Contemporary outcomes of urgent coronary artery bypass graft surgery following non-ST elevation myocardial infarction: urgent coronary artery bypass graft surgery consistently outperforms Global Registry of Acute Coronary Events predicted survival†

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Abstract

OBJECTIVES: The Global Registry of Acute Coronary Events (GRACE) registry reported that the in-hospital risk of death from non-ST elevation myocardial infarction (NSTEMI) is 5%, with an 11% mortality by 6 months. Prospective Registry of Acute Ischaemic Syndromes in the UK demonstrated that the overall risk of death from NSTEMI over 4 years is 25%. In GRACE, while 28% of patients received percutaneous intervention, only 10% received coronary artery bypass graft (CABG). Results of urgent CABG surgery following NSTEMI are difficult to interpret as these often include patients who have had STEMIs and urgent surgery. With increasing multidisciplinary assessment of patients with acute coronary syndromes (ACS), accurate data collection on the outcome of such patients could inform correct revascularization strategy.

METHODS: Three hundred and forty-two consecutive patients who had undergone urgent CABG from April 2004 to April 2009 at a single institution were identified. The GRACE predicted mortality was calculated from hospital records and patients categorized into three groups based upon their predicted risk. Late survival data were obtained from the UK Office of National Statistics.

RESULTS: The GRACE score could be calculated in 270 patients with a confirmed diagnosis of NSTEMI. Of the 304 probable patients with NSTEMI, there were 5 in-hospital deaths (1.6%). Survival at 6 months was higher than GRACE predicted mortality in all groups. At 6 months the predicted versus observed mortality in the low-risk group was 4 versus 2% (P = 0.05), in the medium-risk group it was 12.5 versus 1.9% (P = 0.0001) and in the high-risk group it was 25 versus 20% (P = 0.45).

CONCLUSIONS: In-hospital CABG performed after NSTEMI is associated with a low-mortality risk and survival significantly better than that predicted by the GRACE score.

Keywords: GRACE • NSTEMI • Urgent CABG • Cardiac surgery

INTRODUCTION

The Global Registry of Acute Coronary Events (GRACE) study was a collaboration between 94 hospitals in 14 countries to describe the epidemiology, management, in-hospital and late follow-up of the entire spectrum of acute coronary syndromes (ACSs) [1]. In the GRACE registry, 25% of patients enrolled were diagnosed with a non-ST elevation-ACS (NSTEMI) defined as the presence of ≥1 positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index ECG. Fifty-three per cent of patients with NSTEMI underwent in-hospital angiography, with 28% undergoing percutaneous intervention (PCI) (87% receiving >1 bare metal stent) and 10% undergoing in-hospital coronary artery bypass grafting (CABG). The in-hospital mortality of patients admitted with NSTEMI was 5% with an additional 2% suffering re-infarction, 6% acute renal failure and 5% a major bleeding complication. Further information on the 10% of patients undergoing CABG has not been published.

The GRACE risk score is a simple bedside tool designed to predict the in-hospital and also the 6-month outcome for patients admitted with ACS, with the intention of guiding the appropriate treatment algorithm [2]. It was developed using the

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follow-up cohort of 21,688 patients. The score was further validated for patients with NSTEMI-ACS for in-hospital deaths [3] and death at 6 months post discharge [2, 4].

The recent guidelines for the treatment of patients with a diagnosis of ACS recommend the GRACE score as a tool to aid the decision-making process [5, 6]. The aim of our study was to compare the outcomes of patients undergoing urgent CABG following NSTEMI with the GRACE predicted in-hospital and 6-month survival.

**MATERIALS AND METHODS**

Three hundred forty-two consecutive patients who underwent urgent CABG following NSTEMI between April 2004 and April 2009 were identified from the departmental Patient Administration and Tracking System (PATS) database, which contains prospectively collected data on these patients. Retrospective analysis of case notes by the study investigators was then performed to confirm a diagnosis of NSTEMI according to the ESC guidelines [7]. All patients who met this criterion had their GRACE score and GRACE predicted percentage risk calculated for death in hospital and death at 6 months, using standardized GRACE risk models (available at http://www.outcomes-umassmed.org/grace/). Late outcomes data were obtained from Central Cardiac Audit Database (CCAD) and the NHS Healthcare Commissioning Services (HCS) through the Quality and Outcomes Research Unit (QuORU), and was available on 100% of patients. Patients were tracked for subsequent hospital admission using the Hospital Episode Statistics data, which tracks all hospital activity in England. This study was authorized by University Hospital Birmingham Research and Development (CA2/02826/09).

