**Predicting mortality after acute coronary syndromes in people with chronic obstructive pulmonary disease**

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**Abstract**

**Objective**

To assess the accuracy of Global Registry of Acute Coronary Events (GRACE) scores in predicting mortality at 6 months for people with COPD and to investigate how it might be improved.

**Methods**

Data were obtained on 481,849 patients with acute coronary syndrome (ACS) admitted to UK hospitals between January 2003-June 2013 from the myocardial ischaemia national audit project (MINAP) database. We compared risk of death between chronic obstructive pulmonary disease (COPD) and non-COPD patients at 6 months, adjusting for predicted risk of death. We then assessed whether several modifications improved the accuracy of the GRACE score for people with COPD.

**Results**

The risk of death after adjusting for GRACE score predicted risk of death was higher for COPD patients than for other patients (RR 1.29, 95% CI 1.28-1.33). Adding smoking into the GRACE score model did not improve accuracy for COPD patients. Either adding COPD into the model (RR 1.00, 0.94-1.02) or multiplying the GRACE score by 1.3 resulted in better performance (RR 0.99, 0.96-1.01).

**Conclusion**

GRACE scores underestimate risk of death for people with COPD. A more accurate prediction of risk of death can be obtained by adding COPD into the GRACE score equation, or by multiplying the GRACE score predicted risk of death by 1.3 for people with COPD. This means that one third of COPD patients currently classified as low risk should be classified as moderate risk, and could be considered for more aggressive early treatment after non-ST-elevation myocardial infarction or unstable angina.

**What is already known about this subject?**

Despite being at higher risk of death following admission for acute coronary syndromes, those with chronic obstructive pulmonary disease (COPD) are less likely to receive investigation and treatment than non-COPD patients and this difference may explain some of the difference in mortality. It is recommended that those at moderate (3-6%) or high (>6%) Global Registry of Acute Coronary Events (GRACE) score predicted risk of death at 6 months after admission to hospital for non-ST-segment elevation myocardial infarction or unstable angina receive earlier aggressive investigation and treatment.

**What does this study add?**

This nationwide multicentre study involving 481,849 hospital admissions demonstrates that GRACE scores underestimate risk of death after acute coronary syndromes for those with COPD. This study also found that multiplying the predicted risk of death for those with COPD by 1.3 provides a better approximation for their risk of death.

**How might this impact on clinical practice?**

Using a more accurate estimate of risk of death for those with COPD after admission for acute coronary syndromes one third of COPD patients previously categorised as low risk would be reclassified as moderate risk, and therefore would be eligible for earlier, more aggressive investigation and treatment.

**Introduction**

Accurate prediction of risk of death after acute coronary syndromes (ACS) is important not only for prognostication, but also for decision making about treatment, as individuals at higher risk of death after ACS benefit most from early aggressive treatment[[1](#_ENREF_1), [2](#_ENREF_2)]. Early and accurate assessment of future risk allows clinicians to identify patients who might benefit most from therapies and to avoid unnecessary treatment for those who are less likely to benefit.

GRACE (Global Registry of Acute Coronary Events) scores are used internationally to predict the probability of death at six-months after admission to hospital for ACS. They have been developed and validated in several different settings[[3](#_ENREF_3), [4](#_ENREF_4), [5](#_ENREF_5), [6](#_ENREF_6), [7](#_ENREF_7)]. The predicted risk of death can be used to stratify patients into low (<3%), moderate (3-6%) and high (>6%) risk of death at 6 months post-ACS. Current guidelines recommend that those classified as moderate-high risk of death using the GRACE score should receive more aggressive early therapy after non-ST elevation myocardial infarction (non-STEMI) or unstable angina[[8](#_ENREF_8), [9](#_ENREF_9)].

