BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004425
Article Type:	Research
Date Submitted by the Author:	08-Nov-2013
Complete List of Authors:	Fox, Keith; Royal Infirmary
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Emergency medicine, Medical management
Keywords:	Coronary heart disease < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, ACCIDENT & EMERGENCY MEDICINE

Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation, and outcomes using the updated GRACE risk score

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Keywords: Acute coronary syndromes, risk stratification, GRACE score, outcomes, myocardial infarction

STRUCTURED ABSTRACT (300 words)

Objectives

Risk scores are recommended in guidelines to facilitate the management of patients who present with acute coronary syndromes (ACS). Internationally, such scores are not systematically used because they are not easy to apply and some risk indicators are not available at first presentation. We aimed to derive and externally validate a more accurate version of the GRACE Risk Score for predicting the risk of death or death/myocardial infarction both acutely and over the longer term. The risk score was designed to be suitable for acute and emergency clinical settings and usable in electronic devices.

Design and setting

The GRACE risk score (2.0) was derived in 32,037 patients from the GRACE registry (14 countries, 94 hospitals) and validated externally in the French FAST-MI 2005 registry.

Participants

Patients presenting with ST-elevation and non-ST elevation ACS and with long-term outcomes

Outcome measures

The GRACE Score (2.0) predicts the risk of short and long-term mortality, and death/myocardial infarction, overall and in hospital survivors.

Results

For key independent risk predictors of death (1yr) non-linear associations (versus linear) were found for age (p<.0005), SBP (p<.0001), pulse (p<.0001), creatinine (p<.0001). By employing non-linear algorithms there was improved model discrimination, validated externally. Using the FAST-MI 2005 cohort the C indices for death exceeded 0.82 for the overall population at one year and also at 3 years. Discrimination for death or MI was slightly lower than for death alone (c=0.78). Similar results were obtained for hospital survivors, and with substitutions for creatinine and Killip class, the model performed nearly as well.

Conclusions

The updated GRACE risk score has better discrimination and is easier to use than the previous score based upon linear associations. GRACE Risk (2.0) performed equally well acutely and over the longer-term and can be used in a variety of clinical settings to aid management decisions.

ARTICLE SUMMARY

The updated GRACE risk score (2.0) was derived in 32,037 patients from the GRACE registry and validated externally in the French FAST-MI 2005 registry. This risk score has better discrimination and is easier to use than the previous score based upon linear associations. In addition it allows substitutions for risk markers that may not be available at the time of first patient presentation (creatinine and Killip class). GRACE Risk (2.0) performed equally well acutely and over the longer-term and can be used in a variety of clinical settings to aid management decisions. It is freely available to download to electronic devices.

Strengths and Limitations

- The GRACE 2.0 risk score is derived from the largest multinational registry in acute coronary syndromes (Global Registry of Acute Coronary Events) and validated in an entirely independent dataset with comprehensive long-term outcome data.
- This risk score employs non-linear functions and is more accurate than the original version, and it is now validated over the longer-term (to 1 and 3 years) and with substitutions possible for creatinine values and Killip class (performing almost as well).
- This electronic risk score is designed to be used in mobile electronic devices (approximately 30 seconds to enter data) and presents the risk of death (or death/MI) and relative to the entire ACS population
- The score is designed to assist clinical management decisions and is not a substitute for individual patient clinical assessment. However, it may help to address the current "treatment–risk paradox" whereby low rather than high risk patients are more likely to receive interventional therapies
- Additional factors may influence outcome, especially in geographic populations and healthcare systems not evaluated in the multinational GRACE programme

INTRODUCTION

Acute coronary syndromes (ACS) comprise a heterogeneous spectrum of patients who are currently stratified for management mainly on the basis of ECG characteristics and biomarker results. NICE, SIGN, ESC and North American guidelines separate patients into ST elevation MI or non-ST elevation ACS and they also recommend use of a risk score such as the GRACE score.[1-4] However, systematic risk stratification is not widely performed, despite the evidence and the guidelines.

Why should risk assessment be important for the triage and management of patients with acute coronary disease?

Whether a patient proceeds to an immediate, urgent or delayed coronary angiography and revascularisation and which of acute antithrombotic regimens is chosen depends on patient risk characteristics. Evidence from randomised trials and guideline recommendations all support the use of different strategies according to risk status.[1-4]

In the development of NICE guideline 94 (www.nice.org/cg94) the guideline states that single variables (for example troponin) were not as good as multiple variables in predicting outcome.[1] NICE independently tested all of the published risk scores (GRACE[5,6], TIMI[7], PURSUIT[8], PREDICT[9], EMMACE[10], SRI[11], AMIS[12], UA[13] risk score) in 64,312 patients from the MINAP dataset . They employed a "mini-GRACE score" as many of the MINAP patients lacked creatinine values and Killip classification (substituting history of renal dysfunction and the use of diuretics). The c statistic was 0.825 with 95% confidence bounds 0.82-0.83 and this was superior to the performance of the other risk scores and hence the recommendation from NICE to employ the GRACE risk score.[1] However, the use of substitutions for creatinine and for Killip Class has not been validated in an independent dataset and the prediction of long-term outcome had not been tested. In addition, non-linear functions for continuous variables and for Killip class may improve model discrimination and could be implemented in hand-held electronic devices.

Resolving the "treatment-risk paradox"

We, and others, have revealed a treatment-risk paradox in the management of acute coronary disease.[14,15] In contrast to the evidence and the guideline recommendations, lower risk rather than higher risk patients are more likely to undergo interventional procedures and receive more aggressive antithrombotic and other therapies .[14,15] This phenomenon has now been reported across widely different healthcare systems and different geographic settings. Why is this? Firstly, current treatment decisions rely on clinical assessment and it is difficult for the clinician to weigh up potential benefits against potential hazards and hence lower risk patients are commonly selected for more aggressive treatment (an unintended risk averse approach). However, evidence demonstrates that even excluding those with contra-indications, higher risk cohorts potentially have more to gain. [14]

Why aren't risk scores more widely used?

Internationally, risk scores are not systematically applied for the management of ACS despite the evidence and guideline recommendations. Several factors contribute to this including the misperception that clinician assessment or the use of individual risk indicators is sufficient.[1,2,16] In addition, the most accurate risk scores have been cumbersome to compute (for example requiring look-up tables and many use arbitrary score results). Finally, the parameters necessary for their implementation may not be available at the time of patient's initial presentation.

What this study adds

We aimed to develop and validate a revised and more accurate version of the GRACE risk score suitable for both acute and long-term prediction of risk. Instead of assuming continuous variables such as age and the categorical variable Killip class were linearly associated with risk, we tested for non-linear associations and included them in the revised prediction tool where appropriate. In contrast to the earlier version of the GRACE score which required computing a numerical score (without absolute risks) we derived and externally validated an electronic version with absolute percentage risks. This is suitable for use in hand held electronic devices and smart phones, and the clinical applicability is broadened by using substitutions for creatinine and Killip class. Creatinine values may only be available after hospital admission and many settings do not routinely use Killip class for evaluating heart failure symptoms. Thus, the aim of this study was to develop a simplified risk score suitable for applications in a variety of settings and to test the accuracy of the revised GRACE risk predictor (GRACE Score 2.0) to predict early and long-term risk, as an aid to clinical management.

METHODS

GRACE risk score

The GRACE registry was designed to reflect an unbiased population of patients with acute coronary syndrome and was undertaken over 10 years, in 94 hospitals and 14 countries.[5,6,17,18,19] The design has been reported previously.[17,19]

In-hospital and up to 6 months outcomes and risk scores were derived based upon independent predictors of outcome. These have been described previously (ST segment deviation, age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest at admission, elevated biomarkers of necrosis).[5,6] The GRACE risk score was derived from the original population of 26,267 patients (11,389 for hospital score for patients enrolled through 31 March 2001; 21,688 were used to derive the 6 month risk score for patients enrolled through 30 Sept 2002) with suspected acute coronary syndrome, validated prospectively in a further set of 22,122 patients and validated externally.[5]

Risk characteristics of populations may evolve over time (as management changes) and it is appropriate the GRACE score should be tested in a more recent cohort of ACS patients and with extended follow-up.[20]

The original GRACE score estimated in hospital risk of death or the combination of death or MI and the same outcomes up to 6 months post-discharge. The new version of the GRACE risk score for one year outcomes was derived in 32,037 patients from the GRACE registry enrolled between January 2002 and December 2007. For three year mortality the UK cohort of 1,274 patients with long term follow-up was employed. The characteristics of this study population have been previously reported.[19] The algorithm employed the same independent predictors of outcome as originally derived and reported, but non-linear associations were incorporated to improve model discrimination. In addition, a simplified version of the risk score was developed with substitutions for creatinine (history of renal dysfunction) and substitutions for Killip class (diuretic usage). As previously validated, a parsimonious model of only 8 factors conveyed more than 90% of the predictive accuracy of the complete multivariable model.[5,6]

Consistency of estimates in different GRACE risk models

The GRACE risk score version 2.0 contains slightly more precise estimates of version 1.0 hospital (Granger) and 6 month death (Fox) probabilities. Instead of converting model estimates to a point system, and using intervals for continuous variables such as age, as in version 1.0, version 2.0 directly utilizes model estimates themselves to compute cumulative risk (see: http://www.outcomes-umassmed.org/grace/files/GRACE_RiskModel_Coefficients.pdf).

Because GRACE models were derived in different patient populations from different study periods, differences in cumulative rate estimates for the same interval exist. The one year death model contains the most recent and largest patient populations. Therefore, 6 month and 3 year death models were standardized to conform to estimated Kaplan-Meier cumulative rates for the one year model. The revised version 2.0 6 month cumulative estimates now conform to version 2.0 one year model estimates as of 6 months, and the one year estimates for the version 2.0 3 year model as of one year also conform to version 2.0 one year estimates for the one year model.

External validation

The updated GRACE risk score was validated by testing the algorithm in its full version and simplified version in an entirely separate registry population, the French registry of Acute ST-elevation and non ST-elevation Myocardial Infarction (FAST-MI).[21,22,23] FAST-MI 2005 is a nationwide French registry conducted over a month period at the end of 2005 and it included 3,059 patients with STEMI or non STEMI from 223 centres. All variables required to calculate the new GRACE risk score were available in 2,959 patients (96.7% of the full cohort). The GRACE algorithm was applied to the 2,959 patients using logistic regression and the c statistics calculated for mortality at one year, mortality at 3 years and then for the subsets of patients with ST elevation MI and non ST elevation MI. In addition, c statistics were calculated for death or myocardial infarction. The same analyses were then repeated for hospital survivors only (n=2,806). In addition, goodness of fit was tested using the Hosmer-Lemeshow test. Likewise, the simplified score was tested in the 3,035 patients in whom all variables needed for its calculation were available.

Statistics

The Kaplan-Meier method was used to estimate one and three year outcome rates.

Cox multiple regression models were fitted to outcomes of death and death or MI within one and three years of hospital admission. The same eight factors used in the original GRACE risk scores were used.[6] The method of restricted cubic splines[24] was used to test for possible non-linear associations between outcomes and age, creatinine, pulse, and systolic blood pressure. Killip class using four categories was compared to linear Killip class. Associations that improved model likelihood at the alpha = 0.05 level were retained in final models. Such associations were also plotted and examined for clinical plausibility.

Model performance was evaluated using the May-Hosmer goodness of fit test[25], and Harrell's c index for model discrimination.[26] A prediction tool based on these models uses point estimates and baseline survival to arrive at predicted outcomes for a given patient's covariate experience.[27]

RESULTS

Patient characteristics

For the 32,037 patients from the GRACE registry (table 1) there were 2,422 deaths within 365 days of initial admission, and complete covariate data. The distribution of deaths was as follows: 1,275 in hospital, 983 deaths after discharge within 180 days of admission, 164 deaths from 181-365 days after admission. The estimated 365 day cumulative death rate is 9.3% using the Kaplan-Meier method.

For the 3-year model derived from 1,274 patients from the United Kingdom, there were 261 deaths: 59 in hospital, 51 after discharge within 180 days of admission, and 151 in the remaining two and one half years since admission. The estimated 3-year cumulative death rate is 20.5%.

Performance of the model using non-linear functions

Analyses were undertaken firstly using categorical variables and linear associations for continuous variables and Killip class (as in the original description of the GRACE risk score),[5,6] and then using non-linear associations for age, heart rate, systolic blood pressure and creatinine. Differences were observed between the non-linear and the linear model with the former more likely to classify patients as at high risk (data not shown).

Non-linear associations for the one year mortality model were found for all four continuous measures: systolic blood pressure, pulse, age, and creatinine ($p < 0.001$ vs linear). Restricted cubic spline functions for age and systolic blood pressure had 3 knots at the 10th, 50th, and 90th percentiles of their distributions, 4 knots at the 5th, 35th, 65th and 95th percentiles of pulse and creatinine distributions. Hazard ratio (HR) estimates are reported for selected intervals, to provide a sense of how associations change over covariate ranges (Table 2). Killip class is modelled as 4 distinct groups ($p < 0.001$ vs linear class). The one year death/MI model has similar non-linear associations, while the 3 year death model, has 4 knot cubic spline associations for systolic blood pressure and pulse, linear associations for remaining

factors. Also shown are estimates for the substitute factors of renal insufficiency and diuretics, which can be used to replace creatinine and Killip when they are unavailable. Sample sizes increase somewhat for models using the substitute factors, and model discrimination is only slightly diminished.

The goodness of fit test is partly a function of sample size with larger sample sizes increasing the chance that a small difference between observed and expected numbers of death will be detected. This was observed, with differences mainly in the 9th risk decile, (the model predicted 3-year risk of 17%, estimated observed death 19.5%). The largest difference in remaining deciles is 1.2%.

Based on relative model chi-square values, age is the most important factor in all 3 models, followed by systolic blood pressure, creatinine, and Killip class in the one-year model (all have similar chi-square values), creatinine and Killip class in the one-year death/MI model, and systolic blood pressure and pulse in the 3-year death model. All models show good discrimination (c indices ≥ 0.74), although combining MI with death in the one year model reduces model discrimination, because death and MI are not interchangeable with respect to patient risk profiles.

External validation of the non-linear GRACE risk score in the FAST-MI 2005 registry

The characteristics of the FAST-MI 2005 registry are reflective of the range of patients presenting with ACS (mean 66.9 years ± 14.4 years, 31% women, 53% STEMI, 47% non STEMI, coronary artery disease history 30%, history of stroke 5%, documented diabetes mellitus 24%, documented hypertension 57%, current smoking 30%, documented hypercholesterolemia 47.5%). The FAST-MI 2005 registry has excellent completeness of follow up (3 year follow up 98% complete). Overall survival was 79% and infarct free survival 73%.