Based on the GRACE predicted percentage risk of death at 6 months, patients were divided into three arbitrary risk groups. Group 1 consisting of patients with low GRACE risk of mortality (<10%), Group 2 with intermediate risk of death (10–19%) and Group 3 with a high risk (≥20%). Baseline patient demographics are shown in Table 1.

**Surgical technique**

All patients identified in this study had CABG within the same hospital admission for their ACS. All surgery was performed after 24 h but within 30 days of the index hospital admission. The median length of time from presentation to surgery was 7 days (IQR: 3–16). Aspirin was continued up to the day prior to surgery in all patients but clopidogrel was stopped at least 5 days prior to surgery. An intra-aortic balloon pump was used pre-operatively in patients with on-going symptoms of angina or those with severe left main stem disease at the discretion of the operating team. All surgery was performed using cardiopulmonary bypass with myocardial protection via intermittent antegrade warm or cold blood cardioplegia at the choice of the operating surgeon. Anaesthetic and post-operative management was conducted according to the departmental protocols.

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**Table 1: Pre-operative demographics**

| Variable                        | Group 1          | Group 2          | Group 3          | P-value |
|---------------------------------|------------------|------------------|------------------|---------|
| n                               | 203              | 52               | 15               |         |
| Age (median ± IQR)              | 62 (58–68)       | 72 (67–74)       | 74.5 (70–79)     | 0.001   |
| Gender (male %)                 | 164 (81)         | 37 (71.2)        | 11 (73.3)        | 0.78    |
| CCS (%)                         |                  |                  |                  |         |
| Class I                         | 6 (2.9)          | 3 (57.7)         | 0                | 0.67    |
| Class II                        | 16 (7.9)         | 2 (3.8)          | 0                |         |
| Class III                       | 47 (23.2)        | 8 (15.4)         | 5 (33.3)         |         |
| Class IV                        | 134 (66)         | 39 (75)          | 10 (66.7)        |         |
| NYHA (%)                        |                  |                  |                  |         |
| Class I                         | 57 (28)          | 10 (19.2)        | 3 (20)           | 0.62    |
| Class II                        | 133 (65.5)       | 34 (65.4)        | 12 (80)          |         |
| Class III                       | 10 (4.9)         | 5 (9.6)          | 0                |         |
| Class IV                        | 3 (1.5)          | 3 (57.7)         | 0                |         |
| Previous MI (%)                 | 35 (17.2)        | 14 (26.9)        | 4 (26.6)         | 0.05    |
| Diabetes (%)                    | 55 (27.1)        | 15 (28.8)        | 4 (26.6)         | 0.89    |
| Renal failure (Cr >200) (%)     | 1 (0.5)          | 0                | 0                | 0.93    |
| COPD/asthma (%)                 | 26 (12.8)        | 10 (19.2)        | 4 (26.6)         | 0.03    |
| Triple vessel disease (%)       | 17 (87.2)        | 49 (94.2)        | 13 (86.7)        | 0.93    |
| LMS disease (%)                 | 85 (41.9)        | 32 (61.5)        | 8 (53.3)         | 0.06    |
| Ejection fraction               |                  |                  |                  |         |
| Poor (<30%)                     | 11 (5.4)         | 5 (9.6)          | 0                | 0.89    |
| Moderate (30–49%)               | 62 (30.5)        | 23 (44.2)        | 8 (53.3)         | 0.78    |
| Good (≥50%)                     | 130 (64)         | 23 (44.2)        | 7 (46.7)         | 0.83    |
| IV nitrates until op (%)        | 88 (43.3)        | 29 (55.8)        | 5 (33.3)         | 0.03    |
| IABP pre theatre (%)            | 138 (68)         | 3 (5.7)          | 1 (6.6)          | 0.91    |
| EuroSCORE (median; IQR)         | 5.4 (2.6–7.1)    | 8 (6.1–11.3)     | 8 (6.2–15.3)     | 0.09    |
| Logistic EuroSCORE (median; IQR)| 5.6 (3.1–7.8)    | 10.9 (6.9–12.2)  | 12.3 (7.2–17.1)  | 0.03    |