People with chronic obstructive pulmonary disease (COPD) have a higher risk of MI than people without COPD, and cardiovascular disease is an important cause of death in people with COPD. In addition, COPD is very common in people with MI, with prevalences ranging from 10-17%[[10](#_ENREF_10), [11](#_ENREF_11)]. Several studies have also found an increased risk of death after MI in people with COPD compared to people without COPD[[10](#_ENREF_10), [12](#_ENREF_12), [13](#_ENREF_13)]. Previous work [[14](#_ENREF_14)] has shown that, after adjusting for confounders, even though people with COPD have a higher mortality at 6-months post discharge than non-COPD patients, they are less likely to receive angiography in-hospital after a non-STEMI, or to receive secondary prevention drugs after any MI. One of the reasons for this may be that GRACE scores may not predict risk of death in COPD patients as well as they do in non-COPD patients.

Using data from the UK Myocardial Ischaemia National Audit Project (MINAP) registry, we investigated whether GRACE scores performed as well in people with COPD as they do in people without COPD, and how they might be improved for people with COPD.

**Methods**

***Data source***

MINAP is a UK registry of all admissions for ACS to hospitals in England and Wales. The following variables were collected which are needed for the equation for 6-month mortality (post-admission): age, heart rate, systolic blood pressure, creatinine, heart failure, cardiac arrest at admission, ST-segment deviation and elevated cardiac enzymes[[15](#_ENREF_15)]. Vital status is available through linkage with the Office of National Statistics (ONS) mortality data.

We included all patients with a diagnosis of ST-elevation myocardial infarction (STEMI) from January 2003 to June 2013, or non-STEMI or unstable angina from January 2004 to December 2012. Diagnosis of STEMI, non-STEMI and unstable angina were based on physician diagnosis and records of electrocardiogram and cardiac biomarker findings. Records were excluded if they did not have a patient unique identifier; if patients had missing values for presence of obstructive airway disease or smoking history; or if ONS mortality data were missing.

We identified COPD in MINAP using a strategy previously validated in MINAP data linked with primary care[[14](#_ENREF_14)]. Briefly, we used the obstructive airway disease indicator and a smoking history (ex or current smoker) to identify COPD, and this identified COPD with a misclassification rate of less than 10%.

***Statistical methods***

*GRACE scores*

GRACE scores and predicted risks of death at 6 months were constructed using published nomograms for the Fox model[[16](#_ENREF_16)]. Values available from nomograms were used to construct algorithms to score patients and to convert these to predicted risk death. As Killip class is not recorded in MINAP, we used a previously validated[[17](#_ENREF_17)] method to score patients based on Killip class of heart failure by using in-hospital prescription of diuretics as a proxy.

We estimated the observed and GRACE score predicted risks of death at six months and compared these between people with and without COPD. We estimated the Mantel-Haenszel risk ratio averaged over the GRACE score deciles to estimate the average relative risk for death at six months post-admission for COPD patients with the same GRACE score as non-COPD patients. If GRACE scores work equally well in COPD patients and non-COPD patients, then the risk ratio would be 1. A risk ratio of less than 1 would suggest that GRACE scores overestimate the risks of death in COPD patients after admission; a risk ratio of more than 1 would suggest that GRACE scores underestimate the risks of death in COPD patients. We also compared the risk of death for people with diabetes to people who do not have diabetes, adjusted for GRACE score predicted risk of death.

We then investigated the observed risk of death between COPD and non-COPD patients within GRACE score predicted levels of risk (0-3% low, 3-6% moderate, and >6% high).

We explored the extent of and possible reasons for missingness of GRACE score variables and performed a multiple imputation analysis (details in supplementary material).

*Model modifications*

We investigated several strategies for improving GRACE scores for people with COPD. We prespecified three potential modifications to the GRACE models which might improve their accuracy for COPD patients: 1) Adding COPD into the models as a risk factor; 2) Adding smoking history into the models as a risk factor; and 3) multiplying the predicted risk of death for COPD patients by the RR for risk of death for COPD patients compared to non-COPD patients after adjusting for GRACE score predicted risk of death.

