The Global Registry of Acute Coronary Events, 1999 to 2009 –GRACE

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The Global Registry of Acute Coronary Events, 1999 to 2009—GRACE

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ABSTRACT

The aim of GRACE was to provide a large multinational registry of the full spectrum of patients with acute coronary syndromes (ACS) in order to define patient characteristics and outcomes and derive predictive risk scores. The study was designed and administered by an independent steering committee; data analyses were performed under the guidance of the steering committee at the Center for Outcomes Research of the University of Massachusetts. Regular feedback regarding local, regional and international guideline and performance measures was provided to individual hospitals and clusters of hospitals. Regional and international benchmark data were available to all sites. Main GRACE involved 123 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand. GRACE2 (Expanded GRACE) comprised 154 hospitals in Europe, North and South America, Asia, Australasia and China. Continuous recruitment and follow-up took place between 1999 and 2009. The first 10 -20 patients per site (depending on hospital size) were enrolled each month, resulting in the recruitment of 102 341 patients, who were categorized as having ST-segment elevation myocardial infarction, non-ST-elevation myocardial infarction or unstable angina. Standardized case report forms (datafax or electronic) were completed by trained study coordinators, and included fields relating to demographic factors, comorbid conditions, treatments and in-hospital and post-discharge (6-month) events. Blood sampling, genetic analyses and longer-term follow-up were undertaken in GRACE substudies. Prospective individual patient follow-up was carried out. All sites were audited locally; 10% of individual patient records were audited in a 2-year cycle. Less than 1% of 20 key baseline fields, and less than 1% of discharge diagnosis and discharge status data, were missing. Six-month follow-up was 85% complete. Publications and risk scores are available at http://www.outcome.org/grace. Proposals for specific analyses were considered, in competition, by an independent publications committee.

INTRODUCTION

The Global Registry of Acute Coronary Events (GRACE) programme was established, de novo, in 1999 to resolve major uncertainties into what constitutes an acute coronary syndrome (ACS), to define how patients with an ACS are treated, and to characterise their outcomes. This is a dynamic process and this continuous decade-long study has provided a temporal reflection of practice between 1999 and 2009. This approach differs from cross-sectional 'snapshot' surveys, which provide data only at specific time points.

The GRACE publications have described the spectrum of patients with suspected ACS (including ST-segment elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction and ACS without biomarker release), their risk predictors and their in-hospital and 6-month outcomes. GRACE aimed to narrow the 'gap' between evidence and clinical practice. By providing feedback with a reference standard of robust regional and international data each quarter, a clinician could index local hospital practice to larger datasets and identify opportunities to improve practice. GRACE complements information from randomised trials in selected populations: it defines how practice is applied in a large 'real-world' reflection of the full spectrum of acute coronary disease.

Several large observational studies have been conducted in patients with ACS (table 1),[10–17] and they vary in the extent to which they comply with proposed quality standards of design, reporting and quality assurance.[18] The most critical issue is whether a registry reflects the full spectrum of ACS, rather than a selected population (eg, those treated in interventional centres or patients identified only from cardiac care units).

GRACE METHODS

GRACE was designed to reflect an unselected population of patients with ACS, irrespective of geographical region. A total of 123 hospitals located in 14 countries in North and South America, Europe, Australia and New Zealand have contributed data to this observational cohort study. All participating countries and hospital clusters were established at the outset. To avoid site selection bias clusters were required to include a complete spectrum of hospitals that admit patients with ACS (within a geographical region). This was validated for each region.

To avoid inclusion bias the first 10—20 patients (depending on hospital size) admitted with suspected ACS in each calendar month were 'tracked', irrespective of their eventual hospital location (including cardiac units, medical units, care of the elderly and intensive care units). The cyclic audit programme of all sites (two-year cycle with 10% of all patients audited by a senior GRACE coordinator visiting each cluster) was designed to minimise the risk of inclusion bias. GRACE employed local training, rigorous quality control and audit of participating centres. In the 'warm pursuit' design, the tracking of patients after arrival in the emergency department ensures that patients cared for outside cardiac units (eg, care of the

Table 1 External validation of the GRACE risk score (summary of publications, excluding models based on fewer than 500 cases†)[1–7]