CCS: Canadian Cardiovascular Status; NYHA: New York Heart Association; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; LMS: left main stem; IV: intravenous; IABP: intra aortic balloon pump; EuroSCORE: European System for Cardiac Operative Risk Evaluation; IQR: inter-quartile range.
Data analysis

Continuous data are presented as mean ± 1 SD or median and IQR. The difference between groups for categorical variables was compared by Fisher’s Exact test. Continuous data were compared by paired t-test. Survival data were analysed by Kaplan–Meier life actuarial methods and difference in survival was tested by the log-rank test. The overall performance of the GRACE score was then assessed by the c-statistic. All analysis was performed using SPSS version 12.

RESULTS

From April 2004 to April 2009, 342 consecutive patients underwent urgent CABG following an ACS. Of the 342 patients, 24 were confirmed as having had an NSTEMI, but had inadequate data at the time of admission to calculate the GRACE score accurately. A further 10 patients could not be assessed for the diagnosis of NSTEMI as the notes could not be located. Therefore 270 patients constituted the study population for the analysis of observed versus predicted in-hospital and 6 month mortality (Fig. 1).

The higher risk groups had an increased pre-operative risk profile as estimated by the EuroSCORE (Table 1). This was driven by increasing age, and an increased incidence of female patients, respiratory disease, and patients with impaired ventricular function. Operative details and post-operative outcomes are detailed in Tables 2 and 3, respectively. Cross-clamp time and bypass time were similar in all groups, and 90% of patients in each group had at least 3 bypass grafts. Of the 304 patients with a probable diagnosis of NSTEMI, there were 5 in-hospital deaths (1.6%). Observed in-hospital mortality and GRACE predicted mortality is shown in Table 4. The c-statistic for the GRACE score in predicting in-hospital mortality was 0.53. In this study, there was only one post-operative stroke.

At 6-month follow-up there were a further 6/304 deaths. Observed 6-month and GRACE predicted 6-month mortality is also shown in Table 5. At median follow up of 51.2 months (IQR 34.5–66 months) survival was 96.3, 88.5 and 60% for the low, intermediate and high-risk groups respectively, but this was not significant on log-rank testing, P = 0.11. Late readmission data were available for all 304 patients with a probable diagnosis of NSTEMI. There were nine admissions with myocardial infarction (MI) (2.9%), no patients underwent re-intervention by PCI or CABG and there were no strokes.

Table 3: Post-operative complications by GRACE risk group

| Variable                      | Group 1 | Group 2 | Group 3 | P-value |
|-------------------------------|---------|---------|---------|---------|
| n                             | 203     | 52      | 15      |         |
| In-hospital mortality (%)     | 1 (0.5) | 0       | 2 (13.3)| 0.09    |
| Episode of LCOS (%)           | 44 (21.7)| 23 (44.2)| 14 (26.4)| 0.01    |
| Arrhythmias (%)               | 62 (30.5)| 26 (52  )| 5 (33.3  )| 0.07    |
| Re-operation (%)              | 11 (5.4) | 2 (3.8) | 2 (13.3) | 0.23    |
| Hours ventilated (median, IQR)| 15 (10–12)| 16 (11.5–23.5)| 19.5 (17–28) | 0.67    |
| Respiratory complications (%) | 20 (9.8) | 9 (17.3) | 3 (20)  | 0.08    |
| Post-operative stroke (%)     | 1 (0.5) | 0       | 0       | 0.99    |
| Renal complications (%)       | 12 (5.9)| 3 (5.7) | 1 (6.6) | 0.92    |
| Cr >200 µmol/l                | 4 (1.5) | 1 (1.9) | 1 (6.6) | 0.03    |
| CVVH                          |         |         |         |         |

LCOS: low cardiac output syndrome; IQR: inter-quartile range; Cr: creatinine; CVVH: continuous veno-venous haemofiltration.