For the approaches which involved adding new variables to the models (smoking and COPD), we had to re-specify the GRACE models. We did this by building logistic regression models which included all of the GRACE variables (with or without smoking or COPD) with death at 6 months as the outcome and used these to predict risk of death. As an internal validation procedure, we also bootstrapped the logistic regression models with 100 reps each, and compared the parameter estimates with those from the main analysis.

In order to assess which models performed best, we calculated the Mantel-Haenszel risk ratios to compare the risk of death at 6 months between COPD and non-COPD patients adjusting for predicted risk of death for the model in question. We also calculated C-statistics and Hosmer-Lemeshow goodness of fit tests. Strategies involving multiplication of risk for COPD patients using the existing GRACE model were compared to the existing GRACE model. In order to make a fair comparison, models which involved adding other variables (smoking or COPD) were compared to our models which included all of the GRACE variables. In order to assess how well each model stratified risk, we also plotted the proportion of all deaths by deciles of predicted risk of death at 6 months for the normal GRACE model and for modifications. We calculated how many people would be re-classified in terms of risk level (low, moderate or high) for each modification, we also performed this analysis stratified by type of ACS. Finally, we also calculated the continuous net reclassification improvement (NRI) statistic[[18](#_ENREF_18)] for adding COPD to the GRACE score model.

***Ethics***

This study was approved by LSHTM Observational Ethics Committee (6468) and the MINAP academic group (13-MNP-07).

**Results**

***Patient characteristics***

In total, 481,489 patients with ACS were included, of whom 58,739 (12.2%) had COPD (Figure 1). Patient characteristics of COPD and non-COPD patients are shown in Table 1. In terms of mortality, COPD patients were more likely to have died by 6 months post-admission compared to non-COPD patients (17.7% compared to 11.6%). COPD patients, on average also had higher GRACE score predicted risk of death than non-COPD patients (14.0% (SD, 12.7) compared to 11.7% (SD, 12.3)).

***GRACE score performance***

The Mantel-Haenszel pooled risk ratio comparing risks of death for COPD patients to non-COPD patients after adjusting for GRACE score predicted risk of death was 1.30 (95% CI, 1.27-1.33). Observed and predicted mortality for COPD and non-COPD patients, split by deciles of GRACE score predicted risk of death, is presented in Table 2. These results stratified by year of admission are presented in the supplementary material (Table S1). People with diabetes also had a higher risk of death than those without diabetes with the same GRACE score predicted risk of death; however, this was lower than for people with COPD (RR 1.14, 95% CI, 1.12-1.16).

***Model modifications***

Findings from model modifications are displayed in Table 3. Compared to the MINAP derived GRACE score model using the original variables, the model including COPD as a risk factor resulted in better predictions for COPD patients. Including smoking history as a risk factor in the model did not result in better predictions for COPD patients. Bootstrapped results did not differ from the main analysis. Multiplying the GRACE score predicted risk of death by the RR for risk of death for COPD patients adjusted for GRACE score predicted risk of death (1.3) resulted in a very close approximation to adding COPD into the model as a risk factor. C-statistics were improved for the model which multiplied the risk of death for COPD patients by 1.3 and the model which included COPD as a risk factor. Adding smoking to the GRACE score model did not significantly change the C-statistic. Hosmer-Lemeshow statistics showed that all models tested had adequate calibration.

The proportions of all deaths in COPD patients in deciles of predicted risk for the normal GRACE model, the GRACE model multiplied by 1.3, and the MINAP derived model including COPD are displayed in Figure 2. The plot shows a steeper increase in the proportion of deaths in each decile for the GRACE model multiplied by 1.3, and the MINAP derived model including COPD compared to the normal GRACE model, indicating better stratification for these two modifications. Observed mortality within GRACE score predicted risk groups for the normal GRACE model and for the modifications for COPD and non-COPD patients in presented in Table 4.