Using the FAST-MI 2005 cohort of 2,959 patients. c-statistics for death exceeded 0.82 for the overall population at one year and also at 3 years (table). Discrimination for death in the model was higher in the ST elevation MI population (c= 0.84) at one year compared to the non STEMI population (c=0.80). Discrimination for death or MI was slightly lower than for death alone (c=0.78) both at one year and 3 years. Similar figures were obtained for hospital survivors (see tables 3a and 3b).

Receiver operating characteristic (ROC) curves were constructed as illustrated in Figures 1a, 1b for death at one year (Figure 1a) and death or MI (Figure 1b).

The c-statistics for 3 year death were calculated using the same approach and the ROC curves are illustrated for the whole ACS population at 3 years for death and for death or MI.

The c indices using the simplified GRACE model with substitutions for Killip class and serum creatinine, available for 99.2% of patients, these were 0.82 for both one and three yr models).

In summary, use of non-linear functions for continuous variables improved model performance over the original GRACE risk score using linear functions. The external validation demonstrated good model discrimination at one and 3 years for both death and death or MI, and in sub-types of MI, ST elevation and non ST elevation MI. This has not previously been tested. The risk score performs similarly when considering only the survivors of hospitalisation. The simplified risk score using history of renal dysfunction in place of creatinine values, and use of diuretics in place of Killip class, performed almost as well as the full GRACE score.

DISCUSSION

This study aimed to develop an improved version of the GRACE risk predictor (GRACE score 2.0) incorporating non-linear associations between continuous risk factors and outcomes in a format suitable for ease of use in handheld electronic devices and smart phones (Figure 2). Further, the GRACE score had not been tested for predictive accuracy beyond 6 months and the simplified version of the risk score with substitutions for creatinine and for Killip class had not been tested in an independent population. A key finding is that model likelihood using individual non-linear functions for heart rate, systolic blood pressure, age, and creatinine was significantly improved over a model using linear functions for these factors. In brief, the model with non-linear functions matches observed data more closely. Further, the updated GRACE risk score demonstrated similar high model discrimination at one and 3 years as had previously been demonstrated for in hospital outcomes and outcomes to 6 months. In addition, the reduced version of the GRACE risk score with substitutions for creatinine and Killip class (with history of renal dysfunction and use of diuretics respectively), performs nearly as well as the model with original factors.

What are the implications?

In a diverse range of hospitals in 14 countries worldwide, with on-site angiographic facilities, the frequency of catheterisations and percutaneous coronary interventions exhibited a paradoxical pattern, whereby most interventions were performed in low risk rather than high risk patients (the “treatment-risk paradox”).[14,15]

To counter the criticism that not all high risk patients will be suitable for revascularisation we undertook further analyses in a previous publication according to the frequency of angiography (hospitals with on-site angiographic facilities were divided into tertiles according to the rate of coronary angiography).[14] Hospitals with a high rate of coronary angiography performed substantially more interventions in higher risk patients than those performed in the low rate hospitals, in similar risk patients, demonstrating that these patients were amenable to the intervention procedures.[14]

It is possible to estimate the “deficit” in the frequency of revascularisation based upon the actual differences between high rate and low rate hospitals observed in the GRACE programme. From the overall population 37.8% of patients were in the GRACE high risk group, 36.1% in the GRACE medium risk group and 26.1% in the GRACE lower risk group (categories according to the ESC guidelines).[3] As previously reported[14] individuals in the highest third of GRACE risk score had catheterisation performed in 51% and PCI or CABG in

31.4% of patients whereas those in the medium GRACE risk group had catheterisation in 68% and PCI or CABG in 42.9% and those in the lower risk group had catheterisation in 72% and PCI or CABG in 47.6%.

Taking the performance of hospitals that were in the highest third for the rate of coronary angiography (they performed PCI and CABG in 60.2% of the presenting population) it is possible to calculate the deficit compared to the hospitals with the lowest rate of angiography and revascularisation. The calculation assumes that the low performance hospitals increased their rate of PCI and CABG to the same as was observed in the highest third of hospitals. This projection is based on observed performance data for the rate of angiography. The calculation assumes no more PCI or CABG performed than was observed in the high rate hospitals. In brief, 700 more patients per 10,000 would undergo revascularisation if the same patients presented to high performance hospitals.

The impact of revascularisations on outcomes can be estimated from the pooled analysis of all the randomised trials where patients were randomised to an interventional strategy as a routine, or to a selective strategy based upon symptoms and ischaemia.[28] We previously reported this combined analysis based upon individual patient data from the FRISC-2[29], RITA-3[30] and ICTUS[31] trials and the absolute reduction in cardiovascular deaths and MIs was 11.1 per 100 patients in the highest risk group and 4 per 100 in the medium risk group, over 5 years.[28-31] Thus, based upon the impact of a systematic interventional strategy in the randomised trials, there would be between 30 and 80 fewer cardiovascular deaths or MIs for each 10,000 patients with non ST elevation ACS. The estimate is conservative as it excludes the impact on medium risk patients and the number would be higher if the top quintile of performance was used as the reference standard rather than the top tertile. Thus, consistent with the guideline recommendations a systematic approach for evaluating risk has the potential to increase the rate of revascularisation in high risk patients without contra-indications. Based upon the combined analysis of all the randomised trials with long term outcomes this risk related strategy has the potential to reduce the frequency of cardiovascular death and MI, over the longer term.

Strengths and limitations

The GRACE programme is the largest multi-national programme in acute coronary artery disease and was designed to ensure that the included patients were reflective of the broad spectrum of patients presenting with acute coronary syndrome, and of the range of hospitals in clinical practice. The sites were trained, audited and quality control measures were enacted throughout the study. Use of the UK cohort allowed estimation of long-term outcomes (as previously reported) with complete mortality data to 5 years.[19] The external validation of the updated risk score was performed in the FAST-MI 2005 registry with inclusion of the full spectrum of hospitals admitting patients with ACS and excellent completeness of follow-up.

Although the updated GRACE risk score provides a reliable estimate for stratifying patients both acutely and in the long-term, additional factors contribute to longer term risk. Further refinement of the risk score for long term outcomes may require the inclusion of additional risk factors and biomarkers to increase precision, but the current risk scores' discrimination

allows separation of patients into broad categories relevant for decisions on clinical management.

CONCLUSIONS

The updated GRACE risk score has better model discrimination and is easier to use than previous scores based upon categorical variables. It is accurate in the acute phase and over the longer term and can be used in a variety of clinical settings to aid management decisions.

Acknowledgements

This work was supported by the British Heart Foundation, an award from the Chief Scientist Scotland (CZG/2/455) and unrestricted grant from AstraZeneca to the University of Edinburgh. The GRACE risk score has been made available to download without cost (www.gracescore.co.uk and www.outcomes.org/grace)

Text: 3479 words (introduction to end of acknowledgements)

FUNDING STATEMENT

This work was supported by the British Heart Foundation (CH92010), an award from the Chief Scientist Scotland (CZG/2/455) and unrestricted grant from AstraZeneca to the University of Edinburgh. The FAST-MI registry is a registry of the French Society of Cardiology, supported by unrestricted grants from Pfizer and Servier. Additional support for FAST-MI was obtained from a research grant from the French National Health Insurance System (Caisse Nationale d'Assurance Maladie).

COMPETING INTERESTS STATEMENT

International Committee of Medical Journal Editors (ICMJE) forms completed for all authors and submitted (see attachments)

AUTHORS' CONTRIBUTIONS

KAA Fox initiated the programme of work, performed the analyses in conjunction with co-authors and wrote and revised the manuscript. G FitzGerald led the work deriving the revised risk score, in conjunction with F Anderson, Wei Huang. K Carruthers analysed and interpreted the data. N Danchin in conjunction with E Puymirat, T Simon, P Coste, J Monsegu, P G Steg performed the work on the FAST MI dataset. All authors contributed to the revisions of the manuscript and the interpretation of the findings.

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Legends

Figure 1a

Receiver operator characteristic curve (ROC) for the prediction of death up to one year for the complete FAST-MI 2005 cohort of patients. Area under the curve, c statistic is 0.83.

Figure 1b

Receiver operator characteristic curve (ROC) for the complete FAST-MI 2005 cohort of patients for the prediction of death or MI to one year. Area under the curve 0.78.

Figure 2

Illustration of the GRACE Score 2.0 on a mobile device (suitable for use in iOS, android or web versions). Left panel: values for percentage risk of death or death/MI (or numerical GRACE Score). Remaining panels show the individual patient results as a vertical column superimposed on the entire ACS distribution curve (green column= low risk illustration, yellow column=medium risk, red column= high risk).

Table 1 Characteristics on admission of the 32,037 GRACE ACS patients used in 1-year death model

Demographics	
Age, y	66.6 (56.0-76.4)
Female	33%
Weight, kg	78 (68-89)
Height, cm	170 (162-175)
BMI, kg/m^2	27 (24-30)
Medical history, %	
Angina	44
Atrial fib	7.7
CABG	13
Congestive heart failure	10
Diabetes	26
Dyslipidemia	51
Hypertension	64
MI	30
PCI	19
Peripheral arterial disease	9.0
Renal insufficiency	7.6
Smoking	57
Stroke	8.5
Presentation characteristics	
Pulse, beats/min	76 (65-90)
DBP, mm Hg	80 (70-90)
SBP, mm Hg	140 (120-160)
Killip class I	85%
Killip class II	11%
Killip class III	3.6%
Killip class IV	0.8%
Cardiac arrest	1.9%
Initial cardiac enzymes positive	52%
Initial serum creatinine, mg/dL	1.02 (0.90-1.25)
Electrocardiographic findings, %	
ST-segment elevation	36
ST-segment depression	32
ST-segment deviation	53
T wave inversion	25
ST-segment elevation anterior	16
ST-segment elevation inferior	18
ST-segment depression anterior	15
ST-segment depression inferior	9.2
Any significant Q wave	19
Left bundle branch block	4.7
Prior use of medical therapy, %	
Aspirin	40
ACE inhibitors	30
Statins	32

3307 missing weight, 6098 missing height, 6732 missing BMI; no other variable missing > 300.
Median (IQR) if continuous variable; % if discrete

TABLE 2. Summary of Cox regression models

	Admission to 1 year death	Admission to 1 year death or MI	Admission to 3 year death
Total no. of observations	32,037	32,037	1,274
No of outcomes	2422	3655	261
May-Hosmer goodness of model fit (*P*)	<0.001	0.06	0.60
Harrell's c index	0.829	0.746	0.782
Model estimates	HR (95% CI), χ^2	HR (95% CI), χ^2	HR (95% CI), χ^2
Age per 10 y: <67	1.5 (1.4 - 1.7), 1069	1.2 (1.1 – 1.3), 853	1.8 (1.6 – 2.1), 102
≥ 67	1.9 (1.8 - 2.0)	1.6 (1.5 – 1.6)	n/a (linear)
Systolic blood pressure per -20 mm Hg	≥ 139: 1.1 (1.0 - 1.2), 293	≥ 139: 1.0 (1.0 - 1.1), 200	≥ 160: 0.9 (0.7 – 1.1), 36
	< 139: 1.3 (1.3 - 1.4)	<139: 1.3 (1.2 - 1.3)	130 – 159: 1.6 (1.2 – 2.0)

			< 130: 1.3 (1.0 – 1.6)
Pulse per 30 BPM: <51	1.1 (0.9 - 1.4), 131	1.0 (0.9 – 1.3), 126	1.0 (0.3 – 2.7), 32
51-83	1.5 (1.4 - 1.7)	1.4 (1.2 – 1.5)	1.7 (1.1 – 2.8)
84-118	1.3 (1.2 - 1.4)	1.2 (1.2 – 1.3)	1.6 (1.2 – 2.0)
>118	0.9 (0.8 - 1.0)	0.9 (0.8 – 1.0)	0.9 (0.6 – 1.1)
Creatinine per mg: <1	0.6 (0.4 – 1.0), 305	0.9 (0.6 – 1.3), 338	1.5 (1.3 – 1.8), 23
1 – 2	2.2 (2.0 – 2.4)	1.9 (1.7 – 2.0)	n/a (linear)
>2	1.1 (1.1 – 1.2)	1.1 (1.1 – 1.2)	n/a (linear)
Killip class II (v I)	1.9 (1.7 – 2.1), 305	1.7 (1.6 - 1.9), 288	1.1 (0.8 – 1.4), 18
Killip class III (v I)	2.4 (2.1 – 2.7)	2.0 (1.8 – 2.2)	III-IV v I: 2.3 (1.6 – 3.4)
Killip class IV (v I)	3.7 (3.0 – 4.5)	3.2 (2.6 – 3.9)	n/a
Cardiac arrest at admission	2.4 (2.0 – 2.9), 74	2.0 (1.7 – 2.3), 55	2.9 (1.7 – 5.2), 14
Positive initial enzymes	1.5 (1.3 – 1.6), 72	1.3 (1.2 -1.4), 42	n/a
ST deviation	1.6 (1.4 – 1.7), 109	1.4 (1.3 – 1.5), 92	1.5 (1.2 – 1.9), 10

Substitute factors*: renal insufficiency	1.6 (1.4-1.7), 66	1.6 (1.5 – 1.8), 105	2.0 (1.3 – 3.2), 9
Diuretics in first 24 h	2.0 (1.8-2.1), 266	1.7 (1.6 – 1.8), 236	2.0 (1.5 – 2.6), 27

* Renal insufficiency substituted for creatinine, diuretics for Killip class; sample sizes increase to 33,890 patients with 2585 deaths within a year of admission (c index .820), 33,890 patients with 3882 deaths or MIs within a year of admission (c index .738), 1298 patients with 266 deaths within 3 years of admission (c index .780).