Outcome measure	Population	Author (date) database	Model discrimination c-statistic (mean)
Death—in-hospital	ACS	Granger (2003) GRACE (development)	0.83
		Granger (2003) GRACE (validation)	0.85
		Granger (2003) GUSTO-IIb*	0.79
		Yan (2004) Canadian ACS Registry	0.82
		Yan (2007) Canadian ACS Registry-II	0.81
		Pieper (2009) GRACE (update)	0.84
		Elbarouni (2009) Canadian GRACE	0.84
		Gale (2009) MINAP database	0.80
	STEMI	Granger (2003) GRACE	0.83
		Granger (2002) GUSTO-IIb*	0.77
		Elbarouni (2009) Canadian GRACE	0.83
		Aragam(2009) Michigan	0.84
	NSTE-ACS	Granger (2003) GRACE	0.82
		Granger (2003) GUSTO-IIb*	0.81
		Yan (2004) Canadian ACS Registry	0.83
		Elbarouni (2009) Canadian GRACE	0.84
		Aragam (2009) Michigan	0.85
Death—admission to 6 months	ACS	Fox (2006) GRACE	0.81
		Fox (2006) GRACE (validation)	0.81
		Fox (2006) GUSTO-IIb*	0.82
		Gale (2009) MINAP database	0.80
	STEMI	Fox (2006) GRACE	0.82
		Fox (2006) GRACE (validation)	0.82
		Fox (2006) GUSTO-IIb*	0.80
		Aragam (2009) Michigan	0.72
	NSTE-ACS	Fox (2006) GRACE	0.79
		Fox (2006) GRACE (validation)	0.81
		Fox (2006) GUSTO-IIb*	0.76
		Aragam(2009) Michigan	0.79
Death—discharge to 6 months	ACS	Eagle (2004) GRACE	0.77
		Eagle (2004) GRACE (validation)	0.75
		Alter(2006) SESAMI	0.80
		Bradshaw (2006) EFFECT AMI	0.80
		Tang (2007) New Zealand	0.81
	STEMI	Eagle (2004) GRACE	0.80
		Eagle (2004) GRACE (validation)	0.76
		Bradshaw (2006) EFFECT AMI	0.81
		Tang (2007) New Zealand	0.76
	NSTE-ACS	Eagle (2004) GRACE — NSTEMI	0.78
		Eagle (2004) GRACE — UA	0.75
		Eagle (2004) GRACE (validation) — NSTEMI	0.78
		Eagle (2004) GRACE (validation) — UA	0.70
		Bradshaw (2006) EFFECT AMI — NSTEMI	0.78
		Tang (2007) New Zealand — NSTEMI	0.82
		Tang (2007) New Zealand — UA	0.91
Death at 1 year	ACS	Bradshaw (2006) EFFECT AMI	0.80
		Tang (2007) New Zealand	0.81
	STEMI	Bradshaw (2006) EFFECT AMI	0.81
		Tang (2007) New Zealand	0.81
		Kozieradzka (2009) Poland	0.81
	NSTE-ACS	Yan (2007) Canadian ACS Registry-II	0.79
		Bradshaw (2006) EFFECT AMI — NSTEMI	0.78
		Tang (2007) New Zealand — NSTEMI	0.82
		Tang (2007) New Zealand — UA	0.90
Death at 2 years	ACS	Tang (2007) New Zealand	0.81
	STEMI	Tang (2007) New Zealand	0.78
	NSTE-ACS	Tang (2007) New Zealand — NSTEMI	0.83
		Tang (2007) New Zealand — UA	0.80
Death at 3 years	ACS	Tang (2007) New Zealand	0.81
	STEMI	Tang (2007) New Zealand	0.77
	NSTE-ACS	Tang (2007) New Zealand — NSTEMI	0.84
		Tang (2007) New Zealand — UA	0.80

Continued

Table 1 Continued

Outcome measure	Population	Author (date) database	Model discrimination c-statistic (mean)
Death at 4 years	ACS	Tang (2007) New Zealand	0.80
	STEMI	Tang (2007) New Zealand	0.76
	NSTE-ACS	Tang (2007) New Zealand — NSTEMI	0.83
		Tang (2007) New Zealand — UA	0.82
Death at 5 years	STEMI	Kozieradzka (2009) Poland	0.74

*Data on cardiac arrest were unavailable.
†The study by Lev *et al*[8] was excluded because we believe the c-statistic was computed improperly.[9]
ACS, acute coronary syndrome; AMI, acute myocardial infarction; EFFECT, enhanced feedback for effective cardiac treatment; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

elderly), and those who die shortly after presentation, are appropriately represented in the registry. A detailed case record form was developed and validated during the pilot phase (http://www.outcomes.org/grace) and has been made available to external investigators.

