Abstract

Background: Clinical predictors of future ischemic events in patients with acute coronary syndrome (ACS) are also risk factors for bleeding, with patients often at high-risk of both outcomes. We aimed to define the clinical outcomes and provision of guideline-recommended care in ACS management for different combinations of ischemic and bleeding risk defined using a combined GRACE and CRUSADE score.

Methods: A retrospective observational analysis of a national ACS database was performed for patients with ACS admitted to three tertiary centres from January 2010 to March 2016. Patients were stratified into 9 groups based on possible CRUSADE-GRACE risk combinations. Multiple logistic regression was used to estimate adjusted odds ratios (ORs [95% CI]) for outcomes (in-hospital net adverse cardiac events (NACE), in-hospital all-cause mortality, 30-day mortality and treatment strategy).

Results: A total of 17,701 patients were included in the analysis. We observed a graded risk of mortality and adverse events in the high-risk GRACE strata (Groups 3, 6 and 9). Almost a third of patients with ACS were at a 'dual high-risk' (Group 9, 32%) and were independently associated with higher in-hospital NACE (composite of cardiac mortality, all-cause bleeding and re-infarction): aOR 6.33 [3.55, 11.29], all-cause mortality: aOR 14.17 [5.27, 38.1], all-cause bleeding: aOR 4.82 [1.96, 11.86], and 30-day mortality: aOR 10.79 [5.33, 21.81]. This group was also the least likely to be offered coronary angiography (aOR 0.24 [0.20, 0.29]) and dual anti-platelet therapy (aOR 0.26 [0.20, 0.34]).

Conclusions: One in five patients presenting with an ACS are high ischemic and high bleeding risk, and these patients are more likely to experience poor clinical outcomes and reduced odds of receiving guideline-recommended therapy.

Combinations of bleeding and ischemic risk and their association with clinical outcomes in acute coronary syndrome.

Short title: Combined bleeding-ischemic risk assessment in ACS.

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Introduction

Acute coronary syndromes (ACS) are an important cause of morbidity and mortality worldwide. Current guidelines recommend early management with potent antiplatelet agents and an early invasive coronary intervention strategy for both non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI).[1, 2] [3] The mainstay of pharmacologic treatment for ACS is the use of potent antithrombotic therapy to minimize the risk for further ischemic events, which comes at an expense of an increased risk of bleeding complications that are associated with high rates of morbidity and mortality.[4-7]

Patients presenting with acute coronary syndromes are a heterogeneous population, with often significant overlap of risk factors that are associated with both future ischemic and major bleeding events. Therefore, managing patients with an ACS is a balance of reducing the risk of future ischemic events whilst minimizing the risk of bleeding complications. Risk stratification of ACS patients for likelihood of future ischemic and mortality events is undertaken using a variety of risk scores including the Global Registry of Acute Cardiac Events (GRACE) score, that is recommended to guide an invasive treatment strategy[1, 2, 8, 9] and was initially validated to predict in-hospital and 6-month mortality in acute coronary syndromes[10]. Several parameters comprising the GRACE score are also elements of the 'Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines' (CRUSADE) bleeding score[11], which predicts the baseline risk of major in-hospital bleeding in patients with NSTEMI.

Given the shared risk factor profile in the future risk ischemic and bleeding events, patients presenting with ACS are made up of groups of patients with different balances in the risk of ischemic and bleeding events. Whilst previous studies have investigated outcomes associated with different strata of ischemic and bleeding risk in ACS separately[12-16], they have not considered how these different risk profiles for ischemia and bleeding combine, and

what influence these combinations of risk have on treatment strategies and clinical outcomes in patients presenting with ACS.

The objective of this study was to examine the clinical characteristics of different combinations of ischemic and bleeding risk in an unselected cohort of ACS patients from the Myocardial Infarction National Audit Project (MINAP) registry and to define their clinical outcomes and receipt of guideline-recommended care.

Methods

MINAP Dataset

The Myocardial Ischemia National Audit Project (MINAP) collects prospective data on the management of ACS in the UK. Each centre is responsible for data entry into MINAP, based on agreed definitions and options for each variable. This study had access to data from three large tertiary centres, namely, the Freeman Hospital (Newcastle-upon-Tyne, England), the Royal Stoke Hospital (Stoke-on-Trent, England) and the University Hospital of Wales (Cardiff, Wales).[17] The dataset includes variables detailing patient characteristics, emergency response/admission dates, processes of care and clinical outcomes within hospital discharge. Long-term mortality tracking was available from the Office for National Statistics for English patients and the Welsh Demographic Service for Welsh patients.

Study Design and Population

We performed a retrospective analysis of all patients with a confirmed discharge diagnosis of acute coronary syndrome, including STEMI, NSTEMI and unstable angina (UA). All cases with an 'undetermined' or alternative diagnosis coded on discharge were excluded. A flow chart of the study exclusions is presented in Supplementary Figure 1. Data was missing for several variables necessary for the computation of GRACE 2.0 and

CRUSADE scores using the previously published variables and coefficients.[10, 11] We performed multiple imputation analysis for all missing variables, which generated ten imputed datasets. All analyses were performed in each imputed dataset separately and then pooled using Rubin's Rules.[18] The imputation models included the majority of variables in the MINAP dataset and included each of the outcomes considered in this study. Patients with missing outcome variables were excluded from the analysis of that outcome only (i.e. we did not impute outcomes, but rather used the raw values). Multiple imputation has demonstrated minimal bias in previous publications.[19, 20] The frequencies of missing data for all variables prior to multiple imputation are listed in Supplementary Table 1. Data on ethnicity was not available from one of the contributing centres (Cardiff, Wales) and, therefore, was excluded from univariate analysis.

GRACE score was used to stratify patients in to three categories according to 6-month mortality score: low (<89), intermediate (89-118) and high (>118). CRUSADE score stratifies patient into 5 categories according to bleeding risk: very low (≤20), low (21-30), moderate (31-40), high (41-50) and very high (>50).

For the purpose of combined GRACE and CRUSADE analysis, we reclassified the CRUSADE groups in to three categories by merging 'Very Low-' and 'Low-' risk groups into a 'Low' risk category and 'High-' and 'Very High-' risk groups into a 'High'- risk category to allow a sufficient sample size in each combined risk group for analysis. Patients were subsequently grouped in to 9 risk profiles as a representation of all the possible permutations of combined CRUSADE and GRACE risk groups (key to all groups in Figure 1).

The primary outcome measures were in-hospital net acute cardiovascular events (NACE), in-hospital all-cause mortality, in-hospital all-cause bleeding and 30-day mortality. NACE was defined as a composite of in-hospital cardiac death, in-hospital all-cause bleeding

and re-infarction. All-cause bleeding was defined as any clinically evident bleeding or drop in haemoglobin as coded in the MINAP dataset (any bleeding with fall in Hb of <30g/dL, 30-50g/dL or >50g/dL, 'intracranial bleeding' and 'retroperitoneal haemorrhage'). The secondary outcome was the utilization of guideline-recommended therapy, measured by the rate of receipt of coronary angiography and dual antiplatelet therapy (DAPT).

Statistical Analysis

Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, NY). Continuous variables were presented as means with standard deviation (SD) and compared using ANOVA. Categorical variables were presented as frequencies and analysed using the chi-squared (X^2) test, or a Fisher's exact test whenever the frequency of an event was less than 5. Patients with missing endpoint variables were excluded from the analysis of that endpoint.

Multiple logistic regression was used to investigate association between the combined CRUSADE-GRACE risk groups and clinical outcomes adjusting for the following variables: previous percutaneous coronary intervention (PCI), previous acute myocardial infarction (AMI), previous coronary artery bypass graft (CABG), hypertension, hypercholesterolemia, smoking status, body mass index (BMI) and admitting consultant (Cardiologist vs. General physician). Any covariates that were used to calculate the CRUSADE and/or GRACE scores (i.e. age, sex, renal function, peripheral vascular disease, cardiac arrest on admission, diabetes mellitus, blood pressure, heart rate, haematocrit level, elevated troponin level, Killip Class and ST-segment deviation) were not adjusted for, to avoid collinearity and multiple adjustment. All odds ratios (ORs) are adjusted and expressed as aOR [95% confidence interval], unless otherwise stated.

A ROC analysis was performed to evaluate the performance of CRUSADE and GRACE scores as predictors of the study outcomes (NACE, all-cause mortality, all-cause

bleeding and 30-day mortality). Logistic regression was conducted to generate predicted probabilities for the risk categories of either score.

Results

A total of 17,701 patients with a diagnosis of ACS (STEMI, NSTEMI and UA) were admitted to the three contributing centres between January 2010 and March 2016. The mean age of the study population was 65.9±13.1 years, with 70.8% (n=12530) males and 50.8% (n=9044) with a STEMI diagnosis. Patients' baseline characteristics are presented according to the nine CRUSADE-GRACE group combinations in Table 1, and according to separate GRACE and CRUSADE groups in Supplementary Tables 3 and 4, respectively. A distribution of the cohort by each contributing centre is also available in the supplementary material (Supplementary Table 2). Several variables are common to both GRACE and CRUSADE scores and there was a positive correlation between both scores, although this was relatively modest (Pearson's coefficient: r=0.411, p<0.001). Low GRACE–Low CRUSADE group comprised 5.5% (n=973) of the population whilst High GRACE–High CRUSADE group comprised 32.0% (n=5671) of population.

Several key differences in demographics and clinical characteristics were observed between the CRUSADE-GRACE group combinations (p-value is for trend). Low GRACE strata included the youngest patients and the lowest prevalence of Caucasians, chronic renal failure and peripheral vascular disease but also the highest prevalence of previous PCI; Group 1 (Low CRUSADE – Low GRACE), Group 4 (Moderate CRUSADE – Low GRACE) and Group 7 (High CRUSADE - Low GRACE) while the high-risk CRUSADE strata were less likely to be men; Group 7 (High CRUSADE - Low GRACE), Group 8 (High CRUSADE-Intermediate GRACE) and Group 9 (High CRUSADE-High GRACE) (p<0.001 for all).