The findings for re-classification of risk levels after different model modifications are displayed in Table 5. Compared to the normal GRACE score model, when patients with COPD were stratified into risk groups based on the multiplying the GRACE score predicted risk of death by 1.3, 33.9% of those classified as low risk (<3%) were reclassified as moderate risk (3-6%), and 64.3% of those who were classified as moderate risk were reclassified as high risk (>6%). When stratified by type of ACS, the results were similar to the main analysis, with the exception of change in risk group after a STEMI in the MINAP derived model including COPD (Supplementary material, Tables S2-S4). The NRI for adding COPD to the GRACE score model was 0.133 (p<0.001) indicating an improvement in classification of subjects when COPD is added to the model.

The findings from the multiple imputation analysis were similar to those form the main analysis, and are presented in the supplementary material (Table S5).

**Discussion**

We found that GRACE scores for predicting risk of death at 6 months after ACS do not perform as well for people with COPD compared to those who do not have COPD. On average, COPD patients had a 30% higher risk of death than non-COPD patients with the same GRACE score. In order to improve GRACE scores for COPD patients, one option would be to re-specify the GRACE model including COPD as a risk factor. Alternatively, multiplying GRACE score predicted risk of death by 1.3 for COPD patients provides a very close approximation.

We found that, conditional on GRACE score predicted risk of death, COPD patients had a higher risk of death than non-COPD patients, indicating that these scores underestimate the risks of death in those with COPD. One might argue that this might be true for any co-morbidity; however, when we also estimated the relative risk of death comparing those with diabetes to those without diabetes adjusted for GRACE score predicted risk of death, although we found an increased risk, this was much lower than for COPD. Although the relative risk of death for COPD might seem modest, this may have a large impact on patient treatment. Indeed, our results suggest that a large portion of COPD patients would have been reclassified upwards in terms of level of risk if either of our suggested modifications (multiplying the risk for COPD patients by 1.3 and adding COPD to the model) to the GRACE score had been used. Although we found that GRACE score predicted risk was closer to observed risk in those with COPD, the explanation for this is likely to be that for patients with the same predicted risk of death, COPD patients have always been at higher risk and observed mortality for all patients has fallen since GRACE scores were created such that they now by chance align well for those with COPD. This is consistent with our findings when we tabulated predicted and observed risk stratified by admission year. Although the GRACE score is the most accurate and widely used score for predicting risk of death after admission for ACS, others are in use. Clinicians should be aware that scores which use similar parameters are likely to underestimate risk of death for COPD patients to a similar degree.

Our findings are an important contribution to discussion around the risk-treatment paradox. The paradox is that although those who are at highest risk of death after ACS are most likely to benefit from early aggressive therapy, they are the least likely to receive it[[19](#_ENREF_19)]. This may go some way in explaining why COPD patients receive less in-hospital treatment after MI, such as in-hospital angiography after non-STEMI. Using risk scores and recommendations based on these to guide treatment decisions is one way to resolve this paradox. However, these risk scores must be able to predict risk of death well, they must be able to do this around levels of risk important for decision making, and they must do this for those at high risk of death.

A strength of our study is that it is large and representative of the national population, including all hospital admissions for ACS in England and Wales. A well as our complete case analysis, we also explored reasons for missing data and conducted a multiple imputation analysis. This further analysis did not change our conclusions. We calculated the proportion of COPD patients who would have changed risk category as a result of the increase in predicted risk of death. This allowed us to demonstrate that although the relative risk of death adjusting for GRACE score predicted risk of death may seem modest, at the critical region of 0-6% predicted risk of death, this could have resulted in a change in management for a substantial proportion of COPD patients. One limitation of our study was that we used the NICE amended mini-GRACE score[[17](#_ENREF_17)] rather than the model including Killip class. We used prescription of diuretics in hospital as a surrogate for acute heart failure. However, it is highly unlikely that the differences between COPD and non-COPD patients could be explained by this. In addition, recent work[[17](#_ENREF_17)] has shown that this GRACE score is a very good approximation to the full GRACE score, and the amended mini-GRACE score is being used in practice as it is now available on the GRACE 2.0 calculator[[20](#_ENREF_20)].

