Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: A: The GRACE risk score: a reference standard for the management of acute coronary syndrome

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare; the GRACE risk score (derived using data from 102,000 patients with acute coronary syndrome (ACS) in 30 countries) identifies high-risk ACS patients more effectively than do alternative methods.

Significance: GRACE is now a reference standard and has resulted in international guideline changes. It is estimated to save 30–80 lives for every 10,000 patients presenting with non-ST elevation ACS.

Beneficiaries: Patients with ACS; the NHS and healthcare delivery organisations.

Attribution: All work was led by Fox (UoE) with co-chair Gore (University of Massachusetts) and was developed from Edinburgh-based studies.

Reach: Worldwide: guidelines adopted in more than 55 countries; >10,000 downloads of app.

2. Underpinning research (indicative maximum 500 words)

Prior to 2000, it was well recognised that acute coronary syndrome (ACS) constituted a leading cause of death, but the management and outcome of patients with ACS was poorly defined. Trial populations do not reflect the full spectrum of patients with ACS and hence do not reflect the diversity of clinical practice. Professor Keith Fox (Professor of Cardiology, UoE, 1989–present; Chair) and co-chair, Joel Gore (University of Massachusetts) designed a 10-year programme of research and established the largest multi-national study of acute coronary artery disease [3.1]. This built on underpinning research in Edinburgh [3.2, 3.3 and the British Heart Foundation Randomised Intervention Trials in Angina (RITA) and earlier registry programmes]. GRACE (Global Registry of Acute Coronary Events) involved more than 102,000 patients in 30 countries [3.1]. This has become an international reference standard for the management and outcome of ACS and the data are used as the basis for designing large-scale clinical trials. The GRACE programme was launched in 1999; since then, the group has published 132 manuscripts and presented 119 abstracts at major congresses.

This study, and others, identified the “risk-treatment paradox” applicable irrespective of geographic region and healthcare system. The paradox demonstrates that, in contrast to the evidence, lower-risk rather than higher-risk patients receive more intensive medical treatment and interventional treatment. The GRACE risk score was designed to address this problem by providing clinicians with a powerful yet user-friendly means of identifying higher-risk patients at the time of their first presentation. Previously used clinical parameters are inadequate to define risk; neither is using single biomarkers adequate. To develop the GRACE score, Fox and colleagues derived the independent predictors of outcome in 21,688 patients presenting with ACS and validated the predictions prospectively in a further 22,122 patients, with the aim of predicting both in-hospital and 6-month risk of death, and death or myocardial infarction [3.4]. Moreover, external validation was completed in an independent dataset [3.4]. Nine factors independently predicted both death and the combination of death or myocardial infarction and conveyed more than 90% of the risk. The simplified model was robust with good fit and prospectively validated, with C statistics of 0.81 for predicting death and 0.74 for predicting death or myocardial infarction. The score has been extensively tested by the GRACE team [e.g., 3.5, 3.6] and in many diverse healthcare systems, internationally and on all continents.

By characterising the ACS population, the team was able to define the deficiencies in management

and outcome and to provide a key resource for raising hypotheses for subsequent testing in randomised trials (anti-platelet therapy, anti-thrombin therapy and interventional strategies). A number of independent international trials have now used the GRACE score to define populations at particular risk, and populations with the potential for benefit.

3. References to the research (indicative maximum of six references)

3.1 Fox K, Eagle K, Gore J, Steg P, Anderson F; GRACE and GRACE2 Investigators. The Global Registry of Acute Coronary Events, 1999 to 2009 – GRACE. Heart. 2010;96:1095–101. DOI: 10.1136/hrt2009.190827.

3.2 Fox K, Carruthers K, Dunbar D, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK–Belgian Study). Eur Heart J. 2010;31:2755–64. DOI: 10.1093/eurheartj/ehq326.

3.3 Fox K, Anderson F Jr, Goodman S, et al; GRACE Investigators. Time course of events in acute coronary syndromes: implications for clinical practice from the GRACE registry. Nat Clin Pract Cardiovasc Med. 2008;5580–9. DOI: 10.1038/ncpcardio1302.

3.4 Fox K, Dabbous O, Goldberg R, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091. DOI: 10.1136/bmj.38985.646481.55.

3.5 Fox K, Steg P, Eagle K, et al; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. JAMA. 2007;297:1892–900. DOI: 10.1001/jama.297.17.1892.

3.6 Budaj A, Flasinska K, Gore J,…Fox K; GRACE Investigators. Magnitude of and risk factors for in-hospital and post discharge stroke in patients with acute coronary syndromes: findings from a Global Registry of Acute Coronary Events. Circulation. 2005;111:3242–7. DOI: 10.1161/CIRCULATIONAHA.104.512806.

4. Details of the impact (indicative maximum 750 words)

Impact on public policy

The National Institute for Health and Care Excellence (NICE) tested all of the published risk scores for ACS using an unselected population of approximately 70,000 patients from the United Kingdom. NICE guideline 94 [5.1], published in 2010, European Society of Cardiology (ESC; 2011) [5.2], American Heart Association and American College of Cardiology (2012) [5.3] guidelines now recommend that the GRACE risk score should be used because of its superior performance when compared to the other published risk-scoring tools. Fifty-five countries have pledged to implement the ESC cardiovascular guidelines.