Patients aged 18 years and older admitted with a presumptive diagnosis of ACS at participating hospitals and who were alive at the time of presentation were eligible for inclusion. The qualifying ACS must not have been precipitated or accompanied by a significant non-cardiovascular comorbidity (eg, surgery or trauma). Although rare, the mechanisms of ischaemia in such patients (supply-demand imbalance) differ from spontaneous ACS and hence such patients were not included. In-patients, who were already hospitalised for a non-cardiovascular reason when symptoms of ACS developed (eg, perioperative infarction), were not eligible for enrolment in GRACE. Patients transferred into or out of a registry hospital could be enrolled regardless of the time spent at the transferring hospital. For patients transferred out of a registry hospital, data collection for the initial case report form ended with the transfer and indication of purpose of transfer. Patients hospitalised for less than 1 day who died were enrolled provided that the cause of death was confirmed to be due to ACS. Follow-up was prospective and based on individual patient contact rather than relying on hospital or central records.

PATIENT-IDENTIFICATION APPROACHES

To facilitate the review of medical records in a systematic manner and accommodate the varying ways in which the data were collected, prospective ('warm') and retrospective ('cold') surveillance approaches for identifying cases of ACS, similar to the MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project,[19 20] were adopted.[13] Most study centres adopted warm pursuit, with only a limited number of centres using cold pursuit to identify cases of ACS. The post-hospital follow-up was prospective irrespective of the initial recruitment method.

DATA ABSTRACTION

A six-page standardised case record form was developed, validated and applied for study-wide use. Information was collected on patient demographic characteristics, medical history, duration of prehospital delay from the time of onset of acute symptoms to seeking medical care, presenting symptoms, electrocardiographic findings, clinical characteristics, use of cardiac medications and interventional procedures and hospital-associated outcomes. Standardised definitions of all patient-related variables, clinical diagnoses and hospital complications and outcomes were utilised and can be found on the GRACE website at http://www.outcomes.org/grace. The study included 6-month follow-up direct contact of discharged patients from all hospitals.

DATA QUALITY, ACCURACY, VALIDATION AND COMPLETENESS

Completed case-report forms were transmitted to the international coordinating centre using a web document or facsimile (Center for Outcomes Research, University of Massachusetts Medical School Worcester, Massachusetts, USA), where they were checked and data queries generated to be resolved before processing. A clean dataset was then entered at the Center for Outcomes Research, where statistical analyses were performed. Each enrolling site received a profile of its own data as well as that of its own regional cluster and the whole study, on a quarterly basis. To facilitate communication between the study hospitals, to provide updates about the progress of the study and to enhance quality-control measures, a website for GRACE was created (http://www.outcomes.org/grace).

Data quality and consistency with actual clinical events were monitored continuously and documented. In an audit cycle, a research nurse and physician visited each study site and verified the source documentation for approximately 10% of all patients. The audit process was designed to ensure complete inclusion of patients in each monthly cycle. Less than 1% of the key baseline data (0.79% for 20 key baseline data fields) was missing and less than 1% of in-hospital key outcomes was missing (discharge status missing in 0.2%, discharge diagnosis missing in 0.4%).

The dataset used for all the GRACE publications and for the derivation and validation of the risk scores was based on the main GRACE programme. In addition, an expanded version of GRACE was developed, 'GRACE^2', but without the requirement for geographical representation within clusters and without requiring a comprehensive range of hospitals. This was in response to requests from other centres to index their data to GRACE. GRACE^2 hospitals used an abbreviated case record form.

ROLE OF THE SPONSOR

The sponsor provided an educational grant towards the study and did not participate in data collection or analysis. The design and conduct of the study and the selection of topics for analysis and publication were entirely the responsibility of the steering committee and the publications committee.

BRIEF SUMMARY AND KEY OUTCOMES

GRACE has enabled specific analyses of the characteristics, management, and outcomes of patients with an ACS, and has led to approximately 100 international publications (a detailed bibliography and additional information is available at http://www.outcomes-umassmed.org/GRACE/bibliography.cfm). Briefly, the key findings from GRACE can be summarised into four categories of analyses.