Table 3a the full GRACE risk score tested in FAST-MI 2005

From ACS presentation	Overall population (death) n=2959	STEMI (death) N=1558	Non-STEMI (death) N=1401	Overall Death/MI
1-year Death	0.830	0.839	0.816	0.773
3-year Death	0.820	0.819	0.816	0.773
Hospital Survivors	n=2806	N=1472	N=1334	
1-year Death	0.811	0.816	0.799	0.734
3-year Death	0.802	0.789	0.802	0.749

Table 3b the simplified GRACE risk score, with substitutions for Killip and creatinine (n=3035), tested in FAST-MI 2005

From ACS presentation	Overall population (death) N=3035	STEMI (death) N= 1596	Non-STEMI (death) N=1439	Overall Death/MI
1-year Death	0.822	0.841	0.802	0.779
3-year Death	0.824	0.825	0.815	0.783
Hospital Survivors	N=2872	N=1504	N=1368	
1-year Death	0.804	0.825	0.783	0.743
3-year Death	0.808	0.800	0.803	0.762

Figure 1a

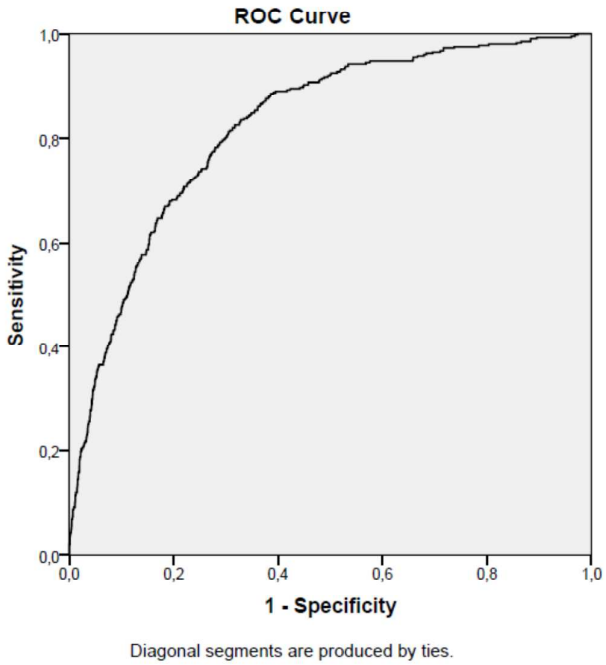

Figure 1b

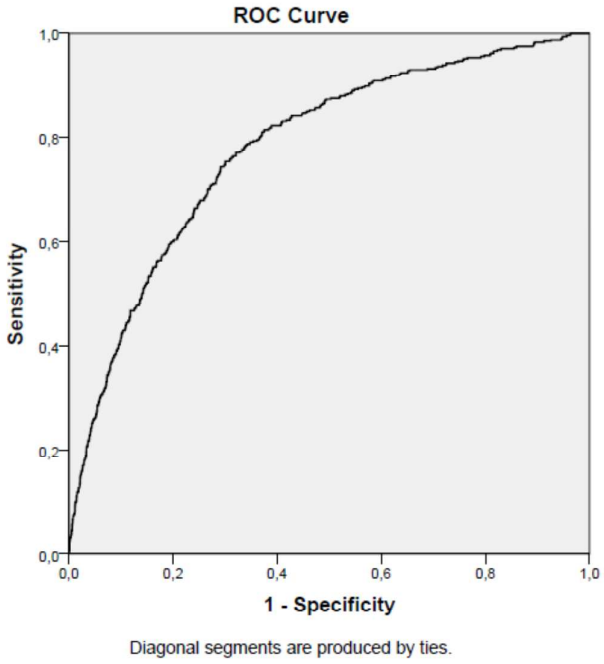

Figure 2

STROBE Statement—checklist of items that should be included in reports of observational studies

"Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation, and outcomes using the updated GRACE risk score" (manuscript ID bmjopen-2013-004425)

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract done
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported done
Objectives	3	State specific objectives, including any prespecified hypotheses done
Methods		
Study design	4	Present key elements of study design early in the paper done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection done
Participants defined	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group done
Bias	9	Describe any efforts to address potential sources of bias done
Study size	10	Explain how the study size was arrived at done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding done
		(*b*) Describe any methods used to examine subgroups and interactions N/A
		(*c*) Explain how missing data were addressed N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy done

(*e*) Describe any sensitivity analyses done

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed done
		(b) Give reasons for non-participation at each stage done
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders done
		(b) Indicate number of participants with missing data for each variable of interest done
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included done
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses done
Discussion		
Key results	18	Summarise key results with reference to study objectives done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence done
Generalisability	21	Discuss the generalisability (external validity) of the study results done
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based done

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation, and outcomes using the updated GRACE risk score

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004425.R1
Article Type:	Research
Date Submitted by the Author:	27-Dec-2013
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Emergency medicine, Medical management
Keywords:	Coronary heart disease < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, ACCIDENT & EMERGENCY MEDICINE

Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation, and outcomes using the updated GRACE risk score

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Keywords: Acute coronary syndromes, risk stratification, GRACE score, outcomes, myocardial infarction

STRUCTURED ABSTRACT (300 words)

Objectives

Risk scores are recommended in guidelines to facilitate the management of patients who present with acute coronary syndromes (ACS). Internationally, such scores are not systematically used because they are not easy to apply and some risk indicators are not available at first presentation. We aimed to derive and externally validate a more accurate version of the GRACE Risk Score for predicting the risk of death or death/myocardial infarction both acutely and over the longer term. The risk score was designed to be suitable for acute and emergency clinical settings and usable in electronic devices.

Design and setting

The GRACE risk score (2.0) was derived in 32,037 patients from the GRACE registry (14 countries, 94 hospitals) and validated externally in the French FAST-MI 2005 registry.

Participants

Patients presenting with ST-elevation and non-ST elevation ACS and with long-term outcomes

Outcome measures

The GRACE Score (2.0) predicts the risk of short and long-term mortality, and death/myocardial infarction, overall and in hospital survivors.

Results

For key independent risk predictors of death (1yr) non-linear associations (versus linear) were found for age (p<.0005), SBP (p<.0001), pulse (p<.0001), creatinine (p<.0001). By employing non-linear algorithms there was improved model discrimination, validated externally. Using the FAST-MI 2005 cohort the C indices for death exceeded 0.82 for the overall population at one year and also at 3 years. Discrimination for death or MI was slightly lower than for death alone (c=0.78). Similar results were obtained for hospital survivors, and with substitutions for creatinine and Killip class, the model performed nearly as well.

Conclusions

The updated GRACE risk score has better discrimination and is easier to use than the previous score based upon linear associations. GRACE Risk (2.0) performed equally well acutely and over the longer-term and can be used in a variety of clinical settings to aid management decisions.

ARTICLE SUMMARY

The updated GRACE risk score (2.0) was derived in 32,037 patients from the GRACE registry and validated externally in the French FAST-MI 2005 registry. This risk score has better discrimination and is easier to use than the previous score based upon linear associations. In addition it allows substitutions for risk markers that may not be available at the time of first patient presentation (creatinine and Killip class). GRACE Risk (2.0) performed equally well acutely and over the longer-term and can be used in a variety of clinical settings to aid management decisions. It is freely available to download to electronic devices.

Strengths and Limitations

- The GRACE 2.0 risk score is derived from the largest multinational registry in acute coronary syndromes (Global Registry of Acute Coronary Events) and validated in an entirely independent dataset with comprehensive long-term outcome data.
- This risk score employs non-linear functions and is more accurate than the original version, and it is now validated over the longer-term (to 1 and 3 years) and with substitutions possible for creatinine values and Killip class (performing almost as well).
- This electronic risk score is designed to be used in mobile electronic devices (approximately 30 seconds to enter data) and presents the risk of death (or death/MI) and relative to the entire ACS population
- The score is designed to assist clinical management decisions and is not a substitute for individual patient clinical assessment. However, it may help to address the current "treatment–risk paradox" whereby low rather than high risk patients are more likely to receive interventional therapies
- Additional factors may influence outcome, especially in geographic populations and healthcare systems not evaluated in the multinational GRACE programme

INTRODUCTION

Acute coronary syndromes (ACS) comprise a heterogeneous spectrum of patients who are currently stratified for management mainly on the basis of ECG characteristics and biomarker results. NICE, SIGN, ESC and North American guidelines separate patients into ST elevation MI or non-ST elevation ACS and they also recommend use of a risk score such as the GRACE score.[1-4] However, systematic risk stratification is not widely performed, despite the evidence and the guidelines.

Why should risk assessment be important for the triage and management of patients with acute coronary disease?

Whether a patient proceeds to an immediate, urgent or delayed coronary angiography and revascularisation and which of acute antithrombotic regimens is chosen depends on patient risk characteristics. Evidence from randomised trials and guideline recommendations all support the use of different strategies according to risk status.[1-4]

In the development of NICE guideline 94 (www.nice.org/cg94) the guideline states that single variables (for example troponin) were not as good as multiple variables in predicting outcome.[1] NICE independently tested all of the published risk scores (GRACE[5,6], TIMI[7], PURSUIT[8], PREDICT[9], EMMACE[10], SRI[11], AMIS[12], UA[13] risk score) in 64,312 patients from the MINAP dataset. They employed a "mini-GRACE score" as many of the MINAP patients lacked creatinine values and Killip classification (substituting history of renal dysfunction and the use of diuretics) and this approach also demonstrated good performance in an independent assessment[14]. The c statistic was 0.825 with 95% confidence bounds 0.82-0.83 and this was superior to the performance of the other risk scores and hence the recommendation from NICE to employ the GRACE risk score.[1] However, the use of substitutions for creatinine and for Killip Class has not been validated in an independent dataset and the prediction of long-term outcome had not been tested. In addition, non-linear functions for continuous variables and for Killip class may improve model discrimination and could be implemented in hand-held electronic devices.

Resolving the "treatment-risk paradox"

We, and others, have revealed a treatment-risk paradox in the management of acute coronary disease.[15,16] In contrast to the evidence and the guideline recommendations, lower risk rather than higher risk patients are more likely to undergo interventional procedures and receive more aggressive antithrombotic and other therapies .[15,16] This phenomenon has now been reported across widely different healthcare systems and different geographic settings. Why is this? Firstly, current treatment decisions rely on clinical assessment and it is difficult for the clinician to weigh up potential benefits against potential hazards and hence lower risk patients are commonly selected for more aggressive treatment (an unintended risk averse approach). However, evidence demonstrates that even excluding those with contra-indications, higher risk cohorts potentially have more to gain. [15]

Why aren't risk scores more widely used?

Internationally, risk scores are not systematically applied for the management of ACS despite the evidence and guideline recommendations. Several factors contribute to this including the misperception that clinician assessment or the use of individual risk indicators is sufficient.[1,2,17] In addition, the most accurate risk scores have been cumbersome to compute (for example requiring look-up tables and many use arbitrary score results). Finally, the parameters necessary for their implementation may not be available at the time of patient's initial presentation.

What this study adds

We aimed to develop and validate a revised and more accurate version of the GRACE risk score suitable for both acute and long-term prediction of risk. Instead of assuming continuous variables such as age and the categorical variable Killip class were linearly associated with risk, we tested for non-linear associations and included them in the revised prediction tool where appropriate. In contrast to the earlier version of the GRACE score which required computing a numerical score (without absolute risks) we derived and externally validated an electronic version with absolute percentage risks. This is suitable for use in hand held electronic devices and smart phones, and the clinical applicability is broadened by using substitutions for creatinine and Killip class. Creatinine values may only be available after hospital admission and many settings do not routinely use Killip class for evaluating heart failure symptoms. Thus, the aim of this study was to develop a simplified risk score suitable for applications in a variety of settings and to test the accuracy of the revised GRACE risk predictor (GRACE Score 2.0) to predict early and long-term risk, as an aid to clinical management.

METHODS

GRACE risk score

The GRACE registry was designed to reflect an unbiased population of patients with acute coronary syndrome and was undertaken over 10 years, in 94 hospitals and 14 countries.[5,6,18,19,20] The design has been reported previously.[18,20]

In-hospital and up to 6 months outcomes and risk scores were derived based upon independent predictors of outcome. These have been described previously (ST segment deviation, age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest at admission, elevated biomarkers of necrosis).[5,6] The GRACE risk score was derived from the original population of 26,267 patients (11,389 for hospital score for patients enrolled through 31 March 2001; 21,688 were used to derive the 6 month risk score for patients enrolled through 30 Sept 2002) with suspected acute coronary syndrome, validated prospectively in a further set of 22,122 patients and validated externally.[5]

Risk characteristics of populations may evolve over time (as management changes) and it is appropriate the GRACE score should be tested in a more recent cohort of ACS patients and with extended follow-up.[21]

The original GRACE score estimated in hospital risk of death or the combination of death or MI and the same outcomes up to 6 months post-discharge. The new version of the GRACE risk score for one year outcomes was derived in the more recent dataset of 32,037 patients from the GRACE registry enrolled between January 2002 and December 2007. For three year mortality the UK cohort of 1,274 patients with long term follow-up was employed. The characteristics of this study population have been previously reported.[20] The algorithm employed the same independent predictors of outcome as originally derived and reported, but non-linear associations were incorporated to improve model discrimination. In addition, a simplified version of the risk score was developed with substitutions for creatinine (history of renal dysfunction) and substitutions for Killip class (diuretic usage). As previously validated, a parsimonious model of only 8 factors conveyed more than 90% of the predictive accuracy of the complete multivariable model.[5,6]

Consistency of estimates in different GRACE risk models

The GRACE risk score version 2.0 contains slightly more precise estimates of version 1.0 hospital[6] and 6 month death[5] probabilities. Instead of converting model estimates to a point system, and using intervals for continuous variables such as age, as in version 1.0, version 2.0 directly utilizes model estimates themselves to compute cumulative risk (see: http://www.outcomes-umassmed.org/grace/files/GRACE_RiskModel_Coefficients.pdf

Because GRACE models were derived in different patient populations from different study periods, differences in cumulative rate estimates for the same interval exist. The one year death model contains the most recent and largest patient populations. Therefore, 6 month and 3 year death models were standardized to conform to estimated Kaplan-Meier cumulative rates for the one year model. The revised version 2.0 6 month cumulative estimates now conform to version 2.0 one year model estimates as of 6 months, and the one year estimates for the version 2.0 3 year model as of one year also conform to version 2.0 one year estimates for the one year model.

External validation

The updated GRACE risk score was validated by testing the algorithm in its full version and simplified version in an entirely separate registry population, the French registry of Acute ST-elevation and non ST-elevation Myocardial Infarction (FAST-MI).[22,23,24] FAST-MI 2005 is a nationwide French registry conducted over a month period at the end of 2005 and it included 3,059 patients with STEMI or non STEMI from 223 centres. Follow-up was conducted by a research team from the Société Française de Cardiologie and investigators[22,23]. Sequentially they consulted death registry data, wrote to family doctors and/or cardiologists and wrote to patients. In many instances, written contact was followed by telephone interviews [22,23]. All variables required to calculate the new GRACE risk score were available in 2,959 of the 3059 patients (96.7% of the full cohort). The GRACE algorithm was applied to the 2,959 patients using logistic regression and the c statistics calculated for mortality at one year, mortality at 3 years and then for the subsets of patients with ST elevation MI and non ST elevation MI. In addition, c statistics were calculated for death or myocardial infarction. The same analyses were then repeated for hospital survivors only (n=2,806). In addition, goodness of fit was tested using the Hosmer-Lemeshow test.

Likewise, the simplified score was tested in the 3,035 patients in whom all variables needed for its calculation were available.

Statistics

The Kaplan-Meier method was used to estimate one and three year outcome rates.

