Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK–Belgian Study)

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Aim
To define the long-term outcome of patients presenting with acute coronary syndrome [ST-segment elevation myocardial infarction (STEMI), and non-STEMI and unstable angina acute coronary syndrome (ACS) without biomarker elevation] and to test the hypothesis that the GRACE (Global Registry of Acute Coronary Events) risk score predicts mortality and death/MI at 5 years.

Methods and results
In the GRACE long-term study, UK and Belgian centres prospectively recruited and followed ACS patients for a median of 5 years (1797 days). Primary outcome events: deaths, cardiovascular deaths (CVDs) and MIs. Secondary events: stroke and re-hospitalization for ACS. There were 736 deaths, 19.8% (482 CVDs, 13%) and 347 (9.3%) MIs (24 h), 261 strokes (7.7%), and 452 (17%) subsequent revascularizations. Rehospitalization was common: average 1.6 per patient; 31.2% had >1 admission, 9.2% had 5+ admissions. These events were despite high rates of guideline indicated therapies. The GRACE score was highly predictive of all-cause death, CVD, and CVD/MI at 5 years (death: $\chi^2$ likelihood ratio 632; Wald 709.9, $P < 0.0001$, C-statistic 0.77; for CVD C-statistic 0.75, $P < 0.0001$; CVD/MI C-statistic 0.70, $P < 0.0001$). Compared with the low-risk GRACE stratum (ESC Guideline criteria), those with intermediate [hazard ratio (HR) 2.14, 95% CI 1.63, 2.81] and those with high-risk (HR 6.36, 95% CI 4.95, 8.16) had two- and six-fold higher risk of later death (Cox proportional hazard). A landmark analysis after 6 months confirmed that the GRACE score predicted long-term death ($\chi^2$ likelihood ratio 265.4; Wald 289.5, $P < 0.0001$). Although in-hospital rates of death and MI are higher following STEMI, the cumulative rates of death (and CVD) were not different, by class of ACS, over the duration of follow-up (Wilcoxon $= 1.5597$, df $= 1$, $P = 0.21$). At 5 years after STEMI 269/1403 (19%) died; after non-STEMI 262/1170 (22%) after unstable angina (UA) 149/850 (17%). Two-thirds (68%) of STEMI deaths occurred after initial hospital discharge, but this was 86% for non-STEMI and 97% for UA.

Conclusion
The GRACE risk score predicts early and 5 year death and CVD/MI. Five year morbidity and mortality are as high in patients following non-ST MI and UA as seen following STEMI. Their morbidity burden is high (MI, stroke, readmissions) and the substantial late mortality in non-STE ACS is under-recognized. The findings highlight the importance of pursuing novel approaches to diminish long-term risk.

Keywords
Acute coronary syndrome • Acute coronary disease management • Outcomes • Myocardial infarction • Non-ST elevation myocardial infarction • Unstable angina

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Introduction

Although the early risks of death and re-infarction have been well-characterized following presentation with acute coronary syndrome (ACS), the late consequences remain poorly defined and based on only small cohorts of patients. In an observational study from Denmark of 654 patients (1999–01), 1 year mortality was 31% in non-ST elevation myocardial infarction (MI) and 21% in ST elevation MI. In contrast, in the Prospective Registry of Acute Ischaemic Syndromes recruited in 1998–99 in the UK (653 patients with non-ST elevation ACS) mortality at 1 year was 10% and at 45 months 22%. Thus, there is considerable uncertainty about the extent of long-term risks of death and other cardiovascular outcome events, especially in the context of more contemporary acute therapy and secondary prevention.