Table 4: Predicted and observed in-hospital mortality by risk group

| GRACE group | Predicted in-hospital % mortality (median, IQR) | Observed in-hospital mortality (%) | P-value |
|-------------|-----------------------------------------------|-----------------------------------|---------|
| Group 1     | 1 (1–2)                                       | 0.5                               | 0.23    |
| (n = 203)   |                                               |                                   |         |
| Group 2     | 5 (4–7.25)                                    | 0                                 | 0.04    |
| (n = 52)    |                                               |                                   |         |
| Group 3     | 15 (10.5–20)                                  | 13.3                              | 0.78    |
| (n = 15)    |                                               |                                   |         |

CPB: cardiopulmonary bypass.
Table 5: Predicted and observed 6-month mortality by risk group

| GRACE group | Predicted 6-month % mortality (median, IQR) | Observed 6-month mortality (%) | P-value |
|-------------|--------------------------------------------|-------------------------------|---------|
| Group 1 (n = 203) | 4 (3–7) | 2.0 | 0.05 |
| Group 2 (n = 52)   | 12.5 (11–16) | 1.9 | 0.001 |
| Group 3 (n = 15) | 25 (21.25–30) | 20 | 0.45 |

DISCUSSION

In this study, urgent CABG (performed >24 h post-NSTEMI) was associated with in-hospital mortality, and a 6-month survival superior to that predicted by the GRACE risk score, and this finding was consistent in all three risk groups. Patients in the medium-risk group had an increased predicted operative risk profile as seen by a higher EuroSCORE, but although the incidence of low cardiac output and post-operative arrhythmias was higher in this group all patients were discharged alive from the hospital. The outcomes of the patients in the high-risk group are difficult to interpret due to the small sample size. However, the EuroSCORE estimated pre-operative risk profile of Group 3 was the highest. The in-hospital mortality rate in this group was 13%; this represented 2 in-hospital deaths out of 15 patients, and was not statistically significant.

A recent meta-analysis has shown a reduction in cardiovascular death and MI with an early invasive revascularization strategy [8] in patients suffering ACS, and the GRACE study demonstrated that morbidity and mortality at 6 months was significantly higher in medically treated patients not undergoing PCI or CABG [9]. However, it is a pre-requisite that early revascularization in such patients should be performed with low in-hospital mortality. The reported results of early surgical revascularization following acute MI are difficult to interpret due to the heterogeneity of patients including those with ACSs, NSTEMI, STEMI and STEMI complicated by post-infarction cardiogenic shock [10–13]. Additionally, in these reports, the timing of surgery from the infarct varies from immediate revascularization, to a strategy of delayed revascularization within the same hospital admission. The impact of the timing of surgery on outcome has been clearly demonstrated in the Veterans Affair non-Q-wave infarction strategies in Hospital (VANQWISH) study. In this study, patients with an ACS randomized to early surgery had an in-hospital mortality of 12%, compared with those undergoing delayed revascularization that had a mortality of 3% [14], and this was probably due to the fact that all the patients had a significant rise in myocardial enzymes indicating a sizeable infarct. In subsequent studies enrolling patients with small rise in enzymes (including RITA and TACTICS) early CABG was not associated with elevated mortality [10, 15].

In our study, the in-hospital mortality compared favourably to that predicted by both the GRACE score and the EuroSCORE. It is currently accepted that the EuroSCORE, and the logistic EuroSCORE in particular over-predict in-hospital mortality [16], and our findings are in line with other published series [17, 18]. The EuroSCORE predicts an increased operative risk for those patients who have suffered a MI within 90 days, but does not discriminate between a patient who has suffered a STEMI within 24 h, to someone who has suffered a NSTEMI within the 90-day period [19, 20], and it may therefore be possible to improve future risk models by including this differentiation.