There are several possible reasons why GRACE score predicted risk of death is not as accurate for COPD patients. Our previous work showed that the relative risk of death after MI for COPD patients is greater after non-STEMIs than STEMIs[[14](#_ENREF_14)], and non-STEMIs will be scored lower than STEMIs, all other things being equal. In addition, the effect of COPD on risk of death after MI was greater for younger COPD patients, and younger people will be scored lower on average. In the development of the GRACE score, although several clinical characteristics, including diabetes, hypertension and hyperlipidemia were tested for inclusion as risk factors, COPD was not[[21](#_ENREF_21)]. Although some of the increased risk of death may be due to differences in treatment, others have concluded that the GRACE score maintains its predictive ability even in groups with different treatment[[22](#_ENREF_22)]. In addition, among a wide range of in-hospital treatments tested, none entered the GRACE score model as predictors of death[[21](#_ENREF_21)]. Previous work has investigated the performance of the GRACE score in other high risk groups such as people with diabetes and people with chronic renal failure[[23](#_ENREF_23)]. However, this work only assessed the C-statistic in these groups, and did not involve assessing the GRACE score in those with COPD. Our findings have important clinical implications for the care of COPD patients after admission to hospital for ACS. Multiplying the GRACE score predicted risk of death by 1.3 for COPD patients would mean that 34% of people with COPD would move from being classified as low risk to moderate risk (<3% to 3-6%). These changes have important implications as recommendations for treatment after non-STEMI and unstable angina are based on classification as moderate or high predicted risk of death. This is particularly relevant as it is known that COPD patients are more likely to present with a non-STEMI than non-COPD patients and that the effect of COPD on risk of death after MI is highest in non-STEMIs, and after adjusting for patient characteristics, they are less likely to receive early invasive treatment after a non-STEMI compared to non-COPD patients[[14](#_ENREF_14), [24](#_ENREF_24)].

**Conclusions**

GRACE score predicted risk of death after ACS does not predict risk of death for people with COPD as well as they do for those who do not have COPD, and underestimates risk of death for this group. When future versions of the GRACE score model are created, those developing the scores may want to include COPD as a risk factor for death. Clinicians should multiply GRACE score predicted risk of death by 1.3 to obtain a more accurate prediction. Using this rule would mean that one third of COPD patients previously considered to be low risk, should be considered moderate risk and would be considered for more aggressive early treatment under current guidelines for non-STEMI and unstable angina.

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**References**

1 Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC, Jr., Pollack CV, Jr., Gibler WB, Ohman EM. Utilization of early invasive management strategies for high-risk patients with non–st-segment elevation acute coronary syndromes: Results from the crusade quality improvement initiative. *JAMA* 2004;**292**:2096-104.

2 Collinson J, Flather MD, Fox KAA, Findlay I, Rodrigues E, Dooley P, Ludman P, Adgey J, Bowker TJ, Mattu R. *Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK)*. 2000.

3 Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, DeYoung JP, Wong GC, Rose B, Grondin FR, Gallo R, Tan M, Casanova A, Eagle KA, Yan AT. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *American Heart Journal* 2009;**158**:392-9.

4 de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R.*TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE‐ACS*. 2005.

5 Khalill R, Han L, Jing C, Quan H. The use of risk scores for stratification of non-ST elevation acute coronary syndrome patients. *Experimental & Clinical Cardiology* 2009;**14**:e25-e30.

6 Abu-Assi E, García-Acuña JM, Peña-Gil C, González-Juanatey JR. Validation of the GRACE Risk Score for Predicting Death Within 6 Months of Follow-Up in a Contemporary Cohort of Patients With Acute Coronary Syndrome. *Revista Española de Cardiología (English Version)* 2010;**63**:640-8.

7 Tang EW, Wong C-K, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. *American Heart Journal* 2007;**153**:29-35.

8 Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Windecker S, Achenbach S, Badimon L, Bertrand M, Bøtker HE, Collet J-P, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann F-J, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)* 2011;**32**:2999-3054.

