, the GRACE 1.0 ACS risk score was updated to GRACE 2.0 (*Table 1*), which has better discrimination and is easier to use than the previous score, as well as providing 1- and 3-year probabilities.[17] GRACE 2.0 has been validated in an independent dataset with comprehensive long-term outcome data.[17] The GRACE risk score has also been shown to predict heart failure admission following ACS, and can therefore be used to target patients with ACS at high risk of congestive heart failure with clinical monitoring and appropriate therapies.[19]

Because patients with ACS are a heterogeneous group, individual treatment decisions–in terms of the urgency of proceeding to coronary angiography and the choice of antithrombotic regimen–will depend on risk profile.[1] A *post hoc* analysis of patients stratified by GRACE risk score has helped to identify patients who are more or less likely to benefit from different therapeutic strategies. For instance, in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial, patients with a GRACE risk score <112 had better outcomes (death/MI at 30 days) if they received fondaparinux rather than unfractionated heparin (UFH) and the reverse was true for patients with a score of >112.[20] In the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial, patients with a GRACE risk score <140 fared better with a delayed invasive strategy; however in those with a score of >140 there was no significant difference between groups.[21]

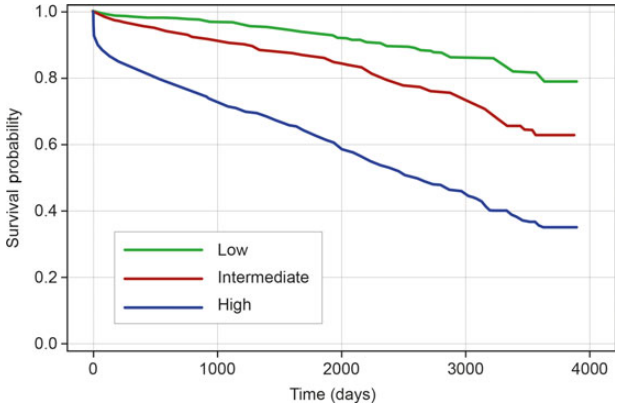

Figure 1 Survival according to the Global Registry of Acute Coronary Events score (score for death in-hospital). The Cox proportional hazards test confirms there is a difference across the strata (x^2 likelihood ratio $\frac{1}{4}$ 632.0, Wald 709.9, $P < 0.0001$). Censored observations: i.e. patient has not had an event and is alive at the point of last follow-up.[16]

Table 1 The Global Registry of Acute Coronary Events risk score Version 2.0[15]

Input data	
Age (years)	Creatinine (mg dL^{-1}/μmol L^{-1})
Heart rate (bpm)	Renal failure
Systolic blood pressure (mmHg)	ST-segment deviation
Congestive heart failure (Killip class)	Cardiac arrest at admission
Diuretic usage	Elevated troponin[a]

[a]Or other necrosis cardiac biomarkers.

The Global Registry of Acute Coronary Events in the guidelines

Major clinical guidelines on the management of ACS recommend risk-stratifying patients using ECG characteristics and biomarker results, together with the use of a risk score such as GRACE to help guide treatment decisions. For example, the 2013 American College of Cardiology Foundation/American Heart Association guidelines on the initial management of non-ST-elevation ACS (NSTE-ACS) recommend an invasive strategy for patients with a high GRACE risk score (i.e. >140), and a conservative approach for patients with a low GRACE risk score (≤140).[22] The 2011 European Society of Cardiology guidelines on the management of NSTE-ACS recommend established risk scores for prognosis (Recommendation IB).[1] A GRACE score <140 is cited as one of the criteria for deciding a patient is suitable for discharge, and a GRACE score of >140 is one of the criteria for choosing an early invasive strategy (<24 h).[1] Similar recommendations are contained in guidelines from the National Institute for Health and Care Excellence from the UK.[23]

Conclusion

The GRACE registry dataset has been harnessed to develop a simple, accurate, and widely used risk-prediction tool, which has been validated in multiple populations. The value of the GRACE risk score is supported by its inclusion in European and American clinical guidelines on the management of ACS.

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