Cox multiple regression models were fitted to outcomes of death and death or MI within one and three years of hospital admission. The same eight factors used in the original GRACE risk scores were used.[6] The method of restricted cubic splines[25] , employs a smooth polynominal function, and was used to test for possible non-linear associations between outcomes and age, creatinine, pulse, and systolic blood pressure. Also, Killip class using four categories was compared to linear Killip class. Associations that improved model likelihood at the alpha = 0.05 level were retained in final models. Such associations were also plotted and examined for clinical plausibility.

Model performance was evaluated using the May-Hosmer goodness of fit test[26], and Harrell's c index for model discrimination.[27] A prediction tool based on these models uses point estimates and baseline survival to arrive at predicted outcomes for a given patient's covariate experience.[28] Plots of estimated model event probabilities for non-linear covariates were produced using baseline survival estimates and risk factor parameter estimates (on the log hazard scale), evaluated at covariate means. These plots describe the shape of the association between the non-linear factors and outcomes, but they do not substitute for entering all a patient's risk factor information into the risk tool.

RESULTS

Patient characteristics

For the 32,037 patients from the GRACE registry (table 1) there were 2,422 deaths within 365 days of initial admission, and complete covariate data. The distribution of deaths was as follows: 1,275 in hospital (53%), 983 deaths after discharge within 180 days of admission (41%), 164 deaths from 181-365 days after admission (7%). The estimated 365 day cumulative death rate is 9.3% using the Kaplan-Meier method.

For the 3-year model derived from 1,274 patients from the United Kingdom, there were 261 deaths: 59 in hospital (23%), 51 after discharge within 180 days of admission (20%), and 151 in the remaining two and one half years since admission (58%). The estimated 3-year cumulative death rate is 20.5%.

Performance of the model using non-linear functions

Analyses were undertaken firstly using categorical variables and linear associations for continuous variables and Killip class (as in the original description of the GRACE risk score), [5,6] and then using non-linear associations for age, heart rate, systolic blood pressure and creatinine (figure 1 a,b,c,d). Differences were observed between the non-linear and the linear model with the former more likely to classify patients as at high risk (data not shown).

Non-linear associations for the one year mortality model were found for all four continuous measures: systolic blood pressure, pulse, age, and creatinine ($p < 0.001$ vs linear). The restricted cubic spline (polynominal curve) functions for age and systolic blood pressure had 3 knots ("inflection points") at the 10th, 50th, and 90th percentiles of their distributions, 4 knots at the 5th, 35th, 65th and 95th percentiles of pulse and creatinine distributions. Hazard ratio (HR) estimates are reported for selected intervals, to provide a sense of how associations change over covariate ranges (Table 2). Killip class is modelled as 4 distinct groups ($p < 0.001$ vs linear class). The one year death/MI model has similar non-linear associations, while the 3 year death model, has 4 knot cubic spline associations for systolic blood pressure and pulse, linear associations for remaining factors. Also shown are estimates for the substitute factors of renal insufficiency and diuretics, which can be used to replace creatinine and Killip when they are unavailable. Sample sizes increase somewhat for models using the substitute factors, and model discrimination is only slightly diminished.

The goodness of fit test is partly a function of sample size with larger sample sizes increasing the chance that a small difference between observed and expected numbers of death will be detected. This was observed, with differences mainly in the 9th risk decile, (the model predicted 3-year risk of 17%, estimated observed death 19.5%). The largest difference in remaining deciles is 1.2%.

Based on relative model chi-square values, age is the most important factor in all 3 models, followed by systolic blood pressure, creatinine, and Killip class in the one-year model (all have similar chi-square values), creatinine and Killip class in the one-year death/MI model, and systolic blood pressure and pulse in the 3-year death model. All models show good discrimination (c indices ≥ 0.74), although combining MI with death in the one year model reduces model discrimination, because death and MI are not interchangeable with respect to patient risk profiles.

External validation of the non-linear GRACE risk score in the FAST-MI 2005 registry

The characteristics of the FAST-MI 2005 registry are reflective of the range of patients presenting with ACS (mean age 66.9 years ± standard deviation 14.4 years, 31% women, 53% STEMI, 47% non STEMI, coronary artery disease history 30%, history of stroke 5%, documented diabetes mellitus 24%, documented hypertension 57%, current smoking 30%, documented hypercholesterolemia 47.5%). The FAST-MI 2005 registry has excellent completeness of follow up (3 year follow up 98% complete). Overall survival was 79% and infarct free survival 73%.

Using the FAST-MI 2005 cohort of 2,959 patients c-statistics for death exceeded 0.82 for the overall population at one year and also at 3 years (table). Discrimination for death in the model was higher in the ST elevation MI population (c= 0.84) at one year compared to the non STEMI population (c=0.80). Discrimination for death or MI was slightly lower than for death alone (c=0.78) both at one year and 3 years. Similar figures were obtained for hospital survivors (see tables 3a and 3b).

The c-statistics for 3 year death were calculated using the same approach for the whole ACS population and at 3 years were 0.82 for death and 0.75 for death or MI.

The c indices using the simplified GRACE model with substitutions for Killip class and serum creatinine, available for 99.2% of patients, these were 0.82 for both one and three yr models).

In summary, use of non-linear functions for continuous variables improved model performance over the original GRACE risk score using linear functions. The external validation demonstrated good model discrimination at one and 3 years for both death and death or MI, and in sub-types of MI, ST elevation and non ST elevation MI. This has not previously been tested. The risk score performs similarly when considering only the survivors of hospitalisation. The simplified risk score using history of renal dysfunction in place of creatinine values, and use of diuretics in place of Killip class, performed almost as well as the full GRACE score.

DISCUSSION

This study aimed to develop an improved version of the GRACE risk predictor (GRACE score 2.0) incorporating non-linear associations between continuous risk factors and outcomes in a format suitable for ease of use in handheld electronic devices and smart phones (Figure 2). In addition, the revised GRACE risk score allows readily available substitutions for missing variables at the time of first patient presentation (creatinine, Killip score) and this allows the healthcare professional to risk score a more complete range of patients hospitalised with ACS. The score is not dependent on key variables – it allows flexibility in light of data availability. Further, the GRACE score had not been tested for predictive accuracy beyond 6 months and the simplified version of the risk score with substitutions for creatinine and for Killip class had not been tested in an independent population. A key finding is that model likelihood using individual non-linear functions for heart rate, systolic blood pressure, age, and creatinine was significantly improved over a model using linear functions for these factors. In brief, the model with non-linear functions matches observed data more closely. Further, the updated GRACE risk score demonstrated similar high model discrimination at one and 3 years as had previously been demonstrated for in hospital outcomes and outcomes to 6 months. In addition, the reduced version of the GRACE risk score with substitutions for creatinine and Killip class (with history of renal dysfunction and use of diuretics respectively), performs nearly as well as the model with original factors.

What are the implications?

In a diverse range of hospitals in 14 countries worldwide, with on-site angiographic facilities, the frequency of catheterisations and percutaneous coronary interventions exhibited a paradoxical pattern, whereby most interventions were performed in low risk rather than high risk patients (the “treatment-risk paradox”).[15,16]

To counter the criticism that not all high risk patients will be suitable for revascularisation we undertook further analyses in a previous publication according to the frequency of angiography (hospitals with on-site angiographic facilities were divided into tertiles

according to the rate of coronary angiography).[15] Hospitals with a high rate of coronary angiography performed substantially more interventions in higher risk patients than those performed in the low rate hospitals, despite a similar range of risks of patients, demonstrating that these patients were amenable to the intervention procedures.[15]

It is possible to estimate the "deficit" in the frequency of revascularisation based upon the actual differences between high rate and low rate hospitals observed in the GRACE programme. From the overall population 37.8% of patients were in the GRACE high risk group, 36.1% in the GRACE medium risk group and 26.1% in the GRACE lower risk group (categories according to the ESC guidelines).[3] As previously reported[15] individuals in the highest third of GRACE risk score had catheterisation performed in 51% and PCI or CABG in 31.4% of patients whereas those in the medium GRACE risk group had catheterisation in 68% and PCI or CABG in 42.9% and those in the lower risk group had catheterisation in 72% and PCI or CABG in 47.6%.

Taking the performance of hospitals that were in the highest third for the rate of coronary angiography (they performed PCI and CABG in 60.2% of the presenting population) it is possible to calculate the deficit compared to the hospitals with the lowest rate of angiography and revascularisation. The calculation assumes that the low performance hospitals increased their rate of PCI and CABG to the same as was observed in the highest third of hospitals. This projection is based on observed performance data for the rate of angiography. The calculation assumes no more PCI or CABG performed than was observed in the high rate hospitals. In brief, 700 more patients per 10,000 would undergo revascularisation if the same patients presented to high performance hospitals.

The impact of revascularisations on outcomes can be estimated from the pooled analysis of all the randomised trials where patients were randomised to an interventional strategy as a routine, or to a selective strategy based upon symptoms and ischaemia.[29] We previously reported this combined analysis based upon individual patient data from the FRISC-2[30], RITA-3[31] and ICTUS[32] trials and the absolute reduction in cardiovascular deaths and MIs was 11.1 per 100 patients in the highest risk group and 4 per 100 in the medium risk group, over 5 years.[29-32] Thus, based upon the impact of a systematic interventional strategy in the randomised trials, there would be between 30 and 80 fewer cardiovascular deaths or MIs for each 10,000 patients with non ST elevation ACS. The estimate is conservative as it excludes the impact on medium risk patients and the number would be higher if the top quintile of performance was used as the reference standard rather than the top tertile. Thus, consistent with the guideline recommendations a systematic approach for evaluating risk has the potential to increase the rate of revascularisation in high risk patients without contra-indications. Based upon the combined analysis of all the randomised trials with long term outcomes this risk related strategy has the potential to reduce the frequency of cardiovascular death and MI, over the longer term. The "High" "Medium" and "Low" risk categories may help guide practice decisions and they correspond with categories used by the European Society of Cardiology Guidelines[3]. However for more precise estimates the GRACE risk score also provides the numerical risk of death (or death/MI) at various time points.

Strengths and limitations

Recognising that population characteristics may differ in comparison with that of the originally derived GRACE model, we employed the most recent GRACE dataset in this study and we externally validated the risk model in an entirely separate dataset (FAST-MI 2005 with yearly follow up to 2010). We have previously reported that the GRACE risk prediction is not subject to significant change over time[33]. The purpose of providing 1 year and 3 year risk estimates was to aid the clinician regarding secondary prevention. The risk prediction estimates at 3 years were consistent with those at one year (although the 3 year data derive from a smaller dataset).

The GRACE programme is the largest multi-national programme in acute coronary artery disease and was designed to ensure that the included patients were reflective of the broad spectrum of patients presenting with acute coronary syndrome, and of the range of hospitals in clinical practice. The sites were trained, audited and quality control measures were enacted throughout the study. Use of the UK cohort allowed estimation of long-term outcomes (as previously reported) with complete mortality data to 5 years.[20] The external validation of the updated risk score was performed in the FAST-MI 2005 registry with inclusion of the full spectrum of hospitals admitting patients with ACS and excellent completeness of follow-up.

Although the updated GRACE risk score provides a reliable estimate for stratifying patients both acutely and in the long-term, additional factors contribute to longer term risk. Further refinement of the risk score for long term outcomes may require the inclusion of additional risk factors and biomarkers to increase precision, but the current risk scores' discrimination allows separation of patients into broad categories relevant for decisions on clinical management. Future studies will determine the impact of risk scoring strategies in various populations including the frail and elderly.

CONCLUSIONS

The updated GRACE risk score has better model discrimination and is easier to use than previous scores based upon categorical variables. It is accurate in the acute phase and over the longer term and can be used in a variety of clinical settings to aid management decisions.

Acknowledgements

This work was supported by the British Heart Foundation, an award from the Chief Scientist Scotland (CZG/2/455) and unrestricted grant from AstraZeneca to the University of Edinburgh. The GRACE risk score has been made available[34] to download without cost (www.gracescore.co.uk and www.outcomes.org/grace)

Text: 3479 words (introduction to end of acknowledgements)

FUNDING STATEMENT

This work was supported by the British Heart Foundation (CH92010), an award from the Chief Scientist Scotland (CZG/2/455) and unrestricted grant from AstraZeneca to the University of Edinburgh. The FAST-MI registry is a registry of the French Society of Cardiology, supported by unrestricted grants from Pfizer and Servier. Additional support for FAST-MI was obtained from a research grant from the French National Health Insurance System (Caisse Nationale d'Assurance Maladie).

AUTHORS' CONTRIBUTIONS

KAA Fox initiated the programme of work, performed the analyses in conjunction with co-authors and wrote and revised the manuscript. G FitzGerald led the work deriving the revised risk score, in conjunction with F Anderson, Wei Huang. K Carruthers analysed and interpreted the data. N Danchin in conjunction with E Puymirat, T Simon, P Coste, J Monsegu, P G Steg performed the work on the FAST MI dataset. All authors contributed to the revisions of the manuscript and the interpretation of the findings.

COMPETING INTERESTS STATEMENT

International Committee of Medical Journal Editors (ICMJE) forms completed for all authors and submitted (see attachments)

DATA SHARING STATEMENT

No further unpublished data

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Legends

Figure 1a,b,c,d
Non-linear associations for the one year mortality model were found for four continuous measures: systolic blood pressure (figure 1a), pulse (figure 1b), age (figure 1c), and creatinine (figure 1c), ($p < 0.001$ vs linear for each comparison).