In contrast to the lowest risk group (Group 1, Low CRUSADE-Low GRACE), the

dual high-ischemic high-bleeding risk patients (Group 9, High CRUSADE-High GRACE) were significantly older (71.9±11.9 vs. 51.8±9.6 years,), less likely to be males (62.7% vs. 80.2%) and more multimorbid with a higher prevalence of cardiovascular risk factors such as previous angina (27.0% vs. 22.1%), previous acute AMI (25.3% vs. 19.3%), previous CABG (6.7% vs. 3.4%), hypertension (62.7% vs. 44.9%), previous PVD (8.6% vs. 1.3%), previous cerebrovascular disease (10.8% vs. 2.8%), asthma/COPD (18.9% vs. 12.5%), chronic renal failure (10.2% vs. 0.1%) and heart failure (6.1% vs. 0.6%) (Table 1, $p<0.001$ for all).

NACE and Mortality

The rates of in-hospital NACE and in-hospital mortality are listed according to CRUSADE-GRACE risk combinations in Table 2 and according to individual CRUSADE and GRACE categories in Supplementary Tables 5 and 6, respectively.

Overall rates of in-hospital NACE, in-hospital all-cause mortality and 30-day mortality were 5.5% (n=974), 3.7% (n=684) and 4.3% (n=761) respectively. An incremental risk of all three events was observed in the high-risk GRACE strata, increasing as the CRUSADE risk component of the groups increased; Group 3 (Low CRUSADE – High GRACE), Group 6 (Moderate CRUSADE- High GRACE) and Group 9 (High CRUSADE – High GRACE) (Figures 2a and 2b). The frequency of adverse events in Groups 3, 6 and 9, respectively were: 3.1%, 5.9% and 10.9% for in-hospital NACE; 1.2%, 3.9% and 8.8% for in-hospital all-cause mortality; and 2.8%, 5.0% and 8.2% for 30-day mortality. There was a notable difference in outcomes between the highest and lowest risk groups (Group 9 vs. Group 1, respectively) for in-hospital NACE (10.9% vs. 1.1%, $p<0.001$), in hospital all-cause mortality (8.8% vs. 0.1%, $p<0.001$) and 30-day mortality (8.2% vs. 0.9%, $p<0.001$).

An overview of the independent associations between different GRACE-CRUSADE categories and in-hospital NACE and all-cause mortality, and 30-day mortality is shown in Table 2b. High-risk GRACE strata were associated with the highest odds of in-hospital

NACE, in-hospital all-cause mortality and 30-day mortality amongst the 9 groups. However, the dual high-risk group (Group 9) was the strongest predictor of adverse events (in-hospital NACE: aOR 6.33 [3.55, 11.29], in-hospital all-cause mortality: aOR 14.17 [5.27, 38.1] and 30-day mortality: aOR 10.79 [5.33, 21.81], p<0.001 all).

Interestingly, the CRUSADE score was superior to the GRACE score in predicting in-hospital NACE (AUC: 0.686 [0.670, 0.703] vs. 0.641 [0.626, 0.656]), in-hospital all-cause mortality (AUC: 0.738 [0.721, 0.755] vs. 0.664 [0.647, 0.680]) and 30-day mortality (AUC: 0.659 [0.639, 0.678] vs. 0.640 [0.623, 0.656]) (Supplementary Figures 2a, 2b and 2d, respectively, p<0.001 for all).

Bleeding

The overall rate of in-hospital all-cause bleeding was 1.5% (n=266) (Table 2). The majority of in-hospital all-cause bleeding events occurred in the 'High-risk' and 'Very High-risk' CRUSADE groups (Supplementary Table 5) and 'High-risk' GRACE group (Supplementary Table 6). Amongst the combined CRUSADE-GRACE risk groups, the highest incidence of bleeding was observed in the 'dual high-risk' group (Group 9; 2.4%), followed by Group 6 (Moderate CRUSADE-High GRACE; 1.9%) and Group 9 (High CRUSADE-High GRACE; 1.1%) (Figure 2a). There was no significant difference in the rates of TIMI major bleeding between combined risk groups (Table 2, p=0.46).

In multivariate analysis, only Groups 6 (Moderate CRUSADE-High GRACE) and 9 (High CRUSADE-High GRACE) were significantly associated with a four to five-fold increase in odds of in-hospital all-cause bleeding (aOR 4.05 [1.60, 10.21] and aOR 4.82 [1.96, 11.86], p≤0.001 for both) (Table 2b). A ROC analysis demonstrated superiority of CRUSADE over GRACE as predictor of in-hospital bleeding (AUC: 0.623 [0.589, 0.657] vs. 0.603 [0.571, 0.634]) (Supplementary Figure 2c).

Treatment strategy

Coronary angiography was performed in the majority (72.3%) of the study cohort (Table 2). However, patients in the 'High- and Very High-' CRUSADE risk categories and those with a 'High'-risk GRACE risk were significantly less likely to undergo coronary angiography compared to the corresponding low-risk categories of the same score (Supplementary Tables 5 and 6, respectively, p<0.001 for both trends). Within the CRUSADE-GRACE group combinations, the highest risk groups had the lowest proportions of patients receiving coronary angiography compared to all other groups (Group 9: 62% and Group 8: 69.7%) (Table 2, Figure 2c). Multivariable regression analysis identified membership of these two groups as independently associated with reduced odds of coronary angiography; Group 9: aOR 0.24 [0.20, 0.29] and Group 8: aOR 0.39 [0.31, 0.48], p<0.001 for both) (Table 2b).

The overall rate of discharge with DAPT after ACS was 84.3%. Within the individual risk groups, 'High'-risk GRACE and 'Very High'-risk CRUSADE groups were notably less likely to receive DAPT on discharge (80.5% and 72.9% respectively, p<0.001 for both trends). A similar trend was observed in the CRUSADE-GRACE combined groups, where Group 9 was significantly less likely to receive DAPT (n=74.6%, aOR 0.26 [0.20, 0.34], p<0.001) (Figure 2c) and more likely to be prescribed aspirin as a single antiplatelet agent (5.6%, crude OR 2.00 [1.60-2.85], p<0.001) on discharge.

Sensitivity Analysis

A sensitivity analysis was performed to assess the difference in outcomes between Non-ST Elevation ACS (NSTEA-ACS) and STEMI patients. Patients presenting with STEMI experiences significantly higher overall rates of NACE (7.4% vs. 3.4%), in-hospital all-cause

mortality (5.2% vs. 2.2%), in-hospital all-cause bleeding (1.7% vs. 1.3%) and 30-day mortality (10% vs. 6.3%) compared to those presenting with NSTE-ACS (Supplementary Tables 7a and 7b, $p<0.001$ for all). However, the trend of outcomes in the combined CRUSADE-GRACE risk groups was similar in both STEMI and NSTE-ACS subgroups to that of the combined ACS cohort, with the highest rates of NACE, in-hospital all-cause mortality, in-hospital all-cause bleeding and 30-day mortality observed in the high-GRACE strata; Groups 3, 6 and 9.

Discussion

Patients presenting with acute coronary syndromes have a large overlap in the risk factor profiles that predict both future ischemic and major bleeding events. Our study suggests that one in three patients admitted with an acute coronary syndrome are at high risk of both bleeding and ischemic events and represent a high-risk group with adverse clinical outcomes, even after adjustment for their adverse baseline risk factor profile. We observe a lack of adherence to guideline-based therapy in this high-risk group, who were less likely to receive both invasive angiography and dual antiplatelet therapy. Balancing the ischemic benefits of revascularization and antiplatelet therapy against the bleeding risk presents a therapeutic dilemma in such patients, who by far have the most to gain from these therapeutic strategies.

Risk assessment of future ischemia and bleeding, using the GRACE (Class I, Level A) and CRUSADE (Class IIb, Level B) scores respectively, is recommended by current guidelines to guide decision on treatment strategies, and is considered an essential quality indicator. [1, 2, 9] Yan et al. demonstrated the superiority of validated scoring systems in identifying high-risk patients that have been otherwise misclassified by physicians as of lower risk.[13] High GRACE score is associated with a greater incidence of MACE and

mortality in patients with NSTEMI, and is an indication for early coronary revascularization.[21] However, the inherent risk of bleeding from commitment to a certain duration of dual antiplatelet therapy remains a concern for clinicians hence reluctance to undertake coronary intervention in patients with dual high bleeding and ischaemic risk. Although the CRUSADE score reliably predicts in-hospital bleeding, the risk of bleeding is not confined to hospitalization.[22] A recent meta-analysis concluded that bleeding after percutaneous coronary intervention independently increases the risk of major acute cardiovascular events (MACE) and mortality by approximately three-fold at 1 year from the time of event.[5]

To the best of our knowledge, this is the largest study to investigate both outcomes of patients of all ACS subtypes, based on their combined bleeding and ischemic risk profile, and evaluate the quality of their management against the latest guidelines. Paiva et al. studied the outcomes of 566 patients with NSTEMI over a mean period of 21 months post-discharge. In their single centre observational analysis, they reported significantly worse in-hospital mortality, bleeding and follow up mortality in the highest bleeding-ischemic risk group when compared with all other risk groups, which correlates with our study findings.[23].

The inverse relationship between patient risk and adherence to guideline-based management has been previously observed in several studies.[13, 24, 25] In an analysis of more than 71000 patients with NSTEMI diagnosis from the NCDR ACTION registry–GWTG^{TM} registry, those at high risk of bleeding and mortality were less likely to receive Clopidogrel (70% vs. 51%), coronary angiography within 48 hours (86% vs. 41%) and revascularization (75% vs. 37%), compared with those at lowest risk of bleeding and mortality.[24] The observations in their analysis, justified as being due to physicians' concerns about 'attributable risk', were consistent with our study findings.