Large-scale observational studies have defined in-hospital and post-discharge outcomes for those presenting with ACSs, but these outcomes are mainly limited to the weeks or months following discharge. Why is longer term outcome important? From the large multinational GRACE (Global Registry of Acute Coronary Events) study our group demonstrated that even having the GRACE risk score was developed and validated for patients with ACS. As part of this programme, the large-scale multinational observational GRACE registry (1999–09) was established to provide reliable and precisely defined data on the treatment, practise patterns, and outcomes of patients with ACS. As part of this programme, the GRACE risk score was developed and validated for patients with ACS, with the aim of guiding the triage and early management of ACS. Guidelines, including the ESC guidelines, the ACC/AHA guidelines and NICE guidelines, recommend the use of such scores in the management of non-ST elevation ACS.

The hypothesis on which we based the present study was that long-term (5 year) outcome can be predicted with similar predictive accuracy to short-term outcome, based on presentation characteristics. To test this hypothesis we used the GRACE cohorts from the UK and Belgium for a median follow-up of survivors of 1797 days.

Methods

Study population

Full details of the GRACE protocol have been published elsewhere. GRACE was designed to enrol an unselected population of patients with ACS, irrespective of geographical region.

Eligible patients were adults (≥18 years old) admitted to participating hospitals with a presumptive diagnosis of ACS and a clinical history of ACS accompanied by at least one of the following: electrocardiographic changes consistent with ACS, serial increases in levels of biochemical markers of cardiac necrosis (troponin or creatine kinase MB fraction, creatine phosphokinase), and documented coronary artery disease (i.e. history of MI, congestive heart failure believed to be due to ischaemia or resuscitated sudden cardiac death; history of, or new, positive stress test or angina, with or without imaging; prior or new cardiac catheterization documenting coronary artery disease, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery). Patients with a non-cardiovascular cause for the clinical presentation, such as trauma, surgery, or aortic aneurysm, were excluded. To determine the occurrence of subsequent MI and death patients were followed up at ∼6 months and at a median of 5 years and up to 10 years. Follow-up to 5 years was only performed in the UK and Belgian cohorts of the GRACE study. Record linkage was performed in the UK population and all patients with the exception of four were successfully linked (99.8%). The main aim of record linkage is to provide a mechanism which links all of an individual’s records together into one dataset by using probability matching. Thus, by permanently grouping an individual’s records any enquiry made regarding an individual’s medical history can be carried out with maximum efficiency. In Scotland, records are linked from the SMR 1 (Scottish Morbidity Record No.1) which is a discharge data collection scheme initiated in 1961. The SMR 1 scheme collects administrative details, diagnostic/operation details (diseases coded using the WHO International Classification of Diseases 10, operations performed), and geographical details (postcode, local government district, health board). An SMR 1 is generated every time a patient is discharged or transferred from a general hospital in Scotland. This main database is also linked to the Register for Death Records. Linkage is dependent on the subject’s name, date of birth, gender, post code of home address, and Community Health Index (CHI) number. These variables are matched with the SMR 1 records and death records to link records for each individual patient. All Belgian patients were followed up by trained study coordinators at 6 months, 2 years and up to 5 years following admission. Methods of follow-up involved one or more of the following: use of hospital records, hospital visits, phone call to the patient’s general physician, and/or phone call to the patient.

Study investigators received approval from their local hospital ethics or institutional review board for the conduct of this study and all patients in the UK and Belgian cohorts signed informed consent. Additional permission was sought to perform the record linkage from the Privacy Advisory Committee attached to the Information Services Division for NHS National Services Scotland.

The study was designed to ensure enrolment of an unselected ACS population, and the UK and Belgian sites prospectively recruited the first 10–20 consecutive eligible patients each month (UK, n = 2065; Belgium, n = 1656). Data were collected by trained study coordinators on standard case report forms and regular audits were performed at all participating hospitals. Demographic characteristics, medical history, presenting symptoms, duration of pre-hospital delay, biochemical and electrocardiographic findings, treatment practises, and a variety of hospital outcome data were collected. Standard definitions of all patient-related variables, clinical diagnoses, and hospital complications and outcomes were used. All cases were assigned (at discharge) to one of the following categories: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (non-STEMI), and ACS without infarction, UA.
Diagnosis and clinical outcomes