9 National Institute for Health and Care Excellence (NICE). Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction. 2010.

10 Andell P, Koul S, Martinsson A, Sundström J, Jernberg T, Smith JG, James S, Lindahl B, Erlinge D. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. *Open Heart* 2014;**1**.

11 Stefan MS, Bannuru RR, Lessard D, Gore JM, Lindenauer PK, Goldberg RJ. The impact of COPD on management and outcomes of patients hospitalized with acute myocardial infarction: a 10-year retrospective observational study. *Chest* 2012;**141**:1441-8.

12 Bursi F, Vassallo R, Weston SA, Killian JM, Roger VL. Chronic obstructive pulmonary disease after myocardial infarction in the community. *American Heart Journal* 2010;**160**:95-101.

13 Rothnie KJ, Yan R, Smeeth L, Quint, JK. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open* 2015;**5**.

14 Rothnie KJ, Smeeth L, Herrett E, Pearce N, Hemingway H, Wedzicha J, Timmis A, Quint JK. Closing the mortality gap after a myocardial infarction in people with and without chronic obstructive pulmonary disease. *Heart* 2015.

15 Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2010;**96**:1264-7.

16

Centre for Outcomes Research. https://www.outcomes-umassmed.org/grace/files/GRACE\_RiskModel\_Coefficients.pdf

17 Simms AD, Reynolds S, Pieper K, Baxter PD, Cattle BA, Batin PD, Wilson JI, Deanfield JE, West RM, Fox KAA, Hall AS, Gale CP. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003–2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 2012.

18 Pencina MJ, D’Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. *Clinical chemistry and laboratory medicine : CCLM / FESCC* 2010;**48**:1703-11.

19 Yan AT, Yan RT, Tan M, Fung A, Cohen EA, Fitchett DH, Langer A, Goodman SG. Management patterns in relation to risk stratification among patients with non–st elevation acute coronary syndromes. *Archives of Internal Medicine* 2007;**167**:1009-16.

20 Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group\*: Insights from the global registry of acute coronary events. *Chest* 2004;**126**:461-9.

21 Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A validated prediction model for all forms of acute coronary syndrome: Estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;**291**:2727-33.

22 Abu-Assi E, Ferreira-González I, Ribera A, Marsal JR, Cascant P, Heras M, Bueno H, Sánchez PL, Arós F, Marrugat J, García-Dorado D, Peña-Gil C, González-Juanatey JR, Permanyer-Miralda G. “Do GRACE (Global Registry of Acute Coronary events) risk scores still maintain their performance for predicting mortality in the era of contemporary management of acute coronary syndromes?”. *American Heart Journal* 2010;**160**:826-34.e3.

23 Gale CP, Manda SOM, Weston CF, Birkhead JS, Batin PD, Hall AS. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. *Heart* 2009;**95**:221-7.

24 Rothnie KJ, Quint JK. COPD and acute myocardial infarction: effects on presentation, management and outcomes. *European Heart Journal - Quality of Care and Clinical Outcomes* 2016.

**Figure legends**

Figure 1. Flow of participants through the study. GRACE= Global Registry of Acute Coronary Events; MINAP=Myocardial Ischaemia National Audit Project; ACS=acute coronary syndromes; OAD=obstructive airway disease; ONS=Office of National Statistics; STEMI=ST-elevation myocardial infarction; non-STEMI=non-ST-elevation myocardial infarction. COPD=chronic obstructive pulmonary disease.

Figure 2. Proportion of deaths occurring in COPD patients in each decile of predicted risk for the Normal GRACE model, the GRACE model multiplied by 1.3 for COPD patients, and the MINAP derived model including COPD. GRACE=Global Registry of Acute Coronary Events; COPD= chronic obstructive pulmonary disease.