Similarly, the ACS2 registry demonstrated significantly lower rates of cardiac

catheterisation in patients with a high risk (adjusted HR 0.45; 95% CI, 0.42-0.47; P<0.001) and intermediate GRACE score (adjusted HR 0.82; 95% CI, 0.77-0.86; P<0.001) compared to lower risk patients.[25] This analysis, however, only studied quality indictors based on ischemic risk, without taking bleeding risk in to account. Our findings underpin the gap in existing evidence on the optimal management strategy for dual high mortality- high bleeding risk patients and emphasizes the need for further prospective studies to inform cardiologists' decision-making of this frequently encountered risk group.

Current treatment strategies for this dual high-risk group are based on clinicians' experience and involve the preferential use of clopidogrel over more potent P2Y12 inhibitors owing to its association with lower non-access related bleeding and the use of drug-coated (DCS) or bare metal stents (BMS) as opposed to drug eluting stents.[26, 27] However, a recent meta-analysis demonstrated no difference in bleeding events between Clopidogrel and newer P2Y12 inhibitors in both elderly and non-elderly patients.[28] Furthermore, there has been no head-to-head comparison of adverse cardiac events and bleeding between DES and DCS in this dual high-risk group to date.

Limitations

There are several limitations to our study. Firstly, despite the high quality of the MINAP database, the retrospective nature of analysis is reliant on the accuracy of data entered by healthcare staff. Secondly, whilst mortality tracking within England is well structured and undertaken through the office of national statistics, all other clinical outcomes and post procedural complications are self-reported without official adjudication and are only captured during the in-hospital episode. Therefore, we were unable to report outcomes beyond the admission episode for adverse events other than mortality. Thirdly, whilst we have adjusted for comorbid conditions and clinical characteristics collected by the MINAP

registry, our data does not have measures of frailty and global comorbid burden that are known to influence outcomes in ACS patients and so our findings may relate to unmeasured confounders. Finally, our database was derived from three large interventional centres in the UK, making our results less generalizable to smaller centres and those in other healthcare systems.

Conclusion

In our unselected cohort of patients admitted with an ACS, we demonstrate that 1 in 3 patients are at high risk of both ischemic and bleeding events as defined by their GRACE and CRUSADE risk scores and represent a high-risk group with adverse clinical outcomes. These patients represent a diagnostic dilemma, since despite being at increased risk of both ischemic and bleeding events, they are less likely to receive guideline recommended therapies such as dual antiplatelet therapy or an invasive approach. Further work is required to identify patients in this high-risk group that would benefit from more aggressive management in line with international guidelines.

Declaration of interest

The authors report no relationships that could be construed as a conflict of interest

Authorship & Contributorship Statement

MAM designed the project. MOM performed the data analysis and wrote the first manuscript draft. MR, CSK, TK, RA, PF, PM, GPM, AZ and MAM have revised and critically reviewed the manuscript for intellectual content. All authors have approved the final version of the manuscript. All named authors have seen and approved the final version of the manuscript.

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Ethical Approval

The National Institute for Cardiovascular Outcomes Research (NICOR) which includes the MINAP database (Ref: NIGB: ECC 1-06 (d)/2011) has support under section 251 of the National Health Service Act 2006 to use patient information for medical research without informed consent. Further ethical approval was not required under current National Health Service research governance arrangements, as all data analysed in the study was pseudonymized and contained no patient identifiable information.

References

[1] Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevationTask Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European Heart Journal. 2016;37:267-315.
[2] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevationThe Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018;39:119-77.
[3] Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary. Circulation. 2014;130:2354.
[4] Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, et al. Associations of

major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. European Heart Journal. 2009;30:1457-66.
[5] Kwok CS, Rao SV, Myint PK, Keavney B, Nolan J, Ludman PF, et al. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. Open Heart. 2014;1.
[6] Happe LE, Rao SV, Horblyuk R, Franklin M, Lunacsek OE, Menditto L. Consequences of major bleeding in hospitalized patients with non-ST segment elevation acute coronary syndromes receiving injectable anticoagulants. Current Medical Research and Opinion. 2009;25:413-20.
[7] Subherwal S, Peterson ED, Dai D, Thomas L, Messenger JC, Xian Y, et al. Temporal Trends in and Factors Associated With Bleeding Complications Among Patients Undergoing Percutaneous Coronary Intervention: A Report From the National Cardiovascular Data CathPCI Registry. Journal of the American College of Cardiology. 2012;59:1861-9.
[8] O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation. 2013;127:e362.
[9] Schiele F, Gale CP, Bonnefoy E, Capuano F, Claeys MJ, Danchin N, et al. Quality indicators for acute myocardial infarction: A position paper of the Acute Cardiovascular Care Association. European heart journal Acute cardiovascular care. 2017;6:34-59.
[10] Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091.
[11] Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline Risk of Major Bleeding in Non–ST-Segment–Elevation Myocardial Infarction. Circulation. 2009;119:1873.
[12] D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omedè P, Sciuto F, et al. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: A meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemporary Clinical Trials.33:507-14.
[13] Yan AT, Yan RT, Huynh T, et al. Understanding physicians' risk stratification of acute coronary syndromes: Insights from the canadian acs 2 registry. Archives of internal medicine. 2009;169:372-8.
[14] Abu-Assi E, Gracía-Acuña JM, Ferreira-González I, Peña-Gil C, Gayoso-Diz P, González-Juanatey JR. Evaluating the Performance of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) Bleeding Score in a Contemporary Spanish Cohort of Patients With Non–ST-Segment Elevation Acute Myocardial Infarction. Circulation. 2010;121:2419.
[15] Flores-Ríos X, Couto-Mallón D, Rodríguez-Garrido J, García-Guimaraes M, Gargallo-Fernández P, Piñón-Esteban P, et al. Comparison of the performance of the CRUSADE, ACUITY-HORIZONS, and ACTION bleeding risk scores in STEMI undergoing primary PCI: insights from a cohort of 1391 patients. European Heart Journal: Acute Cardiovascular Care. 2012;2:19-26.
[16] Correia LC, Ferreira F, Kalil F, Silva A, Pereira L, Carvalhal M, et al. Comparison of ACUITY and CRUSADE Scores in Predicting Major Bleeding during Acute Coronary Syndrome. Arquivos brasileiros de cardiologia. 2015;105:20-7.
[17] Martin GP, Kinnaird T, Sperrin M, Anderson R, Gamal A, Jabbar A, et al. Effect of weekend admission on process of care and clinical outcomes for the management of acute

coronary syndromes: a retrospective analysis of three UK centres. BMJ Open. 2017;7.
[18] Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.
[19] Cattle BA, Baxter PD, Greenwood DC, Gale CP, West RM. Multiple imputation for completion of a national clinical audit dataset. Statistics in medicine. 2011;30:2736-53.
[20] Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
[21] Mehta SR, Granger CB, Boden WE, Steg PG, Bassand J-P, Faxon DP, et al. Early versus Delayed Invasive Intervention in Acute Coronary Syndromes. New England Journal of Medicine. 2009;360:2165-75.
[22] Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Bivalirudin during Primary PCI in Acute Myocardial Infarction. New England Journal of Medicine. 2008;358:2218-30.
[23] Paiva L, Providência R, Barra SN, Dinis P, Faustino AC, Costa M, et al. Improving risk stratification in non-ST-segment elevation myocardial infarction with combined assessment of GRACE and CRUSADE risk scores. Archives of Cardiovascular Diseases. 2014;107:681-9.
[24] Desai NR, Peterson ED, Chen AY, Wiviott SD, Sabatine MS, Alexander KP, et al. Balancing the risk of mortality and major bleeding in the treatment of NSTEMI patients – A report from the National Cardiovascular Data Registry. American heart journal. 2013;166:1043-9.e1.
[25] Yan AT, Yan RT, Tan M, et al. Management patterns in relation to risk stratification among patients with non–st elevation acute coronary syndromes. Archives of internal medicine. 2007;167:1009-16.
[26] Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. New England Journal of Medicine. 2015;373:2038-47.
[27] Gerber Robert T, Arri Satpal S, Mohamed Mohamed O, Dhillon G, Bandali A, Harding I, et al. Age is not a bar to PCI: Insights from the long-term outcomes from off-site PCI in a real-world setting. Journal of Interventional Cardiology. 2017;30:347-55.
[28] Tarantini G, Ueshima D, D'Amico G, Masiero G, Musumeci G, Stone GW, et al. Efficacy and safety of potent platelet P2Y12 receptor inhibitors in elderly versus nonelderly patients with acute coronary syndrome: A systematic review and meta-analysis. American heart journal.195:78-85.

Figure Legends

Figure 1. Key to study groups

Figure 2a. In-hospital adverse events

Figure 2b. 30-day mortality

Figure 2c. Receipt of dual antiplatelet therapy (DAPT) and coronary angiography

Figure 1. Key to study groups

Group 1	C	G	LOW CRUSADE-LOW GRACE
Group 2	C	G	LOW CRUSADE-INTERMEDIATE GRACE
Group 3	C	G	LOW CRUSADE-HIGH GRACE
Group 4	C	G	MODERATE CRUSADE-LOW GRACE
Group 5	C	G	MODERATE CRUSADE-INTERMEDIATE GRACE
Group 6	C	G	MODERATE CRUSADE-HIGH GRACE
Group 7	C	G	HIGH CRUSADE-LOW GRACE
Group 8	C	G	HIGH CRUSADE-MODERATE GRACE
Group 9	C	G	HIGH CRUSADE-HIGH GRACE