Primary outcome events were cardiovascular deaths (CVDs) or MIs and secondary events included re-hospitalization for ACS. A diagnosis of STEMI was made if a new (or presumed new) ST-segment elevation $>1$ mm in any location was seen, or if a new (or presumed new) left-bundle-branch block was identified on the index or a subsequent electrocardiogram, with at least one positive cardiac biochemical marker of necrosis raised above the diagnostic threshold for infarction. Patients were diagnosed as having non-STEMI if the marker of necrosis was raised without ST-segment elevation on the index or a subsequent electrocardiogram. Deaths were recorded during the index period (0–6 days) and subsequently ($\sim$5 year follow-up) was determined and GRACE risk scores were calculated based upon presentation characteristics. The events analysed were death (all deaths and CVDs) MI (or re-infarction) and stroke.

Statistical analysis

Baseline characteristics are summarized as frequencies and percentages for categorical data and as medians and 25th and 75th percentiles for continuous variables. Kaplan–Meier curves reflect the cumulative unadjusted mortality.

Unadjusted rates (hazards) were calculated for different outcomes using the life-table method. The univariate models consisted of baseline characteristics from the GRACE in-hospital risk model for death and for death or MI (age, Killip class, creatinine, positive cardiac markers, ST-deviation, cardiac arrest, systolic blood pressure, peripheral vascular disease, and pulse rate), and the ACS category.

Cox proportional hazards analysis was used to determine if GRACE score was predictive of death or death/MI within 5 years of the index admission. Patients in each group were divided into three predefined categories, consistent with the ESC Guideline of risk scores: from low to highest ($<108, 109–140, >140$). Where GRACE was treated as a continuous variable the result shows the change in odds ratio per unit increase. However, when treated as a categorical variable, the odds ratios presented are the odds of each category compared with the reference category, in this case this means the odds of intermediate risk compared with low-risk and high-risk compared with low-risk. All statistical analyses were performed with SAS software 9.1. Statistical significance was set at $P < 0.05$.

Results

Study population

Patients were prospectively recruited in centres in the UK ($n = 2065$) and Belgium ($n = 1656$) as part of the multinational GRACE programme. The demographic data and prior history are shown in Table 1 for the combined cohorts, by category of ACS. The rate of PCI during initial hospitalization and the secondary prevention medications at discharge are given in Figure 2A and medication at 6 months of follow-up is given in Figure 2B (total cohort). The median duration of follow-up was 1570 days for all patients (inter quartile range Q1 843, Q3 1989). Excluding those who died during follow-up, the median duration was 1797 days (inter quartile range Q1 1117, Q3 2248; UK cohort median 1903 days, Belgian cohort median 1602 days). The demographics and the frequency of prior risk factors are similar to those published in earlier reports from the GRACE programme. The median GRACE risk score for death and for death/MI was...
calculated for each cohort (UK death/MI score 177.0, Belgium death/MI score 165.5) and for the overall population (death score 134.6, death/MI score 171.4). The UK population had a higher risk of death and of death or MI (GRACE Risk Scores) than the Belgian population and higher rates of death and death/MI were observed [total deaths in the UK cohort 428/2065 (21%), Belgian cohort 308/1656 (19%); death/MI UK cohort 567/2065 (27%), Belgian cohort 362/1656 (22%)].

**Primary results**

By 5 years of follow-up, there were 736 deaths, from any cause, and of these, 269 occurred in patients presenting with STEMI, 262 in those presenting with non-STEMI, and 149 in those presenting with UA (Tables 2–4). Despite fulfilling the inclusion criteria for ACS, 135 patients had other cardiac, but non-ACS discharge diagnoses (30 died by 5 years) and 163 had non-cardiac discharge diagnoses (27 died by 5 years). Two-thirds of all deaths were classified as cardiovascular (65%, 482/736). Less than a fifth of all deaths occurred during the initial hospitalization (17%, 129/736 deaths).