Descriptive analyses

GRACE has provided a multinational and robust reference standard for describing the characteristics, management and

outcomes of patients with acute coronary disease.[21 22] A series of additional studies described and analysed the determinants of delay in the provision of care,[23] the occurrence of specific outcome events such as bleeding,[24] heart failure,[25] shock[26] and atrial fibrillation,[27] and the specifics of certain populations (diabetes,[28] renal disease,[29] elderly,[30] peripheral arterial disease[31 32]) or presentations.[33] Description of outcomes in patients characterised using the conventional definitions versus the new, universal troponin-based definition of myocardial infarction were also important.[34]

Descriptive analyses are important, particularly when there is evidence of a major difference between participants randomised to clinical trials and patients from routine clinical practice,[35] even when the latter fit the detailed selection criteria for randomised trials.[36]

Variations in care

The GRACE analyses of the determinants of and impact on outcomes of variations in provision of care, whether related to geography,[37] availability of resources (such as intervention facilities)[38] or adherence to evidence-based guidelines,[39] are of major importance. This is particularly true when they confirm the link between evidence-based care and improved outcomes[40] or, conversely, when they allow the identification of gaps between evidence and actual practice, thereby identifying targets for improving care.

Improving quality of care

In 2002, the GRACE investigators reported that modern reperfusion strategies were not offered to about 30% of eligible patients with acute STEMI.[41] Predictors of no reperfusion such as advanced age, atypical presenting symptoms and previous coronary bypass surgery led to a refocus on missed opportunities to offer potentially life-saving coronary reperfusion rather than fuelling the worldwide debate on which form—either thrombolysis or urgent percutaneous coronary intervention (PCI)—was superior. Five years later, the GRACE investigators reported substantial improvements in reperfusion rates among eligible patients with STEMI based on efforts to mitigate deficiencies identified in the early experience.[42]

In a subsequent report, Nallamothu *et al*[43] analysed the impact of treatment delays in patients with STEMI, illustrating that delays in the provision of thrombolytic drugs had particularly negative consequences for patients. Mehta *et al*[44] provided evidence that among elderly patients with STEMI, primary PCI appears to offer better outcomes, on average, than thrombolysis. Finally, Steg *et al*[45] highlighted concerns about late (up to two years) stent thrombosis in ACS patients treated with drug-eluting stents.

In terms of improving long-term outcomes, the GRACE investigators have shown that adherence to performance measures in the use of medications, both in-hospital and at discharge, is related strongly to mortality.[40] Highest performing hospitals according to standard core measures demonstrated an average 25% reduction in mortality compared with lowest performing hospitals.

A treatment paradox was identified: in settings where routine risk stratification is not applied prospectively, lower-risk rather than higher-risk patients were more likely to receive evidence-based pharmacological and interventional therapies.[46] This work, subsequently validated in independent studies, reinforces the importance of objective risk-stratification tools.

The GRACE investigators also highlighted opportunities to improve care in special populations of ACS including those with diabetes[28] or heart failure,[47] and in women. For example, Dey *et al*[48] showed that among more than 7500 GRACE patients, women undergoing angiography were twice as likely as men (12% vs 6%; $p<0.001$) to have normal or mild disease. Further, this cohort of women was less likely to receive evidence-based medical therapy after their ACS event.

GRACE risk models: impacting on practice worldwide

The derivation and validation of the GRACE risk score and other robust multivariable models to predict important outcomes, such as death, myocardial infarction, stroke or major bleeding are key outputs from GRACE. The GRACE risk models have translated into guidance from both national and international bodies, including the European Society of Cardiology (ESC),[49] the joint guidelines from the American College of Cardiologists (ACC) and the American Heart Association,[50] the SIGN guideline[51] and, recently, the National Institute for Health and Clinical Excellence (NICE) in the UK.[52]

The GRACE risk models have changed the way we think about and treat patients with an ACS.[53–55] In 2003, Granger *et al*[53] reported a simple, eight-variable tool to predict hospital mortality in all ACS patients, based on clinical information obtained on initial clinical assessment and blood testing and electrocardiographic data (figure 1). For both the derivation and validation cohorts, the c-statistics (0.84 and 0.79, respectively) demonstrated remarkable discrimination. In 2004, Eagle *et al*[54] reported a nine-variable prediction model that estimated 6-month mortality based on clinical information available before or at the time of discharge after an ACS (figure 2). Once again the model demonstrated excellent discrimination in more than 15 000 study patients. In 2006, Fox *et al*[55] published a subsequent prediction tool that allowed estimation of a combined endpoint—myocardial infarction or death—at 6 months following discharge for an ACS based on data gathered in more than 43 000 patients.