The difference between predicted survival according to the GRACE score and observed survival at 6 months was more pronounced. In the low-risk group, GRACE predicted mortality at 6 months was 4% compared with an observed mortality of 2%, in the medium-risk group GRACE predicted mortality was 12.5% compared with an observed mortality of 1.9% and in the high-risk group, the GRACE predicted mortality was 25% compared with an observed mortality of 20% (3 deaths from 15 patients). The 6-month survival seen in this study also compares favourably with the more contemporary Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS UK), which has also followed up patients admitted with ACS. This study documented an overall 6-month mortality following NSTEMI of 7.3%, with 5.5% occurring post-discharge [21], compared with an overall 6-month mortality of 3% in this study. In PRAIS UK, the rate of revascularization with CABG was again low with 2% of patients undergoing in-hospital CABG, and a further 7% by 6 months [12].

In this study, 90% of patients had triple vessel coronary artery disease and ~50% of patients had LMS disease. The extent of coronary artery disease in the GRACE registry and the PRAIS UK registry is unknown, but the rate of surgical revascularization with CABG in both of these registries is <10% by 6 months. The SYNTAX study has demonstrated that in patients with triple vessel coronary artery disease, CABG remained the optimum treatment [22], and the increased mortality in these registry data may reflect patients with more extensive coronary artery disease who have not received CABG.

The GRACE score does not predict late mortality but in this study, at a median late follow-up of 51.2 months (IQR: 34.5–66) there were 9 (2.7%) re-infarctions and overall mortality was 10.5% (n = 32/304), results that again compare favourably with the PRIAS UK registry where the 4-year mortality was 25% for patients admitted with NSTEMI.

Study limitations

The admission GRACE score was calculated retrospectively based upon hospital notes at the time of admission, and it should be noted that such retrospective studies have inherent bias. The numbers in this study are small, especially when compared with the numbers studied in the GRACE registry, preventing any meaningful statistical analysis.

CONCLUSION

Urgent CABG following an NSTEMI is associated with acceptable in-hospital mortality and 6-month survival superior to that predicted by the GRACE score in all risk groups in this small single-centre study. The improved survival seen in this group of patients presenting with a NSTEMI may in part be explained by the low rate of revascularization with CABG in the GRACE registry. The GRACE score has been advocated to help plan appropriate therapy for patients admitted with an ACS, and this study suggests in particular, that patients with a predicted 6-month mortality >10% may benefit from revascularization with early
CABG. Further work is needed to determine which patients presenting with ACS should undergo urgent CABG, and future iterations of the EuroSCORE may be improved with more specific definitions of MI.

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APPENDIX. CONFERENCE DISCUSSION

Dr A. Vonk (Amsterdam, Netherlands): Only 28% of patients with NSTEMI admitted in the GRACE study received PCI and only 10% received CABG. This means that 62% of patients with NSTEMI received no treatment leading to any form of revascularization and received no structural prevention of further transmural myocardial damage, which seems imminent in NSTEMI. Since the best treatment for ischaemic myocardium is oxygenated blood, it is therefore very logical that patients that do receive revascularization show better results than patients that did not. This paper underlines this finding.

Unfortunately, this study does not provide us data on all NSTEMI patients in the study hospital, since no data on PCI and medically treated patients is presented. This might have been helpful to explain the very large observed expected differences.

So, it is very good to hear you suggesting that we are doing much better than the screening systems claim, and additionally it’s very important that your data show us that interpretation of these scoring systems can be very difficult, if not misleading.

I have two questions. Do you believe that cardiologists, and maybe we surgeons, according to this study, have to change our interpretation for triage of patients? And can we trust current scoring systems? I think the GRACE score can be used as a tool to inform us within the multidisciplinary team meetings that we are now following in a more robust manner. It’s informative and, as you suggested, we don’t currently have the data for the patients who didn’t undergo surgery - this is something that we’re looking into at the moment - and that will inform us even
more regarding the differences between the surgically treated patients as opposed to the medically treated patients.

The current guidelines also indicate that the GRACE score should be used as a tool in making this decision, and I think this study shows that surgery does provide a better outcome for patients, particularly in the higher risk groups with a GRACE-predicted score of over 10%. And the current guidelines recommend reintervention for patients with a predicted mortality of over 3%. So we are addressing the patients with higher risk and showing that surgery may benefit these patients to a greater extent.