Figure 2
Illustration of the GRACE Score 2.0 on a mobile device (suitable for use in iOS, android or web versions). Left panel: values for percentage risk of death or death/MI (or numerical GRACE Score). Remaining panels show the individual patient results as a vertical column superimposed on the entire ACS distribution curve (green column= low risk illustration, yellow column=medium risk, red column= high risk)[34]. For further information see www.gracescore.co.uk and www.outcomes.org/grace

*Table 1 C*haracteristics on admission of the GRACE ACS patients used in 1-year death model and the FAST-MI patients

	GRACE	FAST-MI 2005
Demographics		
Age, y	66.6 (56.0-76.4)	68.5 (55.9-78.6)
Female	33%	31%
Weight, kg	78 (68-89)	75 (65-85)
Height, cm	170 (162-175)	169 (162-175)
BMI, kg/m^2	27 (24-30)	26 (24-29)
Medical history, %		
Angina	44	30
Atrial fib	7.7	NA
CABG	13	5
Congestive heart failure	10	6
Diabetes	26	24
Dyslipidemia	51	47
Hypertension	64	57
MI	30	17
PCI	19	13
Peripheral arterial disease	9.0	9
Renal insufficiency	7.6	5
Smoking	57	53
Stroke	8.5	6
Presentation characteristics		
Pulse, beats/min	76 (65-90)	77 (66-90)
DBP, mm Hg	80 (70-90)	80 (70-90)
SBP, mm Hg	140 (120-160)	140 (120-158)
Killip class I	85%	77%
Killip class II	11%	113%
Killip class III	3.6%	8%
Killip class IV	0.8%	2%
Cardiac arrest	1.9%	1.7%

Initial cardiac enzymes positive	52%	100%
Initial serum creatinine, mg/dL	1.02 (0.90-1.25)	1.02 (0.85-1.23)
Electrocardiographic findings, %		
ST-segment elevation	36	50
ST-segment depression	32	22
ST-segment deviation	53	72
T wave inversion	25	10
ST-segment elevation anterior	16	21
ST-segment elevation inferior	18	27
ST-segment depression anterior	15	NA
ST-segment depression inferior	9.2	NA
Any significant Q wave	19	12
Left bundle branch block	4.7	3.9
Prior use of medical therapy, %		
Aspirin	40	24
ACE inhibitors	30	19
Statins	32	27

3307 missing weight, 6098 missing height, 6732 missing BMI; no other variable missing > 300.
Median (IQR) if continuous variable; % if discret

TABLE 2. Summary of Cox regression models

	Admission to 1 year death	Admission to 1 year death or MI	Admission to 3 year death
Total no. of observations	32,037	32,037	1,274
No of outcomes	2422	3655	261
May-Hosmer goodness of model fit (*P*)	<0.001	0.06	0.60
Harrell's c index	0.829	0.746	0.782
Model estimates	HR (95% CI), χ^2	HR (95% CI), χ^2	HR (95% CI), χ^2
Age per 10 y: <67	1.5 (1.4 - 1.7), 1069	1.2 (1.1 – 1.3), 853	1.8 (1.6 – 2.1), 102
≥ 67	1.9 (1.8 - 2.0)	1.6 (1.5 – 1.6)	n/a (linear)
Systolic blood pressure per -20 mm Hg	≥ 139: 1.1 (1.0 - 1.2), 293	≥ 139: 1.0 (1.0 - 1.1), 200	≥ 160: 0.9 (0.7 – 1.1), 36
	< 139: 1.3 (1.3 - 1.4)	<139: 1.3 (1.2 - 1.3)	130 – 159: 1.6 (1.2 – 2.0)

			< 130: 1.3 (1.0 – 1.6)
Pulse per 30 BPM: <51	1.1 (0.9 - 1.4), 131	1.0 (0.9 – 1.3), 126	1.0 (0.3 – 2.7), 32
51-83	1.5 (1.4 - 1.7)	1.4 (1.2 – 1.5)	1.7 (1.1 – 2.8)
84-118	1.3 (1.2 - 1.4)	1.2 (1.2 – 1.3)	1.6 (1.2 – 2.0)
>118	0.9 (0.8 - 1.0)	0.9 (0.8 – 1.0)	0.9 (0.6 – 1.1)
Creatinine per mg: <1	0.6 (0.4 – 1.0), 305	0.9 (0.6 – 1.3), 338	1.5 (1.3 – 1.8), 23
1 – 2	2.2 (2.0 – 2.4)	1.9 (1.7 – 2.0)	n/a (linear)
>2	1.1 (1.1 – 1.2)	1.1 (1.1 – 1.2)	n/a (linear)
Killip class II (v I)	1.9 (1.7 – 2.1), 305	1.7 (1.6 - 1.9), 288	1.1 (0.8 – 1.4), 18
Killip class III (v I)	2.4 (2.1 – 2.7)	2.0 (1.8 – 2.2)	III-IV v I: 2.3 (1.6 – 3.4)
Killip class IV (v I)	3.7 (3.0 – 4.5)	3.2 (2.6 – 3.9)	n/a
Cardiac arrest at admission	2.4 (2.0 – 2.9), 74	2.0 (1.7 – 2.3), 55	2.9 (1.7 – 5.2), 14
Positive initial enzymes	1.5 (1.3 – 1.6), 72	1.3 (1.2 -1.4), 42	n/a
ST deviation	1.6 (1.4 – 1.7), 109	1.4 (1.3 – 1.5), 92	1.5 (1.2 – 1.9), 10

Substitute factors*: renal insufficiency	1.6 (1.4-1.7), 66	1.6 (1.5 – 1.8), 105	2.0 (1.3 – 3.2), 9
Diuretics in first 24 h	2.0 (1.8-2.1), 266	1.7 (1.6 – 1.8), 236	2.0 (1.5 – 2.6), 27

* Renal insufficiency substituted for creatinine, diuretics for Killip class; sample sizes increase to 33,890 patients with 2585 deaths within a year of admission (c index .820), 33,890 patients with 3882 deaths or MIs within a year of admission (c index .738), 1298 patients with 266 deaths within 3 years of admission (c index .780).

Table 3a the full GRACE risk score tested in FAST-MI 2005

From ACS presentation	Overall population (death) n=2959	STEMI (death) N=1558	Non-STEMI (death) N=1401	Overall Death/MI
1-year Death	0.83	0.84	0.82	0.77
3-year Death	0.82	0.82	0.82	0.77
Hospital Survivors	n=2806	N=1472	N=1334	
1-year Death	0.81	0.82	0.80	0.73
3-year Death	0.80	0.80	0.80	0.75

Table 3b the simplified GRACE risk score, with substitutions for Killip and creatinine (n=3035), tested in FAST-MI 2005

From ACS presentation	Overall population (death) N=3035	STEMI (death) N= 1596	Non-STEMI (death) N=1439	Overall Death/MI
1-year Death	0.82	0.84	0.80	0.80
3-year Death	0.82	0.83	0.82	0.78
Hospital Survivors	N=2872	N=1504	N=1368	
1-year Death	0.80	0.83	0.78	0.74
3-year Death	0.81	0.80	0.80	0.76

Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation, and outcomes using the updated GRACE risk score

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Keywords: Acute coronary syndromes, risk stratification, GRACE score, outcomes, myocardial infarction

STRUCTURED ABSTRACT (300 words)

Objectives

Risk scores are recommended in guidelines to facilitate the management of patients who present with acute coronary syndromes (ACS). Internationally, such scores are not systematically used because they are not easy to apply and some risk indicators are not available at first presentation. We aimed to derive and externally validate a more accurate version of the GRACE Risk Score for predicting the risk of death or death/myocardial infarction both acutely and over the longer term. The risk score was designed to be suitable for acute and emergency clinical settings and usable in electronic devices.

Design and setting

The GRACE risk score (2.0) was derived in 32,037 patients from the GRACE registry (14 countries, 94 hospitals) and validated externally in the French FAST-MI 2005 registry.

Participants

Patients presenting with ST-elevation and non-ST elevation ACS and with long-term outcomes

Outcome measures

The GRACE Score (2.0) predicts the risk of short and long-term mortality, and death/myocardial infarction, overall and in hospital survivors.

Results

For key independent risk predictors of death (1yr) non-linear associations (versus linear) were found for age (p<.0005), SBP (p<.0001), pulse (p<.0001), creatinine (p<.0001). By employing non-linear algorithms there was improved model discrimination, validated externally. Using the FAST-MI 2005 cohort the C indices for death exceeded 0.82 for the overall population at one year and also at 3 years. Discrimination for death or MI was slightly lower than for death alone (c=0.78). Similar results were obtained for hospital survivors, and with substitutions for creatinine and Killip class, the model performed nearly as well.

Conclusions

The updated GRACE risk score has better discrimination and is easier to use than the previous score based upon linear associations. GRACE Risk (2.0) performed equally well acutely and over the longer-term and can be used in a variety of clinical settings to aid management decisions.

ARTICLE SUMMARY

The updated GRACE risk score (2.0) was derived in 32,037 patients from the GRACE registry and validated externally in the French FAST-MI 2005 registry. This risk score has better discrimination and is easier to use than the previous score based upon linear associations. In addition it allows substitutions for risk markers that may not be available at the time of first patient presentation (creatinine and Killip class). GRACE Risk (2.0) performed equally well acutely and over the longer-term and can be used in a variety of clinical settings to aid management decisions. It is freely available to download to electronic devices.

Strengths and Limitations

- The GRACE 2.0 risk score is derived from the largest multinational registry in acute coronary syndromes (Global Registry of Acute Coronary Events) and validated in an entirely independent dataset with comprehensive long-term outcome data.
- This risk score employs non-linear functions and is more accurate than the original version, and it is now validated over the longer-term (to 1 and 3 years) and with substitutions possible for creatinine values and Killip class (performing almost as well).
- This electronic risk score is designed to be used in mobile electronic devices (approximately 30 seconds to enter data) and presents the risk of death (or death/MI) and relative to the entire ACS population
- The score is designed to assist clinical management decisions and is not a substitute for individual patient clinical assessment. However, it may help to address the current "treatment–risk paradox" whereby low rather than high risk patients are more likely to receive interventional therapies
- Additional factors may influence outcome, especially in geographic populations and healthcare systems not evaluated in the multinational GRACE programme

FUNDING STATEMENT

This work was supported by the British Heart Foundation (CH92010), an award from the Chief Scientist Scotland (CZG/2/455) and unrestricted grant from AstraZeneca to the University of Edinburgh. The FAST-MI registry is a registry of the French Society of Cardiology, supported by unrestricted grants from Pfizer and Servier. Additional support for FAST-MI was obtained from a research grant from the French National Health Insurance System (Caisse Nationale d'Assurance Maladie).

COMPETING INTERESTS STATEMENT

International Committee of Medical Journal Editors (ICMJE) forms completed for all authors and submitted (see attachments)

AUTHORS' CONTRIBUTIONS

KAA Fox initiated the programme of work, performed the analyses in conjunction with co-authors and wrote and revised the manuscript. G FitzGerald led the work deriving the revised risk score, in conjunction with F Anderson, Wei Huang. K Carruthers analysed and interpreted the data. N Danchin in conjunction with E Puymirat, T Simon, P Coste, J

Monsegu, P G Steg performed the work on the FAST MI dataset. All authors contributed to the revisions of the manuscript and the interpretation of the findings.

INTRODUCTION

Acute coronary syndromes (ACS) comprise a heterogeneous spectrum of patients who are currently stratified for management mainly on the basis of ECG characteristics and biomarker results. NICE, SIGN, ESC and North American guidelines separate patients into ST elevation MI or non-ST elevation ACS and they also recommend use of a risk score such as the GRACE score.[1-4] However, systematic risk stratification is not widely performed, despite the evidence and the guidelines.

Why should risk assessment be important for the triage and management of patients with acute coronary disease?

Whether a patient proceeds to an immediate, urgent or delayed coronary angiography and revascularisation and which of acute antithrombotic regimens is chosen depends on patient risk characteristics. Evidence from randomised trials and guideline recommendations all support the use of different strategies according to risk status.[1-4]

In the development of NICE guideline 94 (www.nice.org/cg94) the guideline states that single variables (for example troponin) were not as good as multiple variables in predicting outcome.[1] NICE independently tested all of the published risk scores (GRACE[5,6], TIMI[7], PURSUIT[8], PREDICT[9], EMMACE[10], SRI[11], AMIS[12], UA[13] risk score) in 64,312 patients from the MINAP dataset. They employed a "mini-GRACE score" as many of the MINAP patients lacked creatinine values and Killip classification (substituting history of renal dysfunction and the use of diuretics) and this approach also demonstrated good performance in an independent assessment[14]. The c statistic was 0.825 with 95% confidence bounds 0.82-0.83 and this was superior to the performance of the other risk scores and hence the recommendation from NICE to employ the GRACE risk score.[1] However, the use of substitutions for creatinine and for Killip Class has not been validated in an independent dataset and the prediction of long-term outcome had not been tested. In addition, non-linear functions for continuous variables and for Killip class may improve model discrimination and could be implemented in hand-held electronic devices.

Resolving the "treatment-risk paradox"

We, and others, have revealed a treatment-risk paradox in the management of acute coronary disease.[15,16] In contrast to the evidence and the guideline recommendations, lower risk rather than higher risk patients are more likely to undergo interventional procedures and receive more aggressive antithrombotic and other therapies .[15,16] This phenomenon has now been reported across widely different healthcare systems and different geographic settings. Why is this? Firstly, current treatment decisions rely on clinical assessment and it is difficult for the clinician to weigh up potential benefits against potential hazards and hence lower risk patients are commonly selected for more aggressive treatment (an unintended risk averse approach). However, evidence demonstrates that even excluding those with contra-indications, higher risk cohorts potentially have more to gain. [15]

Why aren't risk scores more widely used?

Internationally, risk scores are not systematically applied for the management of ACS despite the evidence and guideline recommendations. Several factors contribute to this including the misperception that clinician assessment or the use of individual risk indicators is sufficient.[1,2,17] In addition, the most accurate risk scores have been cumbersome to compute (for example requiring look-up tables and many use arbitrary score results). Finally, the parameters necessary for their implementation may not be available at the time of patient's initial presentation.

What this study adds

We aimed to develop and validate a revised and more accurate version of the GRACE risk score suitable for both acute and long-term prediction of risk. Instead of assuming continuous variables such as age and the categorical variable Killip class were linearly associated with risk, we tested for non-linear associations and included them in the revised prediction tool where appropriate. In contrast to the earlier version of the GRACE score which required computing a numerical score (without absolute risks) we derived and externally validated an electronic version with absolute percentage risks. This is suitable for use in hand held electronic devices and smart phones, and the clinical applicability is broadened by using substitutions for creatinine and Killip class. Creatinine values may only be available after hospital admission and many settings do not routinely use Killip class for evaluating heart failure symptoms. Thus, the aim of this study was to develop a simplified risk score suitable for applications in a variety of settings and to test the accuracy of the revised GRACE risk predictor (GRACE Score 2.0) to predict early and long-term risk, as an aid to clinical management.