**Outcomes by category of ACS (death)**

A similar proportion of each category of ACS patients died by 5 years of follow-up (STEMI, $n = 269/1403$, 19%; Non-STEMI, $n = 262/1170$, 22%; UA, $n = 149/850$, 18%). The respective figures for CVDs by 5 years were: STEMI 181 CVDs (13%); non-STEMI 165 (14%); UA 90 (11%).

### Table 2 Total cohort ($n = 3721$) distribution of death from index and up to 5 years post-index hospitalization by index ACS diagnosis

<table>
<thead>
<tr>
<th>Total $n = 3721$</th>
<th>5 Year total no. deaths, $n = 736$ (20%)</th>
<th>Index death, $n = 129$ (3%)</th>
<th>Index cardiovascular death, $n = 114$ (3%)</th>
<th>Post-discharge death, $n = 607$ (16%)</th>
<th>Post-discharge cardiovascular death, $n = 368$ (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (1403)</td>
<td>269 (19%)</td>
<td>88 (6%)</td>
<td>78 (6%)</td>
<td>184 (13%)</td>
<td>103 (7%)</td>
</tr>
<tr>
<td>Non-STEMI (1170)</td>
<td>262 (22%)</td>
<td>36 (3%)</td>
<td>28 (2%)</td>
<td>226 (19%)</td>
<td>137 (13%)</td>
</tr>
<tr>
<td>UA (850)</td>
<td>149 (18%)</td>
<td>4 (1%)</td>
<td>6 (1%)</td>
<td>145 (17%)</td>
<td>84 (10%)</td>
</tr>
<tr>
<td>Other cardiac (135)</td>
<td>30 (22%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
<td>27 (20%)</td>
<td>19 (14%)</td>
</tr>
<tr>
<td>Non-cardiac (163)</td>
<td>27 (17%)</td>
<td>3 (2%)</td>
<td>2 (1%)</td>
<td>25 (15%)</td>
<td>15 (9%)</td>
</tr>
</tbody>
</table>

### Table 3 UK cohort ($n = 2065$) distribution of death from index and up to 5 years post-index hospitalization by index ACS diagnosis

<table>
<thead>
<tr>
<th>UK $n = 2065$</th>
<th>5 Year total no. deaths, $n = 428$ (21%)</th>
<th>Index death, $n = 62$ (3%)</th>
<th>Index cardiovascular death, $n = 62$ (3%)</th>
<th>Post-discharge death, $n = 366$ (18%)</th>
<th>Post-discharge cardiovascular death, $n = 251$ (12%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (663)</td>
<td>143 (22%)</td>
<td>44 (7%)</td>
<td>44 (7%)</td>
<td>98 (15%)</td>
<td>67 (10%)</td>
</tr>
<tr>
<td>Non-STEMI (600)</td>
<td>131 (22%)</td>
<td>14 (2%)</td>
<td>14 (2%)</td>
<td>117 (20%)</td>
<td>86 (14%)</td>
</tr>
<tr>
<td>UA (615)</td>
<td>123 (20%)</td>
<td>3 (0%)</td>
<td>3 (0%)</td>
<td>120 (20%)</td>
<td>76 (12%)</td>
</tr>
<tr>
<td>Other cardiac (60)</td>
<td>16 (27%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>16 (27%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Non-cardiac (127)</td>
<td>16 (13%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>15 (12%)</td>
<td>11 (9%)</td>
</tr>
</tbody>
</table>

### Table 4 Belgian cohort ($n = 1656$) distribution of death from index and up to 5 years post-index hospitalization by index ACS diagnosis