Figure 2a. In-hospital Adverse events

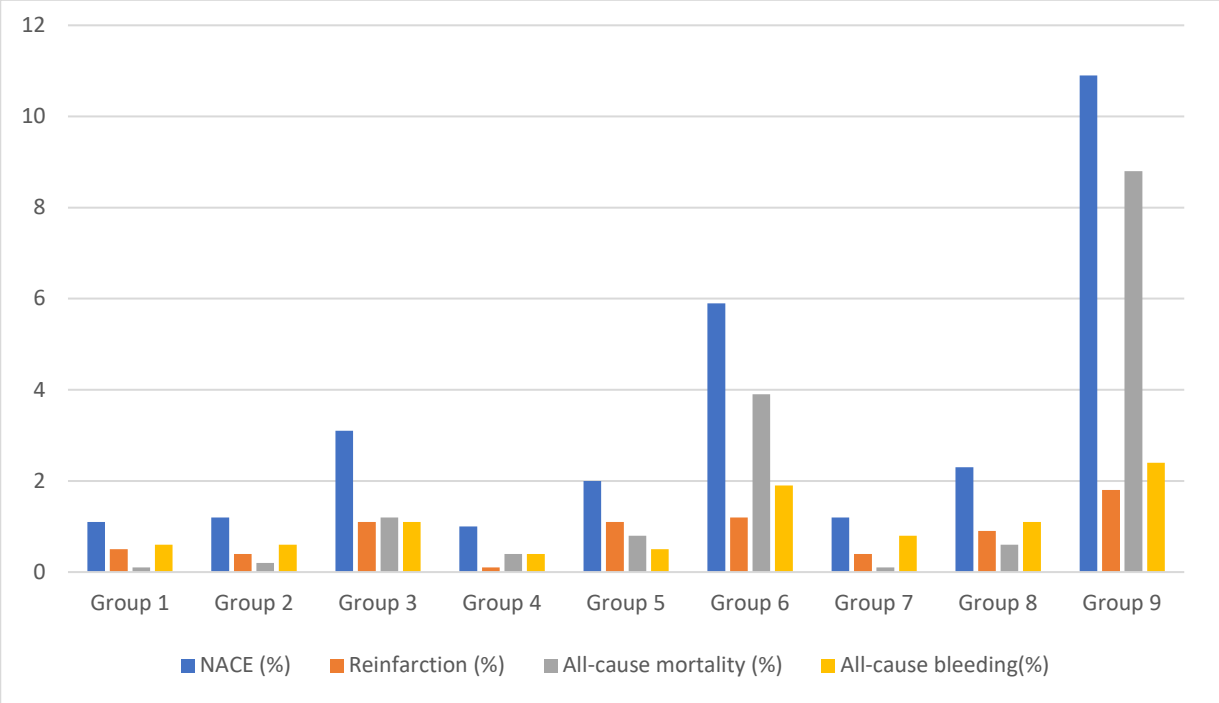


Figure 2b. 30-day mortality

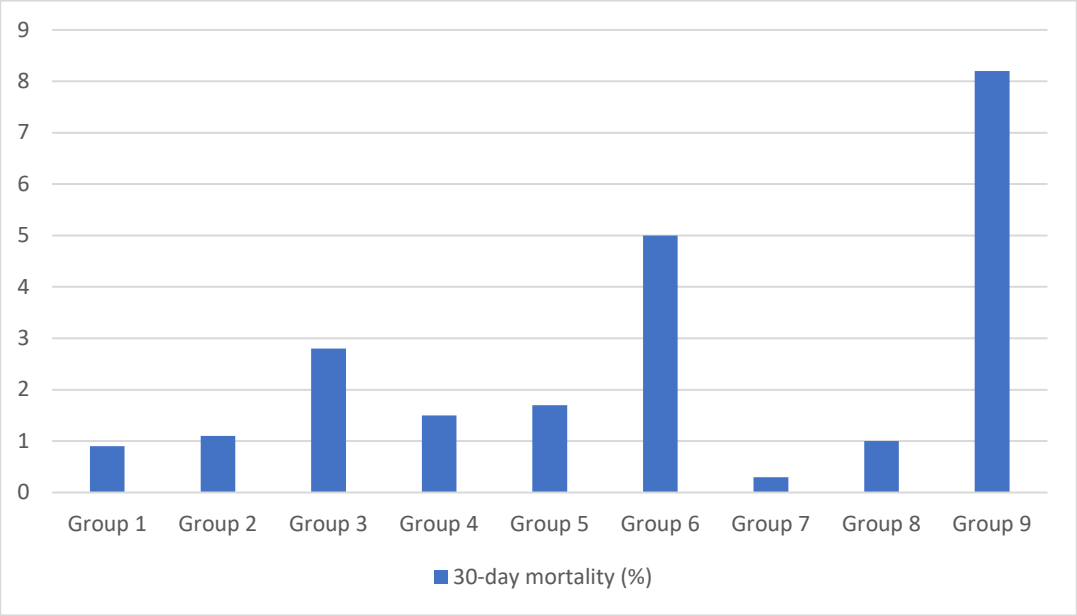


Figure 3. Dual antiplatelet therapy (DAPT) and coronary angiography in study groups.

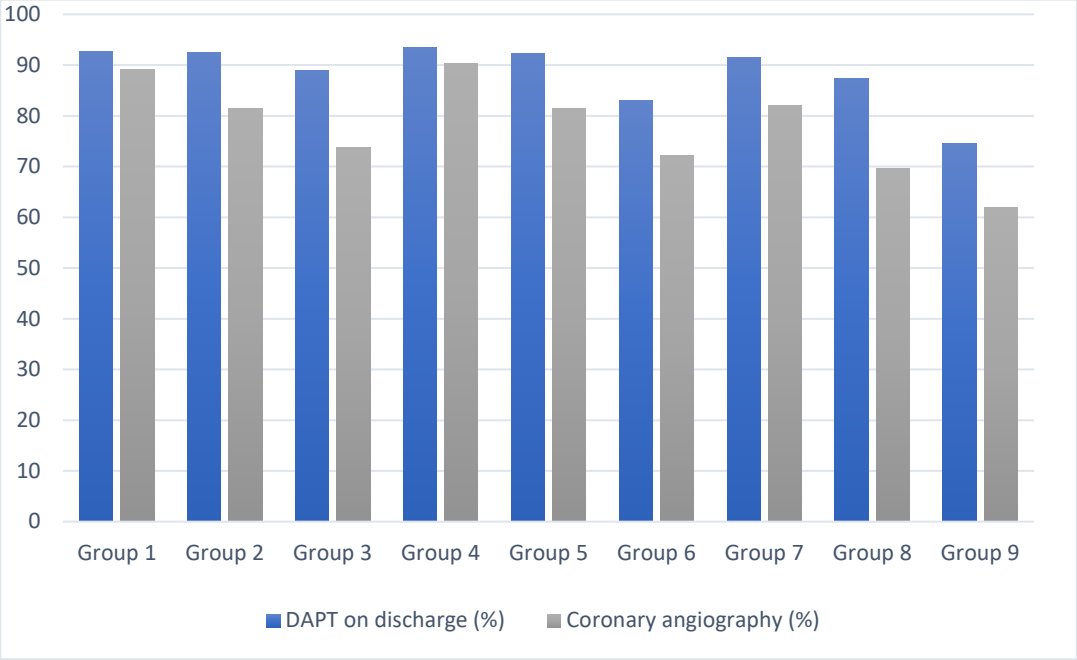


Table 1. Baseline characteristics of combined risk groups

Variable	Group 1 (n=973)	Group 2 (n=2429)	Group 3 (n=3170)	Group 4 (n=239)	Group 5 (n=1040)	Group 6 (n=2736)	Group 7 (n=277)	Group 8 (n=1166)	Group 9 (n=5671)	Total (n=17701)	p-value
	C G	C G	C G	C G	C G	C G	C G	C G	C G		
Age (years), mean (SD)	51.8 (9.6)	58.8 (9.3)	69.3 (11.4)	53.0 (9.6)	57.7 (10.0)	70.5 (11.9)	51.2 (9.7)	57.6 (9.8)	71.9 (11.9)	65.9 (13.1)	<0.001
Males, %	80.2	79.2	77.3	64.8	71.8	69.9	65.6	69.4	62.7	70.8	<0.001
Caucasian, %	79.0	85.3	87.6	79.4	81.5	85.5	72.9	79.8	82.9	83.2	<0.001
STEMI, %	24.6	51.8	57.0	25.0	45.1	54.1	28.7	50.7	53.1	50.8	<0.001
Previous AMI, %	19.3	16.4	18.8	25.6	21.2	24.0	17.1	16.9	25.3	21.4	<0.001
Previous angina, %	22.1	19.7	20.8	32.7	24.5	24.9	18.8	20.5	27.0	23.6	<0.001
Previous PCI, %	15.2	11.9	10.5	21.9	15.1	12.2	13.6	11.6	12.3	12.3	0.001
Previous CABG, %	3.4	3.6	5.1	3.8	5.6	6.0	2.9	4.6	6.7	5.4	<0.001
Hypertension, %	44.9	45.5	52.0	51.4	46.6	56.4	45.3	47.1	62.7	54.0	<0.001
Hypercholesterolaemia, %	41.3	38.5	39.1	52.2	44.0	41.8	38.5	42.5	41.2	40.9	<0.001
Peripheral vascular disease, %	1.3	2.0	1.8	3.6	5.2	4.9	5.9	4.6	8.6	4.9	<0.001
Cerebrovascular disease, %	2.8	4.3	6.5	2.9	4.4	8.7	2.6	5.0	10.8	7.3	<0.001
Asthma or COPD, %	12.5	12.4	13.5	16.1	13.7	16.8	12.7	14.7	18.9	15.6	<0.001
Chronic renal failure, %	0.1	0.3	0.8	0.7	0.7	2.3	0.8	1.7	10.2	3.9	<0.001
Heart Failure, %	0.6	1.0	2.0	1.9	1.1	3.0	1.3	1.5	6.1	3.1	<0.001
Elevated Troponin, %	84.0	93.8	98.1	78.2	91.1	98.6	86.7	92.1	98.6	95.7	<0.001
Previous/current smokers, %	76.6	71.9	66.2	75.1	75.9	66.8	75.6	74.5	66.8	69.3	<0.001
Diabetes											
Dietary control, %	2.3	2.1	2.2	5.2	3.0	3.1	3.1	4.1	5.2	3.5	<0.001
Oral medicine, %	5.1	5.7	5.4	17.9	11.5	11.1	13.7	14.3	15.1	10.6	<0.001