**Table 1 Characteristics of patients included in the analysis**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Non-COPD**  | **COPD**  |
| **Age group (n=481,489)** |  |  |
| <55 | 79,603 (18.8%) | 6,575 (11.2%) |
| 55-64 | 92,446 (21.8%) | 10,858 (18.5%) |
| 65-74 | 101,654 (24.0%) | 17,402 (29.6%) |
| 75-84 | 100,660 (23.8%) | 18,011 (30.7%) |
| ≥85 | 48,747 (11.5%) | 5,893 (10.0%) |
| **Sex (n=481,489)** |  |  |
| Male | 285,502 (67.5%) | 37,135 (63.2%) |
| Female | 137,608 (32.5%) | 21,604 (36.8%) |
| **Diagnosis (n=481,489)** |  |  |
| STEMI | 137,724 (32.6%) | 14,984 (25.5%) |
| Non-STEMI | 183,447 (43.4%) | 29,198 (49.7%) |
| Unstable angina | 101,393 (24.1%) | 3,136 (24.8%) |
| **Previous MI (n=478,530)** | 79,733 (18.9%) | 14,485 (25.1%) |
| **Previous angina (n=477,494)**  | 107,991 (25.7%) | 19,962 (34.7%) |
| **Previously treated hyperlipidemia (n=467,096)** | 135,236 (32.9%) | 18,573 (33.2%) |
| **Previously treated hypertension (n=477,515)** | 201,174 (47.9%) | 28,256 (49.0%) |
| **Peripheral vascular disease (n=473,652)** | 17,216 (4.1%) | 4,182 (7.4%) |
| **Cerebrovascular disease (n=476,863)** | 31,563 (7.5%) | 5,858 (10.3%) |
| **Chronic renal failure (n=476,351)** | 17,368 (4.1%) | 3,697 (6.5%) |
| **Chronic heart failure (n=476,324)** | 18,216 (4.3%) | 4,955 (8.7%) |
| **Previous percutaneous coronary intervention (n=472,614)** | 29077 (7.0%) | 4,256 (7.5%) |
| **Previous coronary artery bypass graft (n=473,891)** | 22,567 (5.4%) | 3,320 (5.8%) |
| **Smoking history (n=481,849)** |  |  |
| Never smoker | 142,254 (33.6%) | 0 (0%) |
| Ex-smoker | 151,560 (35.8%) | 35,103 (59.8%) |
| Current smoker | 129,296 (30.6%) | 23,636 (40.2%) |
| **Raised cardiac markers\* (n=481,849)** | 365,730 (91.8%) | 51,206 (92.2%) |
| **ST segment deviation\* (n=413,253)** | 221,205 (60.7%) | 27,165 (55.3%) |
| **Use of diuretic in hospital\* (n=481,849)** | 93,116 (22.0%) | 19,069 (32.5%) |
| **Mean heart rate\* (n=433,721)** | 80.2 ±21.9 | 87.2 ±23.7 |
| **Mean systolic blood pressure\* (n=432,854)** | 139.9 ±28.6 | 138.2 ±29 |
| **Mean serum creatinine\* (n=287,893)** | 101 ±56.6 | 103.4 ±58.3 |

\* Mean ±SD

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; non-STEMI, non-ST-segment elevation myocardial infarction.

**Table 2** Predicted and observed mortality using normal GRACE model

|  |  |  |  |
| --- | --- | --- | --- |
| **GRACE predicted risk decile** | **Average predicted mortality (%)** | **Observed mortality - non-COPD (%)** | **Observed mortality – COPD (%)** |
| **1** | 1.3 | 0.6 | 0.8 |
| **2** | 2.5 | 1.3 | 2.4 |
| **3** | 4.0 | 2.4 | 4.6 |
| **4** | 5.0 | 3.2 | 6.4 |
| **5** | 6.5 | 4.5 | 7.4 |
| **6** | 8.9 | 7.1 | 12.2 |
| **7** | 12.4 | 10.7 | 17.1 |
| **8** | 17.2 | 16.7 | 21.9 |
| **9** | 26.6 | 27.2 | 32.1 |
| **10** | 48.4 | 44.0 | 47.9 |