<table>
<thead>
<tr>
<th>Belgium $n = 1656$</th>
<th>5 Year total no. deaths, $n = 308$ (19%)</th>
<th>Index death, $n = 67$ (4%)</th>
<th>Index cardiovascular death, $n = 52$ (3%)</th>
<th>Post-discharge death, $n = 241$ (15%)</th>
<th>Post-discharge cardiovascular death, $n = 117$ (7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (740)</td>
<td>126 (17%)</td>
<td>40 (5%)</td>
<td>34 (5%)</td>
<td>86 (12%)</td>
<td>36 (5%)</td>
</tr>
<tr>
<td>Non-STEMI (570)</td>
<td>131 (22%)</td>
<td>22 (4%)</td>
<td>14 (2%)</td>
<td>109 (19%)</td>
<td>61 (11%)</td>
</tr>
<tr>
<td>UA (235)</td>
<td>26 (11%)</td>
<td>1 (0%)</td>
<td>0 (0%)</td>
<td>25 (11%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Other cardiac (75)</td>
<td>14 (19%)</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
<td>11 (15%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Non-cardiac (36)</td>
<td>11 (31%)</td>
<td>2 (2%)</td>
<td>1 (3%)</td>
<td>10 (28%)</td>
<td>4 (11%)</td>
</tr>
</tbody>
</table>
Irrespective of ACS category, the majority of all deaths occurred after hospital discharge (184/272, 68% for STEMI; 226/262, 86% for non-STEMI; 145/149, 97% for UA). However, the distribution of CVDs differed by ACS category (interaction term \(P = 0.0016\)). Almost half (43%) of all CVDs in those presenting with ST-elevation MI occurred during the index hospitalization (78/181 CVDs by 5 years of follow-up; Tables 2–4). Approximately a sixth (15%) of the CVDs in those presenting with non-STEMI occurred in hospital (28/165 CVDs). For UA very few of the CVDs occurred in hospital (6/90 CVDs). Thus, for non-STEMI and UA the great majority of all CVDs occurred after discharge from the initial hospitalization.

Subsequent myocardial infarction, stroke, and hospitalization for unstable angina (UK cohort)

The record linkage programme in the UK allowed analysis of all recurrent infarctions and hospitalizations for ACS and strokes. All patients in the UK cohort except four (99.8%) were successfully linked for long-term follow-up (see Methods).

There were 320 MIs in the period from 24 h after the index event to 5 years follow-up (320/2065 UK cohort). About 12.7% of patients (263/2065) experienced one or more MIs. Of these, 38 experienced two or more infarctions, 14 experienced three or more infarctions, and 5 experienced four or more (Figure 1).

There were 261 strokes in the period up to 5 years of follow-up. About 7.7% (159/2065) of the ACS population sustained one or more strokes during follow-up. Of these, 55 sustained two or more strokes, 22 sustained three or more strokes, and 12 patients experienced four or more strokes (Figure 1).

There were 261 strokes in the period up to 5 years of follow-up. About 7.7% (159/2065) of the ACS population sustained one or more strokes during follow-up. Of these, 55 sustained two or more strokes, 22 sustained three or more strokes, and 12 patients experienced four or more strokes (Figure 1).

Revascularization (percutaneous coronary intervention and coronary artery bypass grafting)

For the combined dataset (\(n = 3721\) patients), there were 2220 PCIs and 402 CABGs; of these 511 PCIs and 326 CABGs were performed after the first 6 days. Information on repeat revascularizations was available from the UK cohort (\(n = 2065\)); there were 393 PCIs in 292 patients and 169 CABG in 169 patients after the first 6 days. Some patients had more than one revascularization (Figure 1).