METHODS

GRACE risk score

The GRACE registry was designed to reflect an unbiased population of patients with acute coronary syndrome and was undertaken over 10 years, in 94 hospitals and 14 countries.[5,6,18,19,20] The design has been reported previously.[18,20]

In-hospital and up to 6 months outcomes and risk scores were derived based upon independent predictors of outcome. These have been described previously (ST segment deviation, age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest at admission, elevated biomarkers of necrosis).[5,6] The GRACE risk score was derived from the original population of 26,267 patients (11,389 for hospital score for patients enrolled through 31 March 2001; 21,688 were used to derive the 6 month risk score for patients enrolled through 30 Sept 2002) with suspected acute coronary syndrome, validated prospectively in a further set of 22,122 patients and validated externally.[5]

Risk characteristics of populations may evolve over time (as management changes) and it is appropriate the GRACE score should be tested in a more recent cohort of ACS patients and with extended follow-up.[21]

The original GRACE score estimated in hospital risk of death or the combination of death or MI and the same outcomes up to 6 months post-discharge. The new version of the GRACE risk score for one year outcomes was derived in the more recent dataset of 32,037 patients from the GRACE registry enrolled between January 2002 and December 2007. For three year mortality the UK cohort of 1,274 patients with long term follow-up was employed. The characteristics of this study population have been previously reported.[20] The algorithm employed the same independent predictors of outcome as originally derived and reported, but non-linear associations were incorporated to improve model discrimination. In addition, a simplified version of the risk score was developed with substitutions for creatinine (history of renal dysfunction) and substitutions for Killip class (diuretic usage). As previously validated, a parsimonious model of only 8 factors conveyed more than 90% of the predictive accuracy of the complete multivariable model.[5,6]

Consistency of estimates in different GRACE risk models

The GRACE risk score version 2.0 contains slightly more precise estimates of version 1.0 hospital[6] and 6 month death[5] probabilities. Instead of converting model estimates to a point system, and using intervals for continuous variables such as age, as in version 1.0, version 2.0 directly utilizes model estimates themselves to compute cumulative risk (see: http://www.outcomes-umassmed.org/grace/files/GRACE_RiskModel_Coefficients.pdf

Because GRACE models were derived in different patient populations from different study periods, differences in cumulative rate estimates for the same interval exist. The one year death model contains the most recent and largest patient populations. Therefore, 6 month and 3 year death models were standardized to conform to estimated Kaplan-Meier cumulative rates for the one year model. The revised version 2.0 6 month cumulative estimates now conform to version 2.0 one year model estimates as of 6 months, and the one year estimates for the version 2.0 3 year model as of one year also conform to version 2.0 one year estimates for the one year model.

External validation

The updated GRACE risk score was validated by testing the algorithm in its full version and simplified version in an entirely separate registry population, the French registry of Acute ST-elevation and non ST-elevation Myocardial Infarction (FAST-MI).[22,23,24] FAST-MI 2005 is a nationwide French registry conducted over a month period at the end of 2005 and it included 3,059 patients with STEMI or non STEMI from 223 centres. Follow-up was conducted by a research team from the Société Française de Cardiologie and investigators[22,23]. Sequentially they consulted death registry data, wrote to family doctors and/or cardiologists and wrote to patients. In many instances, written contact was followed by telephone interviews [22,23]. All variables required to calculate the new GRACE risk score were available in 2,959 of the 3059 patients (96.7% of the full cohort). The GRACE algorithm was applied to the 2,959 patients using logistic regression and the c statistics calculated for mortality at one year, mortality at 3 years and then for the subsets of patients with ST

elevation MI and non ST elevation MI. In addition, c statistics were calculated for death or myocardial infarction. The same analyses were then repeated for hospital survivors only (n=2,806). In addition, goodness of fit was tested using the Hosmer-Lemeshow test. Likewise, the simplified score was tested in the 3,035 patients in whom all variables needed for its calculation were available.

Statistics

The Kaplan-Meier method was used to estimate one and three year outcome rates.

Cox multiple regression models were fitted to outcomes of death and death or MI within one and three years of hospital admission. The same eight factors used in the original GRACE risk scores were used.[6] The method of restricted cubic splines[24] , employs a smooth polynominal function, and was used to test for possible non-linear associations between outcomes and age, creatinine, pulse, and systolic blood pressure. Also, Killip class using four categories was compared to linear Killip class. Associations that improved model likelihood at the alpha = 0.05 level were retained in final models. Such associations were also plotted and examined for clinical plausibility.

Model performance was evaluated using the May-Hosmer goodness of fit test[26], and Harrell's c index for model discrimination.[27] A prediction tool based on these models uses point estimates and baseline survival to arrive at predicted outcomes for a given patient's covariate experience.[28] Plots of estimated model event probabilities for non-linear covariates were produced using baseline survival estimates and risk factor parameter estimates (on the log hazard scale), evaluated at covariate means. These plots describe the shape of the association between the non-linear factors and outcomes, but they do not substitute for entering all a patient's risk factor information into the risk tool.

RESULTS

Patient characteristics

For the 32,037 patients from the GRACE registry (table 1) there were 2,422 deaths within 365 days of initial admission, and complete covariate data. The distribution of deaths was as follows: 1,275 in hospital (53%), 983 deaths after discharge within 180 days of admission (41%), 164 deaths from 181-365 days after admission (7%). The estimated 365 day cumulative death rate is 9.3% using the Kaplan-Meier method.

For the 3-year model derived from 1,274 patients from the United Kingdom, there were 261 deaths: 59 in hospital (23%), 51 after discharge within 180 days of admission (20%), and 151 in the remaining two and one half years since admission (58%). The estimated 3-year cumulative death rate is 20.5%.

Performance of the model using non-linear functions

Analyses were undertaken firstly using categorical variables and linear associations for continuous variables and Killip class (as in the original description of the GRACE risk score),[5,6] and then using non-linear associations for age, heart rate, systolic blood pressure and

creatinine (figure 1 a,b,c,d). Differences were observed between the non-linear and the linear model with the former more likely to classify patients as at high risk (data not shown).

Non-linear associations for the one year mortality model were found for all four continuous measures: systolic blood pressure, pulse, age, and creatinine ($p < 0.001$ vs linear). The restricted cubic spline (polynominal curve) functions for age and systolic blood pressure had 3 knots ("inflection points") at the 10th, 50th, and 90th percentiles of their distributions, 4 knots at the 5th, 35th, 65th and 95th percentiles of pulse and creatinine distributions. Hazard ratio (HR) estimates are reported for selected intervals, to provide a sense of how associations change over covariate ranges (Table 2). Killip class is modelled as 4 distinct groups ($p < 0.001$ vs linear class). The one year death/MI model has similar non-linear associations, while the 3 year death model, has 4 knot cubic spline associations for systolic blood pressure and pulse, linear associations for remaining factors. Also shown are estimates for the substitute factors of renal insufficiency and diuretics, which can be used to replace creatinine and Killip when they are unavailable. Sample sizes increase somewhat for models using the substitute factors, and model discrimination is only slightly diminished.

The goodness of fit test is partly a function of sample size with larger sample sizes increasing the chance that a small difference between observed and expected numbers of death will be detected. This was observed, with differences mainly in the 9th risk decile, (the model predicted 3-year risk of 17%, estimated observed death 19.5%). The largest difference in remaining deciles is 1.2%.

Based on relative model chi-square values, age is the most important factor in all 3 models, followed by systolic blood pressure, creatinine, and Killip class in the one-year model (all have similar chi-square values), creatinine and Killip class in the one-year death/MI model, and systolic blood pressure and pulse in the 3-year death model. All models show good discrimination (c indices ≥ 0.74), although combining MI with death in the one year model reduces model discrimination, because death and MI are not interchangeable with respect to patient risk profiles.

External validation of the non-linear GRACE risk score in the FAST-MI 2005 registry

The characteristics of the FAST-MI 2005 registry are reflective of the range of patients presenting with ACS (mean age 66.9 years ± standard deviation 14.4 years, 31% women, 53% STEMI, 47% non STEMI, coronary artery disease history 30%, history of stroke 5%, documented diabetes mellitus 24%, documented hypertension 57%, current smoking 30%, documented hypercholesterolemia 47.5%). The FAST-MI 2005 registry has excellent completeness of follow up (3 year follow up 98% complete). Overall survival was 79% and infarct free survival 73%.

Using the FAST-MI 2005 cohort of 2,959 patients c-statistics for death exceeded 0.82 for the overall population at one year and also at 3 years (table). Discrimination for death in the model was higher in the ST elevation MI population (c= 0.84) at one year compared to the non STEMI population (c=0.80). Discrimination for death or MI was slightly lower than for

death alone (c=0.78) both at one year and 3 years. Similar figures were obtained for hospital survivors (see tables 3a and 3b).

The c-statistics for 3 year death were calculated using the same approach for the whole ACS population and at 3 years were 0.82 for death and 0.75 for death or MI.

The c indices using the simplified GRACE model with substitutions for Killip class and serum creatinine, available for 99.2% of patients, these were 0.82 for both one and three yr models).

In summary, use of non-linear functions for continuous variables improved model performance over the original GRACE risk score using linear functions. The external validation demonstrated good model discrimination at one and 3 years for both death and death or MI, and in sub-types of MI, ST elevation and non ST elevation MI. This has not previously been tested. The risk score performs similarly when considering only the survivors of hospitalisation. The simplified risk score using history of renal dysfunction in place of creatinine values, and use of diuretics in place of Killip class, performed almost as well as the full GRACE score.

DISCUSSION

This study aimed to develop an improved version of the GRACE risk predictor (GRACE score 2.0) incorporating non-linear associations between continuous risk factors and outcomes in a format suitable for ease of use in handheld electronic devices and smart phones (Figure 2). In addition, the revised GRACE risk score allows readily available substitutions for missing variables at the time of first patient presentation (creatinine, Killip score) and this allows the healthcare professional to risk score a more complete range of patients hospitalised with ACS. The score is not dependent on key variables – it allows flexibility in light of data availability. Further, the GRACE score had not been tested for predictive accuracy beyond 6 months and the simplified version of the risk score with substitutions for creatinine and for Killip class had not been tested in an independent population. A key finding is that model likelihood using individual non-linear functions for heart rate, systolic blood pressure, age, and creatinine was significantly improved over a model using linear functions for these factors. In brief, the model with non-linear functions matches observed data more closely. Further, the updated GRACE risk score demonstrated similar high model discrimination at one and 3 years as had previously been demonstrated for in hospital outcomes and outcomes to 6 months. In addition, the reduced version of the GRACE risk score with substitutions for creatinine and Killip class (with history of renal dysfunction and use of diuretics respectively), performs nearly as well as the model with original factors.

What are the implications?

In a diverse range of hospitals in 14 countries worldwide, with on-site angiographic facilities, the frequency of catheterisations and percutaneous coronary interventions exhibited a paradoxical pattern, whereby most interventions were performed in low risk rather than high risk patients (the “treatment-risk paradox”).[15,16]

To counter the criticism that not all high risk patients will be suitable for revascularisation we undertook further analyses in a previous publication according to the frequency of angiography (hospitals with on-site angiographic facilities were divided into tertiles according to the rate of coronary angiography).[15] Hospitals with a high rate of coronary angiography performed substantially more interventions in higher risk patients than those performed in the low rate hospitals, despite a similar range of risks of patients, demonstrating that these patients were amenable to the intervention procedures.[15]

It is possible to estimate the "deficit" in the frequency of revascularisation based upon the actual differences between high rate and low rate hospitals observed in the GRACE programme. From the overall population 37.8% of patients were in the GRACE high risk group, 36.1% in the GRACE medium risk group and 26.1% in the GRACE lower risk group (categories according to the ESC guidelines).[3] As previously reported[15] individuals in the highest third of GRACE risk score had catheterisation performed in 51% and PCI or CABG in 31.4% of patients whereas those in the medium GRACE risk group had catheterisation in 68% and PCI or CABG in 42.9% and those in the lower risk group had catheterisation in 72% and PCI or CABG in 47.6%.

Taking the performance of hospitals that were in the highest third for the rate of coronary angiography (they performed PCI and CABG in 60.2% of the presenting population) it is possible to calculate the deficit compared to the hospitals with the lowest rate of angiography and revascularisation. The calculation assumes that the low performance hospitals increased their rate of PCI and CABG to the same as was observed in the highest third of hospitals. This projection is based on observed performance data for the rate of angiography. The calculation assumes no more PCI or CABG performed than was observed in the high rate hospitals. In brief, 700 more patients per 10,000 would undergo revascularisation if the same patients presented to high performance hospitals.

The impact of revascularisations on outcomes can be estimated from the pooled analysis of all the randomised trials where patients were randomised to an interventional strategy as a routine, or to a selective strategy based upon symptoms and ischaemia.[29] We previously reported this combined analysis based upon individual patient data from the FRISC-2[30], RITA-3[31] and ICTUS[32] trials and the absolute reduction in cardiovascular deaths and MIs was 11.1 per 100 patients in the highest risk group and 4 per 100 in the medium risk group, over 5 years.[29-32] Thus, based upon the impact of a systematic interventional strategy in the randomised trials, there would be between 30 and 80 fewer cardiovascular deaths or MIs for each 10,000 patients with non ST elevation ACS. The estimate is conservative as it excludes the impact on medium risk patients and the number would be higher if the top quintile of performance was used as the reference standard rather than the top tertile. Thus, consistent with the guideline recommendations a systematic approach for evaluating risk has the potential to increase the rate of revascularisation in high risk patients without contra-indications. Based upon the combined analysis of all the randomised trials with long term outcomes this risk related strategy has the potential to reduce the frequency of cardiovascular death and MI, over the longer term. The "High" "Medium" and "Low" risk categories may help guide practice decisions and they correspond with categories used by the European Society of Cardiology Guidelines[3]. However for more precise estimates the

GRACE risk score also provides the numerical risk of death (or death/MI) at various time points.

Strengths and limitations

Recognising that population characteristics may differ in comparison with that of the originally derived GRACE model, we employed the most recent GRACE dataset in this study and we externally validated the risk model in an entirely separate dataset (FAST-MI 2005 with yearly follow up to 2010). We have previously reported that the GRACE risk prediction is not subject to significant change over time[33]. The purpose of providing 1 year and 3 year risk estimates was to aid the clinician regarding secondary prevention. The risk prediction estimates at 3 years were consistent with those at one year (although the 3 year data derive from a smaller dataset).

The GRACE programme is the largest multi-national programme in acute coronary artery disease and was designed to ensure that the included patients were reflective of the broad spectrum of patients presenting with acute coronary syndrome, and of the range of hospitals in clinical practice. The sites were trained, audited and quality control measures were enacted throughout the study. Use of the UK cohort allowed estimation of long-term outcomes (as previously reported) with complete mortality data to 5 years.[20] The external validation of the updated risk score was performed in the FAST-MI 2005 registry with inclusion of the full spectrum of hospitals admitting patients with ACS and excellent completeness of follow-up.

Although the updated GRACE risk score provides a reliable estimate for stratifying patients both acutely and in the long-term, additional factors contribute to longer term risk. Further refinement of the risk score for long term outcomes may require the inclusion of additional risk factors and biomarkers to increase precision, but the current risk scores' discrimination allows separation of patients into broad categories relevant for decisions on clinical management. Future studies will determine the impact of risk scoring strategies in various populations including the frail and elderly.

CONCLUSIONS

The updated GRACE risk score has better model discrimination and is easier to use than previous scores based upon categorical variables. It is accurate in the acute phase and over the longer term and can be used in a variety of clinical settings to aid management decisions.