Variable	Group 1 (n=973)		Group 2 (n=2429)		Group 3 (n=3170)		Group 4 (n=239)		Group 5 (n=1040)		Group 6 (n=2736)		Group 7 (n=277)		Group 8 (n=1166)		Group 9 (n=5671)		Total (n=17701)	p-value
	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G		
Insulin, %	2.1		1.5		1.3		7.1		4.2		3.0		3.8		5.1		8.1		4.3	<0.001
Cholesterol (mmol/L), mean (SD)	5.1 (1.4)		5 (1.3)		4.7 (1.3)		4.9 (1.4)		5 (1.3)		4.7(1.4)		5(1.2)		5(1.4)		4.5(1.3)		4.8 (1.4)	<0.001
Systolic BP (mmHg), mean (SD)	143(22)		139 (23)		136 (27)		144 (25)		136 (25)		133(29)		144(22)		138(25)		131(31)		135 (28)	<0.001
Heart rate (bpm), mean (SD)	70 (13)		72 (15)		73 (16)		71(16)		73 (17)		76 (19)		71(14)		75 (17)		82 (23)		76 (19)	<0.001
BMI, mean (SD)	29 (6)		28 (6)		28 (5)		31(6)		29 (6)		28(5)		30 (6)		29 (6)		28 (6)		28 (6)	<0.001
Creatinine (umol/L), mean (SD)	72 (13)		75 (15)		82 (20)		74 (11)		80 (18)		93(27)		74 (15)		82(40)		126(101)		96 (64)	<0.001
Haemoglobin (g/L), mean (SD)	144 (20)		142 (19)		137 (21)		139 (21)		141 (20)		133 (23)		141 (22)		139 (21)		129 (25)		135 (23)	<0.001
Admission under a Cardiologist, %	99.4		99.5		98.4		99.1		99.6		97.5		97.8		98.9		95.0		97.5	<0.001
Loop diuretics, %	3.4		5.2		14.6		7.9		7.5		21.7		3.7		10.3		35.5		19.4	<0.001
Warfarin, %	2.3		3.7		5.1		2.1		2.6		6.2		1.3		2.9		7.8		5.4	<0.001
Family history of CHD, %	65.5		57.1		48.4		65.6		61.5		50.1		61.1		54.9		44.6		51.4	<0.001
Killip class, %																				
I, %	96.3		91.7		73.4		92.2		83.9		62.0		94.0		82.7		45.9		68.5	<0.001
II, %	3.6		7.2		17.0		7.5		14.8		22.7		5.6		15.7		29.8		19.3	<0.001
III, %	0.1		0.7		5.9		0.3		1.0		9.1		0.4		1.3		14.4		7.3	<0.001
IV, %	0.0		0.4		3.8		0.0		0.4		6.3		0.0		0.3		9.8		4.9	<0.001
Cardiac arrest on admission, %	0.0		0.5		8.1		0.0		0.4		5.7		0.0		0.8		6.4		4.5	<0.001

Table 2. Clinical outcomes and quality indicators of combined risk groups

Variable	Group 1 (n=973)		Group 2 (n=2429)		Group 3 (n=3170)		Group 4 (n=239)		Group 5 (n=1040)		Group 6 (n=2736)		Group 7 (n=277)		Group 8 (n=1166)		Group 9 (n=5671)		Total (n=17701)	p-value
	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G		
In-hospital NACE, %	1.1		1.2		3.1		1.0		2.0		5.9		1.2		2.3		10.9		5.5	<0.001
In-hospital cardiac mortality, %	0.1		0.2		1.1		0.4		0.7		3.3		0.1		0.6		7.9		3.3	<0.001
In-hospital all-cause mortality, %	0.1		0.2		1.2		0.4		0.8		3.9		0.1		0.6		8.8		3.9	<0.001
30-day mortality, %	0.9		1.1		2.8		1.5		1.7		5.0		0.3		1.0		8.2		4.3	<0.001
In-hospital re-infarction, %	0.5		0.4		1.1		0.1		1.1		1.2		0.4		0.9		1.8		1.2	<0.001
In-hospital TIMI major bleeding, %	0.1		0.0		0.0		0.0		0.0		0.1		0.0		0.0		0.1		0.1	0.46
In-hospital all-cause bleeding, %	0.6		0.6		1.1		0.4		0.5		1.9		0.8		1.1		2.4		1.5	<0.001
Receipt of coronary angiography, %	89.2		81.4		73.8		90.3		81.4		72.2		82.0		69.7		62.0		72.3	<0.001
Beta-blockers on discharge, %	98.4		97.8		97.1		97.5		97.5		96.6		95.6		97.1		95.3		96.6	<0.001
ACEI on discharge, %	94.7		96.4		95.5		95.2		96.6		94.3		91.4		92.4		91.6		93.9	<0.001
Statin on discharge, %	98.6		99.2		98.3		98.8		98.5		97.6		98.7		98.6		95.5		97.5	<0.001
Aspirin only on discharge, %	2.8		2.2		3.0		3.0		2.3		4.5		3.1		4.4		5.6		4.0	<0.001
P2Y12 inhibitor only on discharge	0.9		0.8		1.6		1.0		0.9		1.9		0.6		1.4		2.7		1.8	<0.001

Variable	Group 1 (n=973)		Group 2 (n=2429)		Group 3 (n=3170)		Group 4 (n=239)		Group 5 (n=1040)		Group 6 (n=2736)		Group 7 (n=277)		Group 8 (n=1166)		Group 9 (n=5671)		Total (n=17701)	p-value
	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G		
DAPT on discharge, %	92.7		92.4		88.9		93.4		92.2		83.0		91.6		87.4		74.6		84.3	<0.001

DAPT: dual antiplatelet therapy; NACE: net adverse cardiac events; TIMI: thrombosis in myocardial infarction criteria

Table 3. Group predictors of adverse events and receipt of guideline-based care.

Outcome/Groups		Multivariable analysis	
		aOR [95% CI]	p-value
In-hospital NACE			
GROUP 1 (reference)	C G		
GROUP 2	C G	0.70 [0.35, 1.39]	0.307
GROUP 3	C G	1.85 [1.01, 3.39]	0.046
GROUP 4	C G	0.94 [0.26, 3.37]	0.924
GROUP 5	C G	1.26 [0.62, 2.57]	0.522
GROUP 6	C G	3.23 [1.78, 5.85]	<0.001
GROUP 7	C G	0.78 [0.22, 2.78]	0.696
GROUP 8	C G	1.56 [0.79, 3.07]	0.196
GROUP 9	C G	6.33 [3.55, 11.29]	<0.001
In-hospital all-cause mortality			
GROUP 1 (reference)	C G		
GROUP 2	C G	0.31 [0.08, 1.26]	0.101
GROUP 3	C G	2.12 [0.76, 5.93]	0.154
GROUP 4*	C G	0.96 [0.11, 8.65]	0.971
GROUP 5	C G	1.69 [0.53, 5.42]	0.377
GROUP 6	C G	5.82 [2.13, 15.87]	0.001
GROUP 7*	C G	0.76 [0.09, 6.87]	0.809
GROUP 8	C G	1.39 [0.43, 4.53]	0.587

GROUP 9	**C G**	14.17 [5.27, 38.1]	<0.001
In-hospital all-cause bleeding			
GROUP 1 (reference)	**C G**		
GROUP 2	**C G**	1.08 [0.38, 3.03]	0.888
GROUP 3	**C G**	2.26 [0.88, 5.82]	0.091
GROUP 4	**C G**	0.86 [0.10, 7.44]	0.894
GROUP 5	**C G**	1.24 [0.38, 4.07]	0.726
GROUP 6	**C G**	4.05 [1.60, 10.21]	0.001
GROUP 7	**C G**	1.37 [0.26, 7.07]	0.711
GROUP 8	**C G**	2.23 [0.78, 6.34]	0.134
GROUP 9	**C G**	4.82 [1.96, 11.86]	<0.001
30-day mortality			
GROUP 1 (reference)	**C G**		
GROUP 2	**C G**	1.67 [0.77, 3.64]	0.197
GROUP 3	**C G**	3.79 [1.83, 7.84]	<0.001
GROUP 4*	**C G**	2.87 [0.93, 8.87]	0.066
GROUP 5	**C G**	2.54 [1.11, 5.82]	0.028
GROUP 6	**C G**	6.93 [3.38, 14.2]	<0.001
GROUP 7*	**C G**	0.45 [0.06, 3.61]	0.452
GROUP 8	**C G**	1.02 [0.39, 2.66]	0.967
GROUP 9	**C G**	10.79 [5.33, 21.81]	<0.001
Receipt of coronary angiography			
GROUP 1 (reference)	**C G**		
GROUP 2	**C G**	0.61 [0.50, 0.74]	<0.001
GROUP 3	**C G**	0.39 [0.32, 0.47]	<0.001
GROUP 4	**C G**	1.04 [0.69, 1.58]	0.848
GROUP 5	**C G**	0.62 [0.49, 0.78]	<0.001
GROUP 6	**C G**	0.38 [0.32, 0.46]	<0.001
GROUP 7	**C G**	0.68 [0.48, 0.95]	0.025
GROUP 8	**C G**	0.39 [0.31, 0.48]	<0.001
GROUP 9	**C G**	0.24 [0.20, 0.29]	<0.001

Receipt of DAPT on discharge			
GROUP 1 (reference)	**C** **G**		
GROUP 2	**C** **G**	0.97 [0.70, 1.32]	0.827
GROUP 3	**C** **G**	0.68 [0.51, 0.90]	0.007
GROUP 4	**C** **G**	1.04 [0.56, 1.93]	0.901
GROUP 5	**C** **G**	0.92 [0.63, 1.34]	0.658
GROUP 6	**C** **G**	0.42 [0.31, 0.55]	<0.001
GROUP 7	**C** **G**	0.91 [0.55, 1.52]	0.723
GROUP 8	**C** **G**	0.56 [0.39, 0.80]	0.002
GROUP 9	**C** **G**	0.26 [0.20, 0.34]	<0.001

aOR: adjusted odds ratio; CI: confidence interval; NACE: net adverse cardiac events; DAPT: dual antiplatelet therapy.