Secondary prevention therapies

The deaths, MIs, and strokes during follow-up occurred despite relatively high rates of guideline-indicated therapies on discharge from hospital (consistent with contemporaneous guidelines;
A relatively high proportion of ACS patients were maintained on secondary prevention therapy at 6 months of follow-up (total cohort, Figure 2B). During the initial hospitalization, 68.9% of STEMI underwent PCI. For those alive at follow-up, 83% of STEMI, 80% of non-STEMI, and 79% of UA were still on aspirin. The corresponding figures for beta-blocker were 77, 71, 64%; ACE inhibitor/ARB, 77, 63, 50%; statin, 66, 71, 71%. Thus, relatively similar proportions of patients were maintained on secondary prevention therapies, irrespective of ACS category (Figure 2B). In contrast, approximately half of those with ‘other cardiac’ diagnoses and less than a third of those with ‘non-cardiac’ discharge diagnoses were maintained on secondary prevention therapy at 6 months follow-up (data not shown).

Grace score and long-term outcome

Using Cox proportional hazards analysis, the GRACE score was highly predictive of death or death/MI within 5 years of the index admission. For all deaths: \( \chi^2 \) likelihood ratio 632.0, Wald 709.9, \( P < 0.0001 \). For death or MI: \( \chi^2 \) likelihood ratio 321.1; Wald 340.4, \( P < 0.0001 \). Compared with the low-risk GRACE stratum, those with intermediate [hazard ratio (HR) 2.14, 95% CI 1.63–2.81] and those with high-risk (HR 6.36, 95% CI 4.95, 8.16) had a substantially higher risk of later death (Figure 3). Similarly, the GRACE score was highly predictive of death or MI (Table 5) and of CVD/MI (\( P < 0.0001 \)).

The GRACE score was similarly powerful in predicting CVDs both for the in-hospital phase and at 5 years follow-up. For CVDs in hospital \( \chi^2 \) likelihood ratio was 230.1, Wald, 181.4, \( P < 0.0001 \), and C-statistic, 0.88. The respective figures for CVDs up to 5 years also showed high predictive accuracy (\( \chi^2 \) likelihood ratio 353.0, Wald 279.4, \( P < 0.0001 \), C-statistic 0.75).

Similarly, the GRACE score showed good predictive accuracy for the combined endpoint of CVD or MI in hospital (\( \chi^2 \) likelihood ratio 219.2, Wald 85.2, \( P < 0.0001 \), C-statistic 0.86) and the same combined endpoint at 5 years (\( \chi^2 \) likelihood ratio 477.1, Wald 214.7, \( P < 0.0001 \), C-statistic 0.68). There were consistent findings in both UK and Belgian cohorts; the GRACE risk score was associated with late death and death/MI. When considering the STEMI or the non-STEMI/UA cohorts separately, the GRACE score showed consistent and high predictive accuracy (Table 6).

The Kaplan–Meier plot (Figure 4) demonstrates the cumulative rates of late events following presentation with ST elevation or non-ST elevation MI/UA. There was no evidence for a difference in all-cause death over the duration of follow-up (HR 1.026, 95% CI 0.89, 1.18). Similarly, using the Wilcoxon test there was no evidence for a difference in survival (Wilcoxon = 1.5597, df = 1, \( P = 0.21 \)).

Although in-hospital rates of death and MI are higher following ST elevation MI, the rate of CVD or MI is higher following discharge after non-ST elevation ACS. This is despite the impact of ST elevation MI on myocardial function, heart failure, and arrhythmias. For those presenting with non-ST elevation MI, the
post-discharge rate of CVD or MI within 5 years was 31.2%, for ST elevation MI it was 27.2%, and for UA without biomarker elevation it was 23.7%.

To determine whether the findings were mainly a reflection of events in the first 6 months after presentation, a landmark analysis was conducted for those surviving 6 months (182 days). The results (Figure 5) confirm that even having excluded events in the first 6 months after initial presentation, the GRACE risk score predicts late death ($\chi^2$ likelihood ratio 265.4, Wald 289.5, $P < 0.0001$).