**Table 3** – Predictive ability of modifications to the GRACE score in COPD patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Method for obtaining predicted risk of death** | **M-H pooled RR (95% CI) for death at 6 months adjusted for predicted risk of death** | **C-statistic** | **Hosmer-Lemshow p-value** |
| **Normal GRACE score (comparator for 1)** | **1.29 (1.28-1.33)** | **0.8166** | **>0.999** |
| 1. Normal GRACE score – multiply risk of death by 1.3 for COPD patients | 0.99 (0.96-1.01) |  0.8181(p<0.001)\* | **>0.999** |
| **MINAP derived GRACE score (comparator for 2-3)** | **1.23 (1.20-1.26)** | **0.8322** | **>0.999** |
| 2. MINAP derived GRACE score + smoking | 1.20 (1.17-1.23) | 0.8323(p=0.274)\* | **>0.999** |
| 3. MINAP derived GRACE score + COPD | 1.00 (0.94-1.02) |  0.8333(p<0.001)\* | **>0.999** |

**\*p-values compare the C-statistics for the modified models compared to either the normal GRACE score or the MINAP derived GRACE score.**

**Table 4** – Observed mortality at 6 months for COPD and non-COPD patients stratified by different versions of the GRACE score predicted risk of death

|  |
| --- |
| **Normal GRACE score** |
| **GRACE score predicted risk level** | **Observed mortality - non-COPD (%)** | **Observed mortality – COPD (%)** |
| **Low (<3%)** | 1.0 | 1.9 |
| **Med (3-6%)** | 3.1 | 5.8 |
| **High (>6%)** | 18.4 | 23.3 |
| **Normal GRACE score x 1.3 for COPD patients** |
| **GRACE score predicted risk level** | **Observed mortality - non-COPD (%)** | **Observed mortality – COPD (%)** |
| **Low (<3%)** | 1.0 | 1.3 |
| **Med (3-6%)** | 3.1 | 3.8 |
| **High (>6%)** | 18.4 | 21.4 |
| **MINAP derived GRACE score** |
| **GRACE score predicted risk level** | **Non Observed mortality - non-COPD (%)** | **Observed mortality – COPD (%)** |
| **Low (<3%)** | 1.1 | 1.1 |
| **Med (3-6%)** | 3.4 | 6.0 |
| **High (>6%)** | 20.6 | 25.2 |
| **MINAP derived GRACE score & COPD** |
| **GRACE score predicted risk level** | **Observed mortality - non-COPD (%)** | **Observed mortality – COPD (%)** |
| **Low (<3%)** | 1.1 | 1.4 |
| **Med (3-6%)** | 3.7 | 4 |
| **High (>6%)** | 21.0 | 23.3 |

|  |  |
| --- | --- |
|  | **Multiplying risk by 1.3** |
| **GRACE score predicted risk of death** | **Low risk (<3%)** | **Moderate risk (3-6%)** | **High risk (≥6%)** |
| **Low risk (<3%)** | 4,107 (66.1%) | 2,108 (33.9%) | 0 |
| **Moderate risk (3-6%)** | 0 | 2,000 (35.7%) | 3,609 (64.3%) |
| **High risk (>6%)** | 0 | 0 | 20,799 (100.0%) |
|  | **Adding COPD into MINAP derived GRACE model** |
| **GRACE score predicted risk of death** | **Low risk (<3%)** | **Moderate risk (3-6%)** | **High risk (≥6%)** |
| **Low risk (<3%)** | 4,635 (71.5%) | 1,582 (25.5%) | 184 (3.0%) |
| **Moderate risk (3-6%)** | 681 (12.2%) | 2,792 (50.0%) | 2,117 (37.9%) |
| **High risk (>6%)** | 15 (0.1%) | 994 (4.8%) | 19,527 (95.1%) |

**Table** **5** Changes in level of risk for COPD patients after modifications