Dr. Vonk: So what you’re saying is that we should apply a slightly more aggressive conclusion on the GRACE score in an individual patient?

Dr. Sarkar (Calcutta, India): Do you think in your Group 3 patients the incremental mortality could be addressed a little bit with techniques of myocardial protection? In other words, avoiding global ischaemia by considering on-pump beating heart or intra-aortic balloon-assisted off-pump? I mean, the imposition of global ischaemia in these category Group 3 patients, is it adding onto the risk factor?

Dr. Senanayake: I agree with your comments. The first comment that I would make is that the Group 3 patients were a small number; we had only 15 patients in that group. So this is something that we could look into in the future to prospectively collect more data in these high-risk groups. The practice in our Trust and in our department is to perform all surgery on-pump, so this is data that I can’t comment on, but there might be a beneficial role for what you suggested.

Dr. Sarkar: And I wasn’t really clear on your technique of cardioplegia. Was it antegrade, retrograde or was it just antegrade?

Dr. Senanayake: All patients had antegrade cardioplegia, but the difference between surgeons is between warm and cold blood cardioplegia, but it is all antegrade on-pump.

Dr. Sarkar: There was no retrograde used?

Dr. Senanayake: No.

Dr. G. Wimmer-Greinecker (Bad Bevensen, Germany): One question. You showed us that patients who had surgery up to 30 days after NSTEMI were included, and you said this was the index admission. So what was the reason for such a long hospital stay until they finally got their treatment?

Dr. Senanayake: All patients were within the index admission. There was variability depending on what time the surgery was performed from the time they were admitted. It’s difficult to comment on whether this would have caused a difference in their outcome. But particularly, the difficulty that we have is performing these surgeries within a short amount of time due to the pressure within the department.

Dr. Wimmer-Greinecker: So that’s a logistical issue?

Dr. Senanayake: Yes.

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EDITORIAL COMMENT

Non-ST elevation myocardial infarction? Intervene!

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The GRACE score, derived from the Global Registry of Acute Coronary Events, is an easily applicable and validated tool for triage decision making in patients after non-ST elevation myocardial infarction (NSTEMI) [1, 2]. In short, if patients with NSTEMI are admitted with a low GRACE score, a less aggressive diagnostic approach can be followed than in patients with a high GRACE score. The presence of NSTEMI suggests non-transmural necrosis, which therefore did not lead to end-stage infarction. NSTEMI should be considered alarming since so much can be gained from prevention of further transmural infarction. In this respect, only 28% of the patients with NSTEMI admitted in the GRACE study received a percutaneous coronary intervention (PCI) and 10% received coronary artery bypass grafting (CABG). PCI was performed with a mean delay of 83 h in NSTEMI patients and 62 h in STEMI patients. Five percent of patients with NSTEMI received thrombolysis. This means that 57% of patients with NSTEMI received no treatment leading to any form of revascularization and 62% received no PCI or CABG, preventing further myocardial damage [3]. Those patients who were treated with some form of intervention were treated relatively late compared with those treated according to the modern standard. It is therefore very likely that analysing data from patients who were treated according to today’s management of NSTEMI will show better results than those treated differently. This applies especially if surgery can be postponed for at least two days [4]. The GRACE study unfortunately lacks data on the outcome per subgroup with or without intervention and per CABG and PCI. Senanayake et al. [5] show, in this issue, that application of a modern approach to surgically treat NSTEMI leads to excellent results. However, this study does not provide data on the number, the method of treatment and the outcome of all NSTEMI patients admitted to the study hospital, since no data on PCI patients and medically treated patients are available. In the study population that needed surgery, 90% of patients were identified as having three-vessel disease and 50% had left main stenosis. Therefore, many cases of NSTEMI did not reach the criteria for surgery. More importantly, those who did receive CABG may have benefitted the most from surgical intervention. It is possible, if not likely, that a larger percentage of patients were treated with PCI or CABG than those in the GRACE study. A