Impact on clinical practice

Recent publications from others have extended the role of the GRACE risk score to other indications including pulmonary embolism [5.4] and contrast renal nephropathy. In addition, an independent study demonstrated that the score predicts outcome (whereas stress imaging does not) in follow-up patients after chest pain [5.5]. Similarly, the GRACE risk score remains accurate at predicting hospital and long-term fatality in ACS patients in the era of high-sensitivity troponin and B-type natriuretic peptide [5.6]. The GRACE risk score has been extensively tested, and implemented internationally: PubMed (May 2013) retrieved 291 published manuscripts and 4034 citations involving the GRACE risk score, and on Google there are 46 pages of citations using the term “GRACE risk score”. Examples [5.4–5.8] include studies from clinical settings as diverse as Brazil, Portugal and China that demonstrate the superiority of the GRACE score.

The GRACE Steering Committee (Chair, K Fox) made the GRACE risk score freely available to download to a mobile device (2011; more than 10,000 downloads from Google Play alone). In addition, a simplified version of the GRACE risk score was developed in 2012, externally validated in the French Acute MI FAST registry; the updated version is now implemented and freely available (July 2013). The GRACE risk score app provides a user-friendly interface of the variables that

convey 90% of the risk of the full multivariable GRACE risk model. The clinician uses this information alongside his or her clinical evaluation to guide management of the patient. The app received coverage in UK and international media (The Times [5.9], The Times of India and many others) and has been requested by NHS England's Pan-London Clinical Leadership Advisory Group for Cardiology for use in its inter-hospital transfer system [5.10]. The GRACE score will also be incorporated into a "pocket guidelines" app developed by the ESC for distribution to clinicians in the 55 affiliated countries.

Impact on health and welfare

The GRACE programme identified that survivors of non-ST elevation ACS (previously perceived as minor or threatened heart attacks) had higher long-term risks of death and recurrent myocardial infarction and ST-elevation myocardial infarction [3.1, 3.2]. In consequence, a series of international randomised trials has focussed on improving outcomes in non-ST elevation ACS, including Fox's British Heart Foundation-funded RITA 3 trial. By facilitating appropriate treatment, the GRACE risk score has contributed to a change in practice and improved outcomes [3.5]. Fox and colleagues demonstrated temporal changes in outcomes, improved use of evidence-based therapies, a decline in deaths and myocardial infarction and approximately a halving of new heart failure [3.5]. These findings for international GRACE sites are corroborated by British Heart Foundation statistics. Modelling by the UoE team suggests that implementation of the GRACE score results in a saving of 30–80 lives for every 10,000 patients presenting with non-ST elevation ACS.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 NICE guideline 94 (March 2010). Unstable angina and NSTEMI The early management of unstable angina and non-ST-segment-elevation myocardial infarction. http://www.nice.org.uk/nicemedia/live/12949/47921/47921.pdf.

5.2 Hamm C, Bassand J, Agewall S, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999–3054. DOI: 10.1093/eurheartj/ehr236.

5.3 Jneid H, Anderson J, Wright R, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2012;126:875–910. DOI: 10.1161/CIR.0b013e318256f1e0.

5.4 Paiva L, Providencia R, Barra S, Faustino A, Botelho A, Marques A. Cardiovascular risk assessment of pulmonary embolism with the GRACE risk score. Am J Cardiol. 2013;111: 425–31. DOI: 10.1016/j.amjcard.2012.10.020.

5.5 van der Zee P, Verberne H, Cornel J, et al. GRACE and TIMI risk scores but not stress imaging predict long-term cardiovascular follow-up in patients with chest pain after a rule-out protocol. Neth Heart J. 2011;19: 324–30. DOI: 10.1007/s12471-011-0154-9.

5.6 Meune C, Drexler B, Haaf P, et al. The GRACE score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and B-type natriuretic peptide. Heart. 2011;97:1479–83. DOI: 10.1136/hrt2010.220988.

5.7 D'Ascenzo F, Biondi-Zoccai G, Moretti C, et al. TIMI, GRACE and alternative risk scores in acute coronary syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemp Clin Trials. 2012;33:507–14. DOI:

10.1016/j.cct2012.01.001.

5.8 Abu-Assi E, Garciá Acuña J, Peña-Gil C, González-Juanatey J. Validation of the GRACE risk score for predicting death within 6 months of follow-up in a contemporary cohort of patients with acute coronary syndrome. Rec Esp Cardiol 2010; 63(6):640–8. DOI: 10.1016/S1885-5857(10)70138-9.

5.9 The Times (3rd Sep 2013). Scots university app aids cardiac diagnosis. http://www.thetimes.co.uk/tto/news/uk/scotland/article3859051.ece.

5.10 Letter from the Pan-London Clinical Leadership Advisory Group for Cardiology (August 2013), requesting use of the GRACE risk score app for the inter-hospital transfer system. *[Available on request.]*