Supplementary Table 1. Variables of GRACE and CRUSADE scores and missing frequencies

GRACE 2.0	CRUSADE	Missing frequency (n=)*
Killip class	HF on admission	6925
BP	BP	2574
Heart Rate	Heart rate	630
Age		461
Creatinine		266
Cardiac Arrest		39
ST segment deviation		39
Elevated troponin		350
	Creatinine Clearance (Cockroft-Gault formula)**	560
	Haematocrit (derived from haemoglobin)	484
	Sex	None
	Peripheral Vascular disease	109
	Diabetes Mellitus	730

**All missing variables were imputed; ** Derived from creatinine, age, weight, sex*

Supplementary Table 2. Baseline characteristics according to contributing centre.

Variable	Cardiff (n=3107)	Newcastle (n=7625)	Stoke (n=6969)	Total (n=17701)	p-value
Age, mean (SD)	65.7 (13.6)	65.3 (12.8)	66.9 (13.1)	65.9 (13.1)	<0.001
Males, %	69.6	71.0	71.0	70.8	<0.001
Caucasian, %*	*	90.3	75.5	83.2	0.001
STEMI, %	57.5	45.2	54.7	50.8	<0.001
Previous AMI, %	18.6	24.6	18.8	21.4	<0.001
Previous angina, %	22.3	34.3	10.4	23.6	<0.001
Previous PCI, %	10.4	17.3	6.9	12.3	<0.001
Previous CABG, %	4.5	5.4	5.8	5.4	<0.001
Hypertension, %	52.9	58.9	48.3	54.0	<0.001
Hypercholesterolaemia, %	32.1	49.8	34.0	40.9	<0.001
Peripheral vascular disease, %	6.0	7.8	0.6	4.9	<0.001

Cerebrovascular disease, %	8.6	8.5	5.2	7.3	<0.001
Asthma or COPD, %	17.9	16.8	12.9	15.6	<0.001
Chronic renal failure, %	5.2	3.2	4.2	3.9	<0.001
Heart Failure, %	5.6	3.8	1.0	3.1	<0.001
Elevated Troponin, %	97.3	92.6	99.2	95.7	<0.001
Previous/current smokers, %	70.3	68.8	69.4	69.3	0.002
Diabetes	3.2	3.8	3.2		
Dietary control, %	10.7	10.5	10.8	3.5	<0.001
Oral medicine, %	3.6	5.0	3.8	10.6	<0.001
Insulin, %				4.3	<0.001
Cholesterol (mmol/L), mean (SD)	4.8 (1.2)	4.7 (1.4)	4.9 (1.3)	4.8 (1.4)	<0.001
Systolic BP (mmHg), mean (SD)	134 (26)	131 (28)	141 (27)	135 (28)	<0.001
Heart rate (bpm), mean (SD)	78 (19)	74 (18)	79 (20)	76 (19)	<0.001
BMI, mean (SD)	28 (4)	28 (5)	28 (7)	28 (6)	0.774
Creatinine (umol/L), mean (SD)	94 (61)	97 (57)	95 (73)	96 (64)	0.001
Haemoglobin (g/L), mean (SD)	135 ()	135 (21)	135 (27)	135 (23)	0.716
Admission under a Cardiologist, %	91.1	100.0	97.6	97.5	<0.001
Loop diuretics, %	26.6	20.2	14.7	19.4	<0.001
Warfarin, %	5.7	4.8	6.0	5.4	<0.001
Family history of CHD, %	27.4	48.2	71.4	51.4	<0.001
Killip class, %					<0.001
I, %	68.0	90.9	39.6	68.5	<0.001
II, %	21.4	2.1	40.7	19.3	<0.001
III, %	7.7	4.7	10.5	7.3	<0.001
IV, %	2.8	2.4	9.3	4.9	<0.001
Cardiac arrest on admission, %	4.6	4.2	5.0	4.5	<0.001

*Ethnicity data for 2 centres only

Supplementary Table 3. Baseline characteristics of CRUSADE categories

Variable	Very Low (n=2848)	Low (n=3924)	Moderate (n=3902)	High (n=3247)	Very High (n=3780)	Total (n=17701)	p-value
Age, mean (SD)	61.3 (11.8)	63.9 (12.6)	66.1 (13.0)	67.3 (13.3)	69.7 (13.0)	65.9 (13.1)	<0.001
Males, %*	86.6	72.9	70.1	69.5	59.3	70.8	<0.001
Caucasian, %	86.1	85.1	84.1	84.3	80.0	83.2	<0.001
STEMI, %	50.2	50.3	50.0	52.7	51.0	50.8	0.062
Previous AMI, %	16.8	18.8	23.4	21.7	25.2	21.4	<0.001
Previous angina, %	19.2	21.5	25.3	24.8	26.3	23.6	<0.001
Previous PCI, %	11.5	11.8	13.6	12.1	12.4	12.3	<0.001
Previous CABG, %	3.5	4.9	5.8	5.7	6.6	5.4	<0.001
Hypertension, %	46.1	50.2	53.5	57.3	61.3	54.0	<0.001
Hypercholesterolaemia, %	37.5	40.3	43.0	42.7	40.2	40.9	<0.001
Peripheral vascular disease, %	0.8	2.5	4.9	5.0	10.2	4.9	<0.001
Cerebrovascular disease, %	4.3	5.7	7.2	8.3	10.4	7.3	<0.001
Asthma or COPD, %	12.5	13.3	15.9	17.2	18.5	15.6	<0.001
Chronic renal failure, %	0.3	0.6	1.8	4.3	11.9	3.9	<0.001
Heart Failure, %	1.0	1.6	2.4	4.2	5.9	3.1	<0.001
Elevated Troponin, %	94.4	94.5	95.4	95.9	98.1	95.7	<0.001
Previous/current smokers, %	71.5	68.7	69.7	69.1	68.0	69.3	<0.001
Diabetes							<0.001
Dietary control, %	1.1	2.9	3.2	3.8	5.8	3.5	<0.001
Oral medicine, %	2.8	7.3	11.6	12.5	17.0	10.6	<0.001
Insulin, %	0.6	2.1	3.6	4.9	9.5	4.3	<0.001
Cholesterol (mmol/L), mean (SD)	4.9 (1.3)	4.9 (1.3)	4.8 (1.4)	4.7 (1.3)	4.6 (1.4)	4.8 (1.4)	<0.001
Systolic BP (mmHg), mean (SD)	140 (22)	137 (26)	134 (28)	134 (28)	131 (31)	135 (28)	<0.001
Heart rate (bpm), mean (SD)	70 (13)	74 (16)	75 (18)	77 (20)	83 (23)	76 (19)	<0.001
BMI, mean (SD)	28 (6)	28 (6)	28 (5)	28 (6)	28 (5)	28 (6)	0.714
Creatinine (umol/L), mean (SD)	75 (15)	80 (20)	89 (25)	101 (51)	130 (117)	96 (64)	<0.001
Haemoglobin (g/L), mean (SD)	141 (20)	138 (21)	136 (22)	134 (23)	128 (5)	135 (23)	<0.001

Admission under a Cardiologist, %	99.4	98.6	98.1	97.5	94.2	97.5	<0.001
Loop diuretics, %	6.3	11.6	17.2	23.7	35.4	19.4	<0.001
Warfarin, %	3.5	4.6	5.0	6.4	7.1	5.4	<0.001
Family history of CHD, %	54.7	53.9	54.1	48.4	46.0	51.4	<0.001
Killip class, %	91.4	78.1	69.5	66.8	43.1	97.5	<0.001
I, %	6.1	15.0	19.7	19.4	32.6	68.5	<0.001
II, %	1.5	4.2	6.5	8.9	14.0	19.3	<0.001
III, %	1.0	2.7	4.3	4.9	10.3	7.3	
IV, %	91.4	78.1	69.5	66.8	43.1	4.9	<0.001
Cardiac arrest on admission, %	4.1	4.1	4.0	4.3	6.4	4.5	<0.001

*Ethnicity data for 2 centres only

Supplementary Table 4. Baseline characteristics of GRACE categories

Variable	Low (n=1633)	Intermediate (n=4769)	High (n=11299)	Total (n=17701)	p-value
Age, mean (SD)	51.9 (9.6)	58.3 (9.6)	70.8 (11.8)	65.9 (13.1)	<0.001
Males, %	75.0	75.1	68.5	70.8	<0.001
Caucasian, %*	78.2	83.3	85.0	83.2	0.001
STEMI, %	25.5	50.0	54.4	50.8	<0.001
Previous AMI, %	19.9	17.6	23.2	21.4	<0.001
Previous angina, %	23.2	21.0	24.8	23.6	<0.001
Previous PCI, %	16.0	12.5	11.8	12.3	0.047
Previous CABG, %	3.4	4.3	6.1	5.4	<0.001
Hypertension, %	46.0	46.2	58.3	54.0	<0.001
Hypercholesterolaemia, %	42.5	40.7	40.8	40.9	<0.001
Peripheral vascular disease, %	2.5	3.4	5.9	4.9	<0.001
Cerebrovascular disease, %	2.8	4.5	9.1	7.3	<0.001
Asthma or COPD, %	13.2	13.3	16.9	15.6	<0.001
Chronic renal failure, %	0.3	0.7	5.7	3.9	<0.001
Heart Failure, %	0.9	1.1	4.2	3.1	<0.001
Elevated Troponin, %	83.6	92.8	98.5	95.7	<0.001