The strength of the GRACE risk models is that they have been derived and validated in large, unselected cohorts of patients from around the world, and this explains their superior discriminatory accuracy compared with models derived in clinical trial cohorts. These risk models relate to all forms of ACS, including STEMI, non-STEMI and unstable angina, and have been tested and validated in a range of non-GRACE cohorts (table 1).[1–7 52] The GRACE risk score consistently outperformed other risk models (table 1). The GRACE models are simple to apply, irrespective of whether the electronic risk calculator (http://www.outcomes.org/grace), also available for download to a personal digital assistant or computer (figure 1), or the more traditional paper risk calculator is used. The GRACE investigators also recently updated the models to ensure accuracy based on patients treated in the current era.[56] The GRACE risk models are currently being used in hospitals around the world, and their utility in the provision of modern acute coronary care has been endorsed in guidelines put forth by the ESC,[49] the ACC/AHA[50] and NICE.[52] The NICE group systematically compared a variety of risk scores, including TIMI (Thrombolysis In Myocardial Infarction),[57] PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy),[58] GRACE,[53] PREDICT,[59] EMMACE (Evaluation of Methods and Management of Acute Coronary Events) Simple Risk Index,[60] AMIS (Acute Myocardial Infarction in Switzerland) risk score[61] and UA (unstable angina) risk score,[62] and the published evidence, and then tested the GRACE risk score (restricted to the six widely available components) against the completely unselected MINAP (Myocardial Infarction

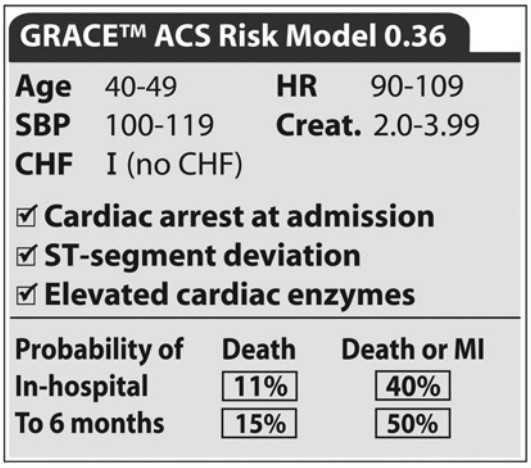

Figure 1 GRACE risk model nomogram[53] for PDA (http://www.outcomes.org/grace).

National Audit Project) dataset of all patients (n=75 627) admitted to all hospitals in England and Wales over a two-year period.[63] The model performed extremely well and NICE therefore proposed that the GRACE risk score (or other scoring system) should be applied as soon as the patient presents.[52]

Risk models are also important in clinical practice because even powerful and discriminative biomarkers such as troponins cannot predict accurately individual risk in ACS.[64] In addition to the widely used risk calculators for mortality and myocardial infarction, the GRACE investigators created and tested a multivariable model to predict in-hospital major bleeding,[24] one for predicting stroke in ACS,[65] and one to predict the risk of coronary artery bypass graft surgery.[66] Finally, GRACE has allowed us to model 'low risk',[67] and even to build a model to predict freedom from adverse clinical events in ACS.[68]

Time trends: a decade of change in ACS care

Over the decade of data collection in GRACE, large numbers of patients were recruited each year. Thus, GRACE provides a unique perspective on how ACS care and outcomes have evolved between 1999 and 2009. As both timely reperfusion and more systematic use of evidence-based therapies have been embraced,[42] both the observed and risk-adjusted in-patient mortality have fallen.[69] However, 'gaps' between evidence and care remain.[42] In short, GRACE has shown that, 'we're getting better, but we've still room for improvement.'