Acknowledgements

This work was supported by the British Heart Foundation, an award from the Chief Scientist Scotland (CZG/2/455) and unrestricted grant from AstraZeneca to the University of Edinburgh. The GRACE risk score has been made available[34] to download without cost (www.gracescore.co.uk and www.outcomes.org/grace)

Text: 3479 words (introduction to end of acknowledgements)

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34. Website support for use of the GRACE risk score: www.gracescore.co.uk and www.outcomes.org/grace

Legends

Figure 1a,b,c,d

Non-linear associations for the one year mortality model were found for four continuous measures: systolic blood pressure (figure 1a), pulse (figure 1b), age (figure 1c), and creatinine (figure 1c), ($p < 0.001$ vs linear for each comparison).

Figure 2

Illustration of the GRACE Score 2.0 on a mobile device (suitable for use in iOS, android or web versions). Left panel: values for percentage risk of death or death/MI (or numerical GRACE Score). Remaining panels show the individual patient results as a vertical column superimposed on the entire ACS distribution curve (green column= low risk illustration, yellow column=medium risk, red column= high risk)[34]. For further information see www.gracescore.co.uk and www.outcomes.org/grace

Table 1 Characteristics on admission of the GRACE ACS patients used in 1-year death model and the FAST-MI patients

	GRACE	FAST-MI 2005
Demographics		
Age, y	66.6 (56.0-76.4)	68.5 (55.9-78.6)
Female	33%	31%
Weight, kg	78 (68-89)	75 (65-85)
Height, cm	170 (162-175)	169 (162-175)
BMI, kg/m^2	27 (24-30)	26 (24-29)
Medical history, %		
Angina	44	30
Atrial fib	7.7	NA
CABG	13	5
Congestive heart failure	10	6
Diabetes	26	24
Dyslipidemia	51	47
Hypertension	64	57
MI	30	17
PCI	19	13
Peripheral arterial disease	9.0	9
Renal insufficiency	7.6	5
Smoking	57	53
Stroke	8.5	6
Presentation characteristics		
Pulse, beats/min	76 (65-90)	77 (66-90)
DBP, mm Hg	80 (70-90)	80 (70-90)
SBP, mm Hg	140 (120-160)	140 (120-158)
Killip class I	85%	77%
Killip class II	11%	113%
Killip class III	3.6%	8%
Killip class IV	0.8%	2%
Cardiac arrest	1.9%	1.7%
Initial cardiac enzymes positive	52%	100%
Initial serum creatinine, mg/dL	1.02 (0.90-1.25)	1.02 (0.85-1.23)
Electrocardiographic findings, %		
ST-segment elevation	36	50
ST-segment depression	32	22
ST-segment deviation	53	72
T wave inversion	25	10
ST-segment elevation anterior	16	21
ST-segment elevation inferior	18	27
ST-segment depression anterior	15	NA
ST-segment depression inferior	9.2	NA
Any significant Q wave	19	12
Left bundle branch block	4.7	3.9
Prior use of medical therapy, %		
Aspirin	40	24
ACE inhibitors	30	19
Statins	32	27

3307 missing weight, 6098 missing height, 6732 missing BMI; no other variable missing > 300.
Median (IQR) if continuous variable; % if discrete

TABLE 2. Summary of Cox regression models

	Admission to 1 year death	Admission to 1 year death or MI	Admission to 3 year death
Total no. of observations	32,037	32,037	1,274
No of outcomes	2422	3655	261
May-Hosmer goodness of model fit (*P*)	<0.001	0.06	0.60
Harrell's c index	0.829	0.746	0.782
Model estimates	HR (95% CI), χ^2	HR (95% CI), χ^2	HR (95% CI), χ^2
Age per 10 y: <67	1.5 (1.4 - 1.7), 1069	1.2 (1.1 – 1.3), 853	1.8 (1.6 – 2.1), 102
≥ 67	1.9 (1.8 - 2.0)	1.6 (1.5 – 1.6)	n/a (linear)
Systolic blood pressure per -20 mm Hg	≥ 139: 1.1 (1.0 - 1.2), 293	≥ 139: 1.0 (1.0 - 1.1), 200	≥ 160: 0.9 (0.7 – 1.1), 36
	< 139: 1.3 (1.3 - 1.4)	<139: 1.3 (1.2 - 1.3)	130 – 159: 1.6 (1.2 – 2.0)

			< 130: 1.3 (1.0 – 1.6)
Pulse per 30 BPM: <51	1.1 (0.9 - 1.4), 131	1.0 (0.9 – 1.3), 126	1.0 (0.3 – 2.7), 32
51-83	1.5 (1.4 - 1.7)	1.4 (1.2 – 1.5)	1.7 (1.1 – 2.8)
84-118	1.3 (1.2 - 1.4)	1.2 (1.2 – 1.3)	1.6 (1.2 – 2.0)
>118	0.9 (0.8 - 1.0)	0.9 (0.8 – 1.0)	0.9 (0.6 – 1.1)
Creatinine per mg: <1	0.6 (0.4 – 1.0), 305	0.9 (0.6 – 1.3), 338	1.5 (1.3 – 1.8), 23
1 – 2	2.2 (2.0 – 2.4)	1.9 (1.7 – 2.0)	n/a (linear)
>2	1.1 (1.1 – 1.2)	1.1 (1.1 – 1.2)	n/a (linear)
Killip class II (v I)	1.9 (1.7 – 2.1), 305	1.7 (1.6 - 1.9), 288	1.1 (0.8 – 1.4), 18
Killip class III (v I)	2.4 (2.1 – 2.7)	2.0 (1.8 – 2.2)	III-IV v I: 2.3 (1.6 – 3.4)
Killip class IV (v I)	3.7 (3.0 – 4.5)	3.2 (2.6 – 3.9)	n/a
Cardiac arrest at admission	2.4 (2.0 – 2.9), 74	2.0 (1.7 – 2.3), 55	2.9 (1.7 – 5.2), 14
Positive initial enzymes	1.5 (1.3 – 1.6), 72	1.3 (1.2 -1.4), 42	n/a
ST deviation	1.6 (1.4 – 1.7), 109	1.4 (1.3 – 1.5), 92	1.5 (1.2 – 1.9), 10

Substitute factors*: renal insufficiency	1.6 (1.4-1.7), 66	1.6 (1.5 – 1.8), 105	2.0 (1.3 – 3.2), 9
Diuretics in first 24 h	2.0 (1.8-2.1), 266	1.7 (1.6 – 1.8), 236	2.0 (1.5 – 2.6), 27

* Renal insufficiency substituted for creatinine, diuretics for Killip class; sample sizes increase to 33,890 patients with 2585 deaths within a year of admission (c index .820), 33,890 patients with 3882 deaths or MIs within a year of admission (c index .738), 1298 patients with 266 deaths within 3 years of admission (c index .780).

Table 3a the full GRACE risk score tested in FAST-MI 2005

From ACS presentation	Overall population (death) n=2959	STEMI (death) N=1558	Non-STEMI (death) N=1401	Overall Death/MI
1-year Death	0.83	0.84	0.82	0.77
3-year Death	0.82	0.82	0.82	0.77
Hospital Survivors	n=2806	N=1472	N=1334	
1-year Death	0.81	0.82	0.80	0.73
3-year Death	0.80	0.80	0.80	0.75

Table 3b the simplified GRACE risk score, with substitutions for Killip and creatinine (n=3035), tested in FAST-MI 2005

From ACS presentation	Overall population (death) N=3035	STEMI (death) N= 1596	Non-STEMI (death) N=1439	Overall Death/MI
1-year Death	0.82	0.84	0.80	0.80
3-year Death	0.82	0.83	0.82	0.78
Hospital Survivors	N=2872	N=1504	N=1368	
1-year Death	0.80	0.83	0.78	0.74
3-year Death	0.81	0.80	0.80	0.76