Previous/current smokers, %	76.2	73.5	66.6	69.3	<0.001
Diabetes					
Dietary control, %	2.9	2.8	3.9	3.5	<0.001
Oral medicine, %	8.8	9.1	11.5	10.6	<0.001
Insulin, %	3.2	3.0	5.0	4.3	<0.001
Cholesterol (mmol/L), mean (SD)	5.0 (1.4)	5.0 (1.3)	4.6 (1.3)	4.8 (1.4)	<0.001
Systolic BP (mmHg), mean (SD)	143 (22)	138 (24)	132 (29)	135 (28)	<0.001
Heart rate (bpm), mean (SD)	71 (13)	73 (16)	78 (21)	76 (19)	<0.001
BMI, mean (SD)	30 (6)	29 (6)	28 (5)	28 (6)	<0.001
Creatinine (umol/L), mean (SD)	73 (13)	78 (25)	106 (75)	96 (64)	<0.001
Haemoglobin (g/L), mean (SD)	142 (21)	141 (20)	132 (24)	135 (23)	<0.001
Admission under a Cardiologist, %	99.1	99.4	96.5	97.5	<0.001
Loop diuretics, %	4.2	7.0	26.5	19.4	<0.001
Warfarin, %	2.1	3.2	6.7	5.4	<0.001
Family history of CHD, %	64.7	57.5	47.0	51.4	<0.001
Killip class, %	99.1	99.4	96.5	97.5	<0.001
I, %	95.2	87.7	57.3	68.5	<0.001
II, %	4.6	11.0	24.6	19.3	<0.001
III, %	0.2	0.9	10.8	7.3	
IV, %	0.0	0.4	7.3	4.9	<0.001
Cardiac arrest on admission, %	0.0	0.5	6.7	4.5	<0.001

*Ethnicity data for 2 centres only

Supplementary Table 5. Outcomes according to CRUSADE categories

Variable	Very Low (n=2848)	Low (n=3924)	Moderate (n=3902)	High (n=3247)	Very High (n=3780)	Total (n=17701)	p-value
In-hospital NACE, %	1.6	2.3	4.6	5.9	11.9	5.5	<0.001
In-hospital cardiac mortality, n%	0.3	0.8	2.5	3.5	8.8	3.3	<0.001
In-hospital all-cause mortality, n%	0.4	0.9	2.9	3.7	9.9	3.7	<0.001
30-day mortality, n%	1.5	2.1	3.9	3.9	9.1	4.3	<0.001

In-hospital re-infarction, n%	0.7	0.8	1.1	1.4	1.8	1.2	0.06
In-hospital TIMI major bleeding, n%	0.0	0.0	0.1	0.0	0.2	0.1	<0.001
In-hospital all-cause bleeding, %	0.7	0.9	1.5	1.6	2.5	1.5	<0.001
Receipt of coronary angiography, n%	80.4	77.9	75.7	70.5	58.6	72.3	<0.001
Beta-blockers on discharge, n%	97.7	97.4	96.9	96.4	95.0	96.6	<0.001
ACEI on discharge, n%	96.3	95.3	94.9	93.5	90.3	93.9	<0.001
Statin on discharge, n%	98.9	98.5	97.9	97.1	95.3	97.5	<0.001
Aspirin only on discharge, n%	2.2	3.0	3.8	4.0	6.3	4.0	<0.001
P2Y12 inhibitor only on discharge	1.0	1.4	1.6	2.3	2.5	1.8	<0.001
DAPT on discharge, n%	91.7	90.1	86.0	82.6	72.9	84.3	<0.001

ACEI: angiotensin converting enzyme inhibitor; DAPT: dual antiplatelet therapy; NACE: net adverse cardiac events; TIMI: thrombosis in myocardial infarction criteria

Supplementary Table 6. Outcomes according to GRACE categories

Variable	Low (n=1633)	Intermediate (n=4769)	High (n=11299)	Total (n=17701)	p-value
In-hospital NACE, %	1.1	1.6	7.6	5.5	<0.001
In-hospital cardiac mortality, n%	0.2	0.4	4.9	3.3	<0.001
In-hospital all-cause mortality, n%	0.2	0.4	5.6	3.7	<0.001
30-day mortality, n%	0.9	1.2	6.0	4.3	<0.001
In-hospital re-infarction, n%	0.4	0.7	1.5	1.2	0.153
In-hospital TIMI major bleeding, n%	0.0	0.0	0.1	0.1	<0.001
In-hospital all-cause bleeding, %	0.6	0.7	1.9	1.5	<0.001
Receipt of coronary angiography, n%	88.0	78.5	66.7	72.3	<0.001
Beta-blockers on discharge, n%	97.8	97.6	96.1	96.6	<0.001
ACEI on discharge, n%	94.2	95.5	93.3	93.9	<0.001
Statin on discharge, n%	98.7	98.9	96.7	97.5	<0.001
Aspirin only on discharge, n%	2.9	2.8	4.6	4.0	<0.001
P2Y12 inhibitor only on discharge	0.9	1.0	2.2	1.8	<0.001
DAPT on discharge, n%	92.6	91.1	80.5	84.3	<0.001

ACEI: angiotensin converting enzyme inhibitor; DAPT: dual antiplatelet therapy; NACE: net adverse cardiac events; TIMI: thrombosis in myocardial infarction criteria

Supplementary Table 7a. Clinical outcomes of NSTE-ACS subgroup (sensitivity analysis)

Variable	Group 1 (n=729)		Group 2 (n=1168)		Group 3 (n=1349)		Group 4 (n=179)		Group 5 (n=568)		Group 6 (n=1246)		Group 7 (n=197)		Group 8 (n=576)		Group 9 (n=2647)		Total (n=8659)	p-value
	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G		
In-hospital NACE, %	1.1		0.9		2.2		0.8		2.1		3.9		0.7		1.4		6.6		3.4	<0.001
In-hospital cardiac mortality, %	0.1		0.1		0.8		0.1		0.5		1.5		0.0		0.2		4.2		1.7	<0.001
In-hospital all-cause mortality, %	0.1		0.1		1.1		0.1		0.7		2.2		0.0		0.3		5.3		2.2	<0.001
30-day mortality, %	0.9		1.2		2.7		1.5		1.8		3.8		0.5		1.1		6.3		3.4	<0.001
In-hospital re-infarction, %	0.4		0.4		0.7		0.1		0.9		1.1		0.3		0.8		1.5		0.9	<0.001
In-hospital TIMI major bleeding, %	0.1		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.2		0.1	<0.001
In-hospital all-cause bleeding, %	0.7		0.5		0.9		0.6		1.0		1.8		0.5		0.6		2.0		1.3	<0.001
Receipt of coronary angiography, %	98.9		98.1		92.5		97.7		97.9		87.7		99.6		96.7		77.3		89.4	<0.001
DAPT on discharge, %	92.9		93.1		88.6		94.2		93.5		83.5		94.4		88.7		75.9		85.6	<0.001

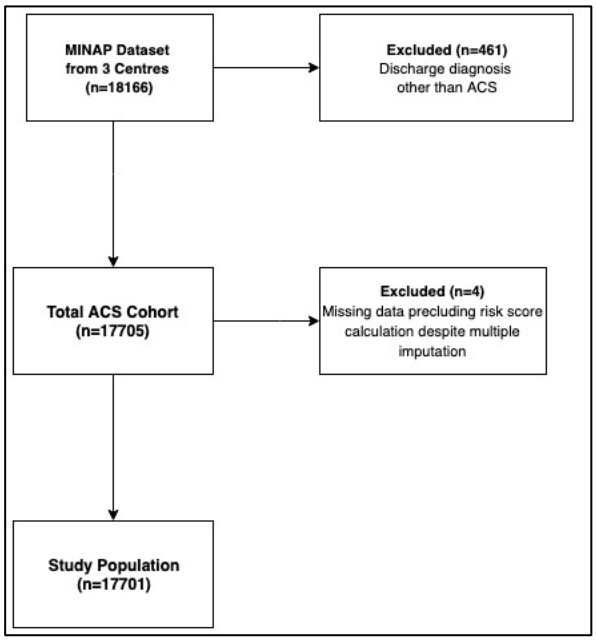
DAPT: dual antiplatelet therapy; NACE: net adverse cardiac events; NSTE-ACS: Non-ST Elevation Acute Coronary Syndrome; TIMI: thrombosis in myocardial infarction criteria

Supplementary Table 7b. Clinical outcomes of STEMI subgroup (sensitivity analysis)