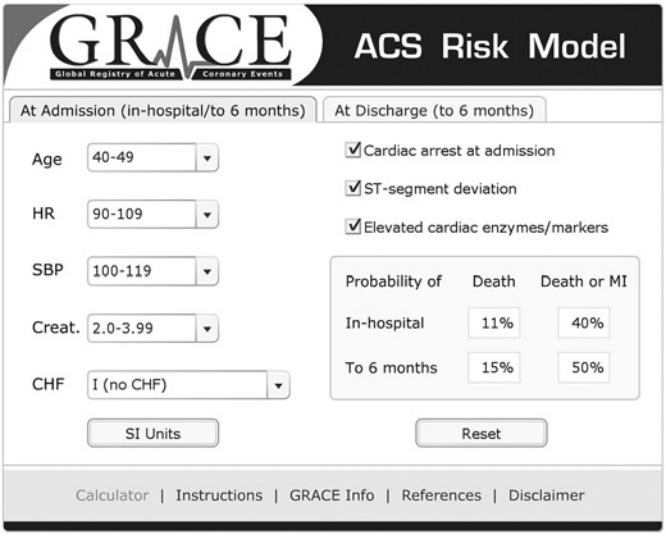

Figure 2 GRACE electronic risk calculator for all-cause mortality from discharge to 6 months (http://www.outcomes.org/grace).

Strengths and limitations

GRACE was designed to reflect the diversity of the ACS population rather than practice in specific geographical locations.

Strengths of GRACE

- Large multinational registry (Main GRACE: 123 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand)
- Full spectrum of hospitals admitting patients with ACS
- Decade-long study providing temporal trends
- Independently defined prospective criteria for diagnosis of ACS and outcome events (not dependent on local interpretations)
- Recruitment method designed to avoid selection bias (first 10-20 patients at each hospital "tracked" from first presentation, irrespective of hospital location). This was designed to avoid "recruitment fatigue", which may influence a continuous recruitment strategy
- All sites: on-site training, quality control and audit (10% of case records). Plus central audit and quality control.
- Funded GRACE study nurse for each cluster of hospitals
- Study designed and conducted by an independent steering committee. Data collection and analysis by an independent group with expertise in outcomes research (University of Massachusetts Center for Outcomes Research)
- In-hospital and 6-month outcomes with individual patient follow-up (not dependent on hospital records)

Limitations of GRACE

- Unbiased method of patient sampling, but this involves clusters of hospitals in specific regions rather than all hospitals in a country
- Although the participating sites were designed to reflect the full spectrum of hospitals admitting patients with ACS, this was not a random sample
- In keeping with other trials and registries, detection of re-myocardial infarction, especially early after initial presentation, may be underestimated
- Approximately 85% follow-up completeness of all patients at 6 months
- The timing of in-hospital events is recorded but post-discharge events may only be detected at the time of patient review
- In keeping with other observational studies, unmeasured variables may impact upon outcomes, and registries are not the appropriate method for resolving whether one treatment strategy is better than another.
- The study reflects practice and outcomes but does not replace the need for randomised trials.

CONCLUSIONS

The GRACE programme (including expanded GRACE, or GRACE[2]) involves 247 hospitals, 102 341 patients and 30 countries, and the work of many investigators and study coordinators. It is the largest multinational observational cohort study to include the complete spectrum of patients with an ACS. The study has defined the characteristics and outcome of patients with ACS and has identified opportunities to improve care. By providing an international reference of management and

outcome, the programme has enabled participants to index local care to regional, national and international data. As demonstrated in the GRACE publications, the "gap" between evidence and practice is narrowing and outcomes are improving, but much remains to be done. The registry has fuelled a growing international resolve to measure care in a manner that continues to inform practice. Approximately 100 peer-reviewed publications have provided a robust and accessible data resource, and the GRACE risk score calculator is freely available and is recommended in international guidelines. What has GRACE taught us? *To measure, to challenge, to change, to learn*. The programme provides insights that can only be tested in randomised trials and hence it is neither a competitor nor a replacement for randomised trials. Trials test hypotheses in defined populations; registries provide a real-world perspective on clinical practice. The combination of highly organised clinical trials and rigorous registries has led to a decade of unprecedented progress in understanding the clinical diversity of ACS and in improving outcomes.

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Competing interests Grants and honoraria from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline and Lilly.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of each institution, as necessary.

Provenance and peer review Commissioned; externally peer reviewed.

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