Figure 1a

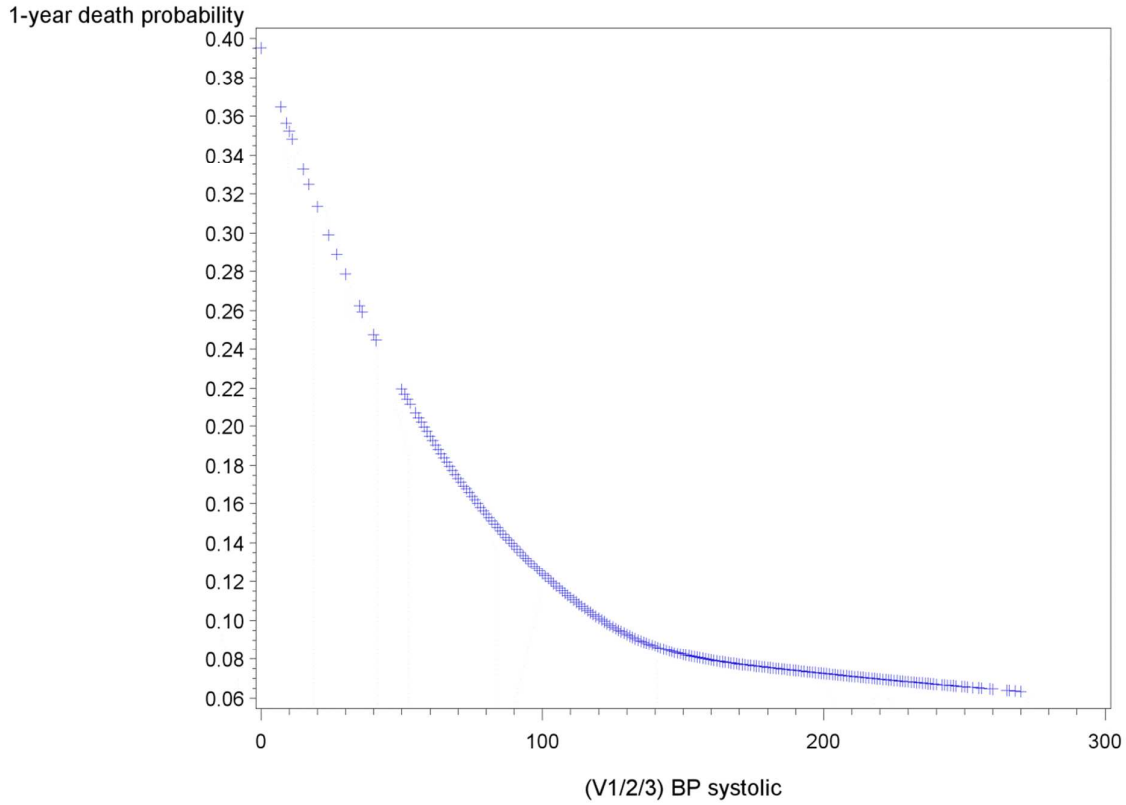

Figure 1b

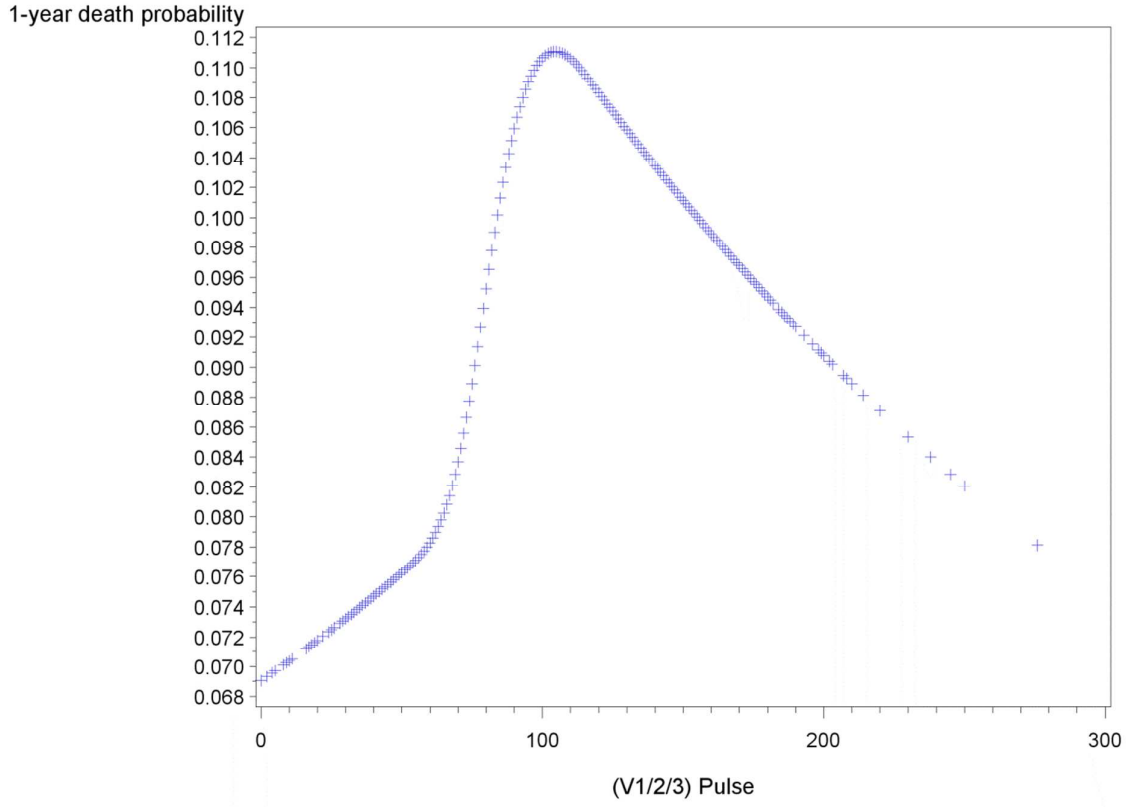

Figure 1c

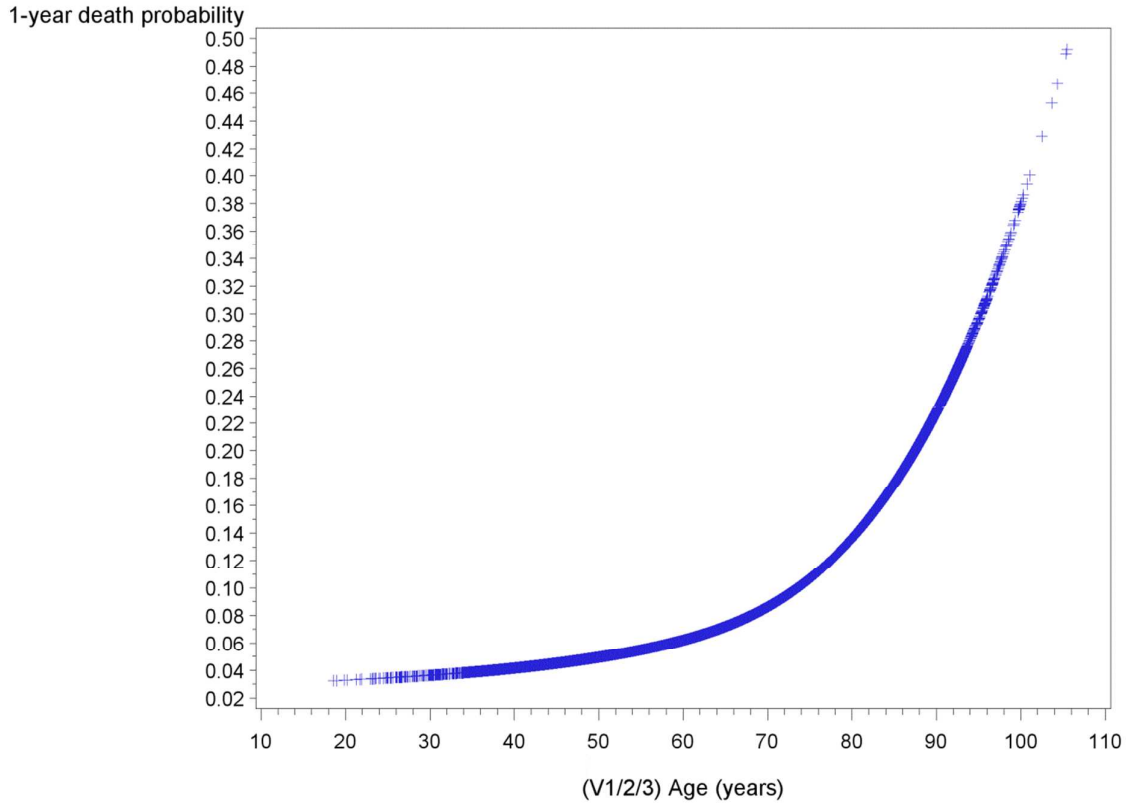

Figure 1d

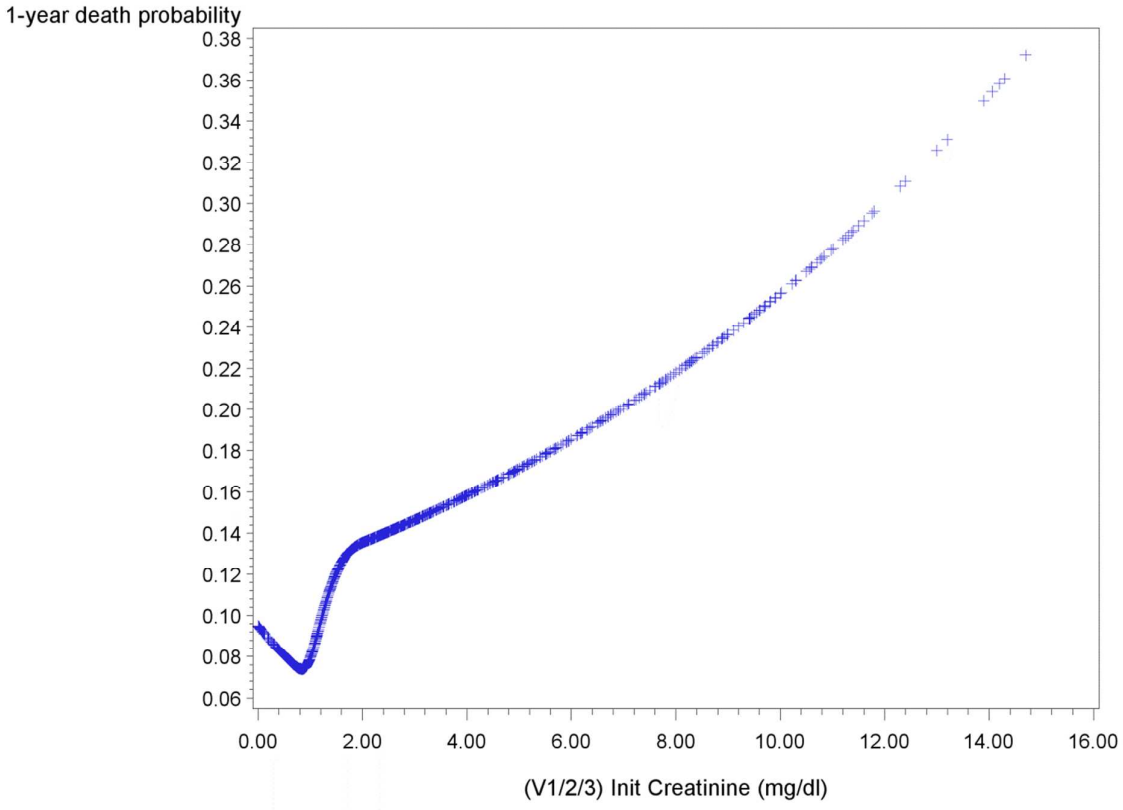

Figure 2

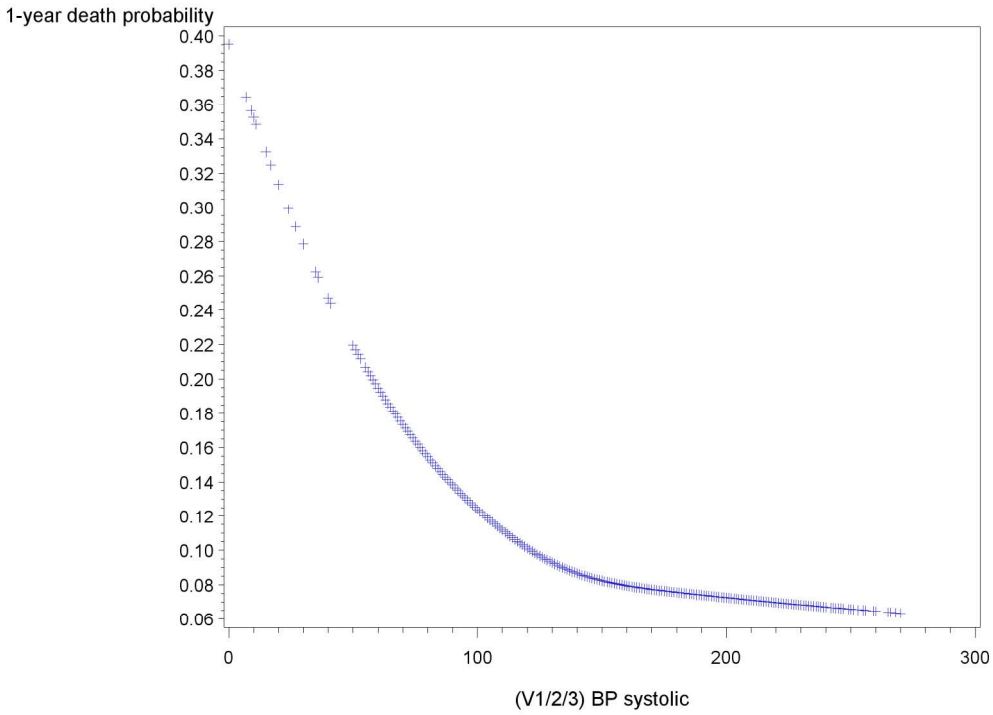

Figure 1a
177x127mm (300 x 300 DPI)

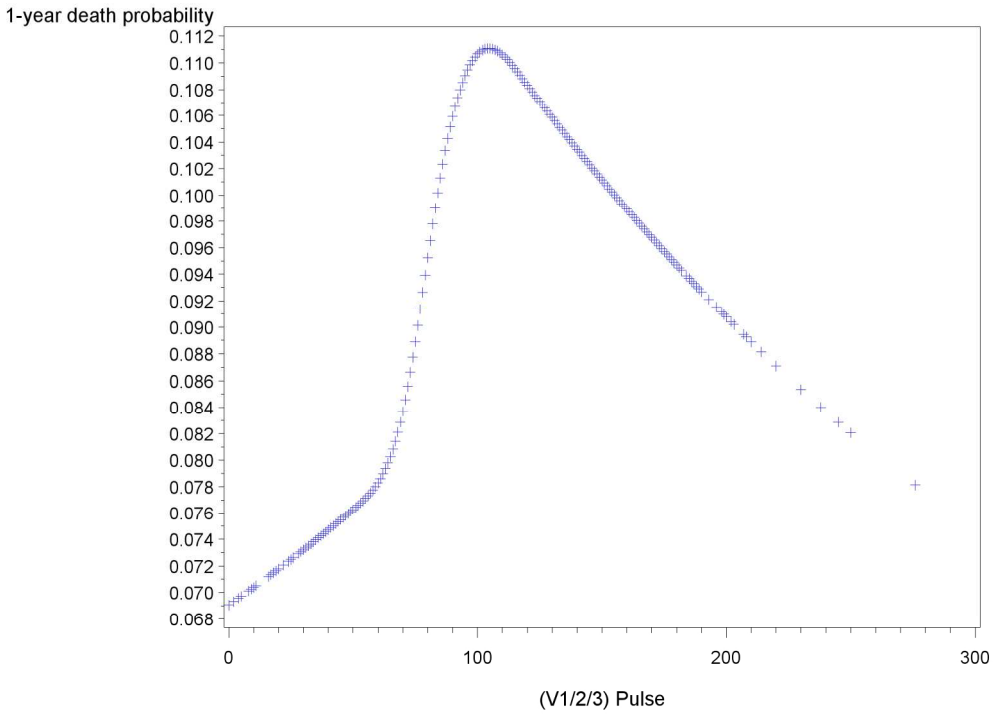

Figure 1b
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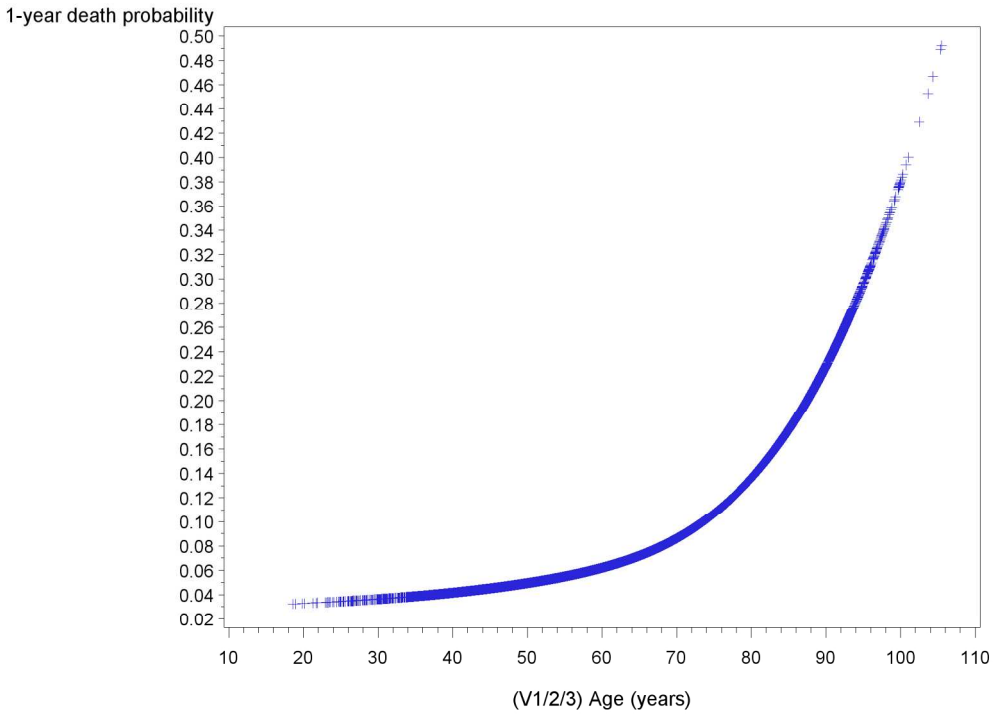

Figure 1c
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Figure 2

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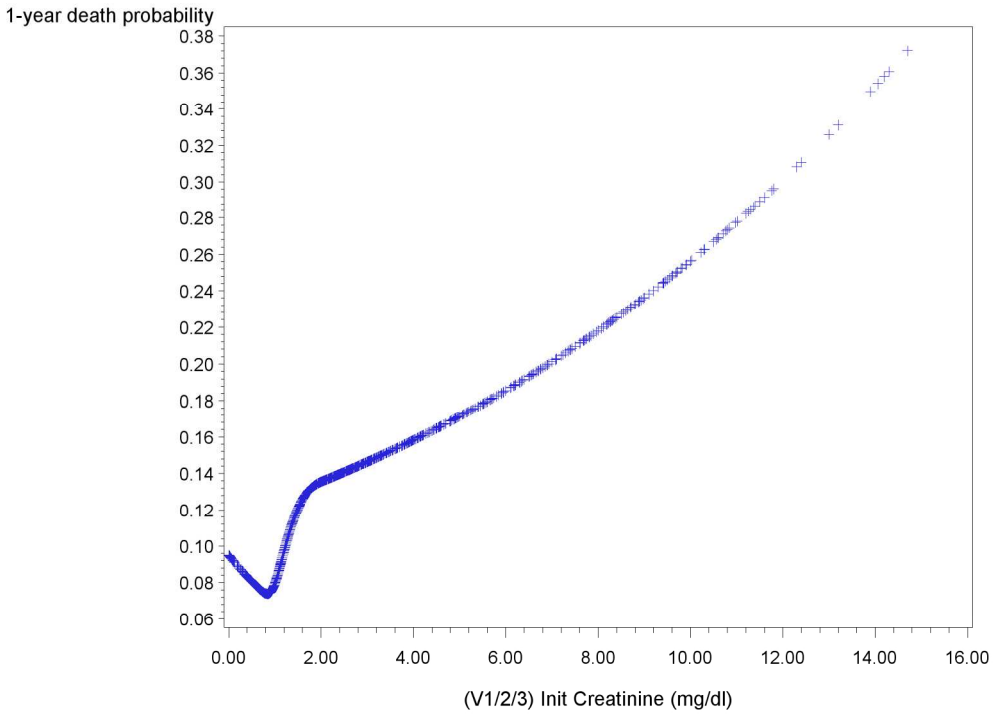

Figure 1d
177x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

"Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation, and outcomes using the updated GRACE risk score" (manuscript ID bmjopen-2013-004425)

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract done
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported done
Objectives	3	State specific objectives, including any prespecified hypotheses done
Methods		
Study design	4	Present key elements of study design early in the paper done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection done
Participants defined	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group done
Bias	9	Describe any efforts to address potential sources of bias done
Study size	10	Explain how the study size was arrived at done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding done
		(*b*) Describe any methods used to examine subgroups and interactions N/A
		(*c*) Explain how missing data were addressed N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy done

(*e*) Describe any sensitivity analyses done

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed done
		(b) Give reasons for non-participation at each stage done
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders done
		(b) Indicate number of participants with missing data for each variable of interest done
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included done
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses done
Discussion		
Key results	18	Summarise key results with reference to study objectives done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence done
Generalisability	21	Discuss the generalisability (external validity) of the study results done
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based done

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.