**Discussion**

This long-term prospective registry study demonstrates very similar outcomes in the two country cohorts, from the UK and Belgium. During the initial in-hospital phase, 3% of the UK and 4% of the Belgian cohorts died and during follow-up to 5 years 18% (UK) and 15% (Belgium) died. The consistency of the overall data for all deaths and for CVDs provides evidence that the findings are not restricted to clinical practise in a particular country. Having adjusted for baseline risk, the outcomes in the two country cohorts were not different. In addition, the baseline characteristics from the ACS population are very similar to those reported previously from the overall multinational GRACE registry (the overall programme was limited to in-hospital and 6 month outcomes).12,18

The key findings of this study demonstrate that the late consequences of presentation with ACS, in terms of death, MI, and stroke are substantially greater than those seen during the initial in-hospital phase. There were almost five-fold more deaths during follow-up than in the initial in-hospital admission with ACS (607 vs. 129). Similarly, there were three-fold more CVDs (368 vs.
The follow-up was also complicated by 18.2% experiencing one or more MIs and for 12.9% one or more strokes. The category of ACS influenced the distribution of subsequent deaths, but by 5 years there were remarkably similar rates of total mortality (19–22% mortality). Compared with STEMI, for those presenting with non-STEMI or UA far more of the deaths occurred during follow-up than during the initial hospital phase. This study has revealed a large morbidity and resource burden of recurrent admissions for suspected ACS (about 1.6 admissions per patient), although <10% of these admissions was associated with MI.

Current guidelines for ACS focus mainly on management during the in-hospital phase and evidence supports the impact of therapies on the decline in acute complications of ACS. However, this study has revealed the morbidity and mortality burden of late complications despite higher use of secondary prevention measures than seen in other published registries and surveys (EuroAspire Survey and EHS II).

Although acute markers of ischaemia on the electrocardiogram and markers of myocyte necrosis (e.g. troponin) are helpful in guiding management of ACS they do not predict the risk of late complications; those with ST elevation and non-ST elevation MI and those with UA (without biomarker elevation) had similar late mortality. The GRACE risk score was derived and validated for in-hospital and 6 month outcomes and this study shows that it has similarly high predictive accuracy for long-term outcomes. Further, the landmark analysis shows that the predictive accuracy of the GRACE score is maintained even excluding those dying in the first 6 months. The accuracy for predicting long-term death (C-statistic 0.74) is better than for prediction of recurrent MI (C-statistic 0.66), and more work needs to be done to improve identification of those at particular risk of recurrent MI. The challenge for the clinician, based on these findings, is to improve the long-term management of ACS and to recognize the extent of future risks, especially among ACS patients who did not present initially with ST elevation.

Strengths and limitations

GRACE was designed to recruit an unselected cohort of patients presenting to the hospital with features of ACS. The UK and
Belgian cohorts of patients reflect the spectrum of ACS within the geographic catchment regions presenting to the participating hospitals but they are not intended to reflect the entire populations for the respective countries. Nevertheless, the consistency of the findings in two contemporaneous populations of patients with ACS suggests that the findings are not specific to one or other cohort.

The GRACE risk score was derived to provide an accurate method of identifying those at higher risk of subsequent events. The score has been validated in independent large populations.7,14,15 Additional risk factors will contribute to long-term risk, including clinical management after discharge, but these are beyond the scope of this report.

Conclusions

The late consequences of presentation with ACS demonstrate a substantially higher frequency of subsequent CVD and subsequent MI (each three to four-fold higher) than seen in the index hospitalization. The greatest absolute risk from discharge to long-term follow-up is among those with non-ST elevation ACS at index presentation. These outcomes are seen despite high compliance with secondary prevention and guideline indicated therapies. The GRACE risk score demonstrates similar predictive accuracy for the in-hospital phase and long-term follow-up. The findings highlight the importance of improving the accuracy with which clinicians can identify those at particular risk of cardiovascular complications, including MI, and pursuing novel therapies to diminish long-term risk.

Acknowledgments

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Conflict of interest: none declared.

References