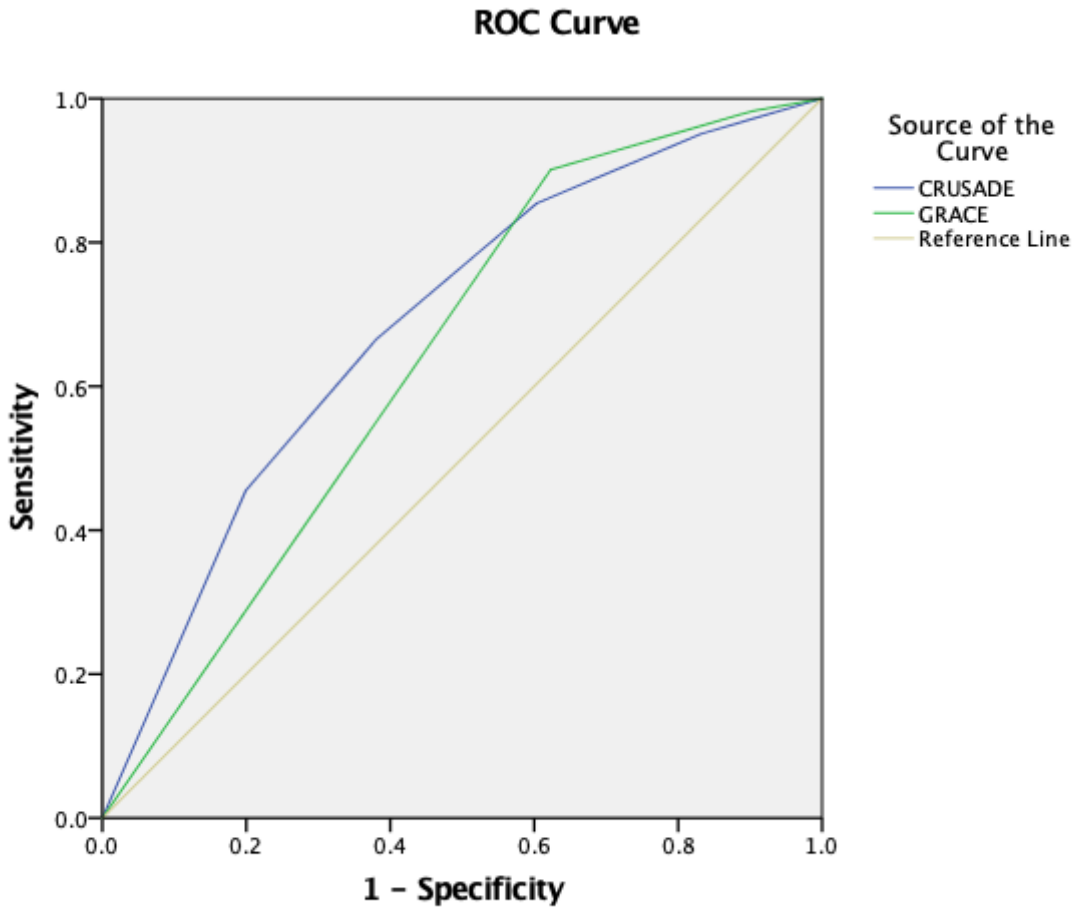
Variable	Group 1 (n=245)		Group 2 (n=1261)		Group 3 (n=1820)		Group 4 (n=60)		Group 5 (n=472)		Group 6 (n=1490)		Group 7 (n=81)		Group 8 (n=589)		Group 9 (n=3024)		Total (n=9042)	p-value
	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G	C	G		
In-hospital NACE, %	1.2		1.4		3.7		1.5		1.9		7.6		2.2		3.2		14.7		7.4	<0.001
In-hospital cardiac mortality, %	0.2		0.3		1.3		1.2		0.9		4.9		0.4		1.0		11.2		4.9	<0.001
In-hospital all-cause mortality, %	0.2		0.3		1.4		1.2		0.9		5.3		0.4		1.0		11.8		5.2	<0.001
30-day mortality, %	0.6		1.0		2.8		1.5		1.7		6.0		0.0		0.8		10.0		5.2	<0.001
In-hospital re-infarction, %	0.7		0.4		1.4		0.3		1.2		1.4		0.7		1.1		2.1		1.4	<0.001
In-hospital TIMI major bleeding, %	0.0		0.0		0.1		0.0		0.0		0.2		0.0		0.0		0.1		0.1	<0.001
In-hospital all-cause bleeding, %	0.4		0.7		1.3		0.0		0.0		2.0		1.3		1.6		2.7		1.7	<0.001
Receipt of coronary angiography, %	59.1		65.6		59.5		67.5		60.9		58.9		35.8		42.5		48.3		55.4	<0.001
DAPT on discharge, %	92.0		91.7		89.2		91.1		90.6		82.6		84.6		86.3		73.3		83.1	<0.001

DAPT: dual antiplatelet therapy; NACE: net adverse cardiac events; TIMI: thrombosis in myocardial infarction criteria

Supplementary Figure 1. Flow chart of study exclusions

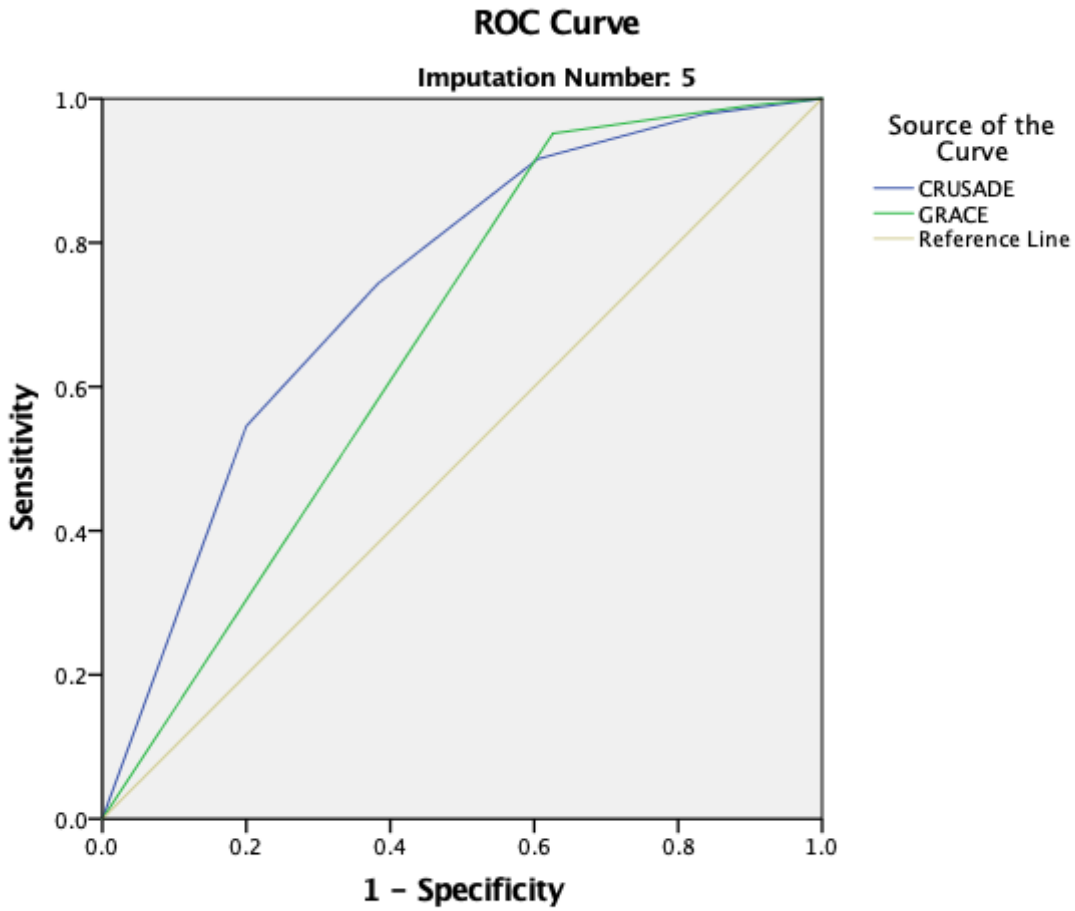


Supplementary Figure 2a. ROC of CRUSADE and GRACE scores as predictors of NACE



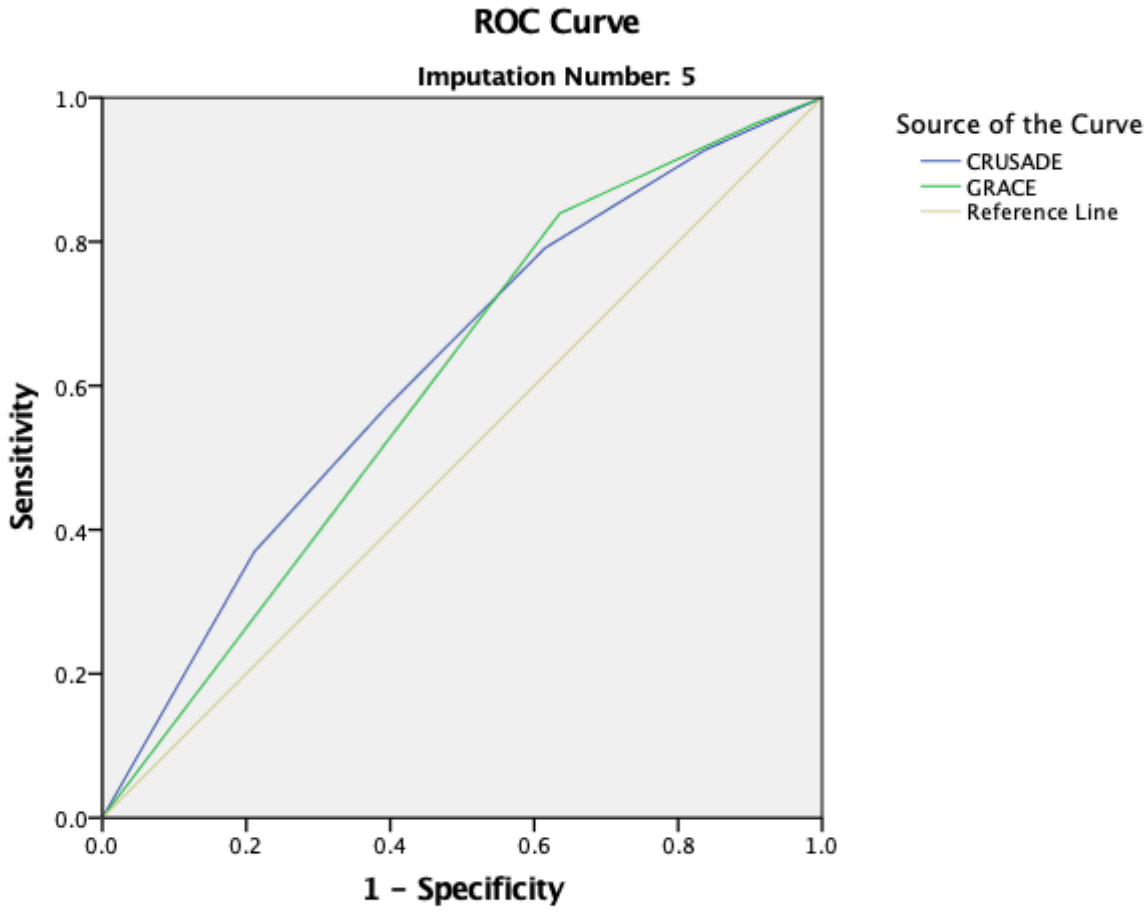
Score	AUC	95% CI UL		p-value
		UL	LL	
CRUSADE	0.686	0.670	0.703	<0.001
GRACE	0.641	0.626	0.656	<0.001

Supplementary Figure 2b. ROC of CRUSADE and GRACE scores as predictors of all-cause mortality



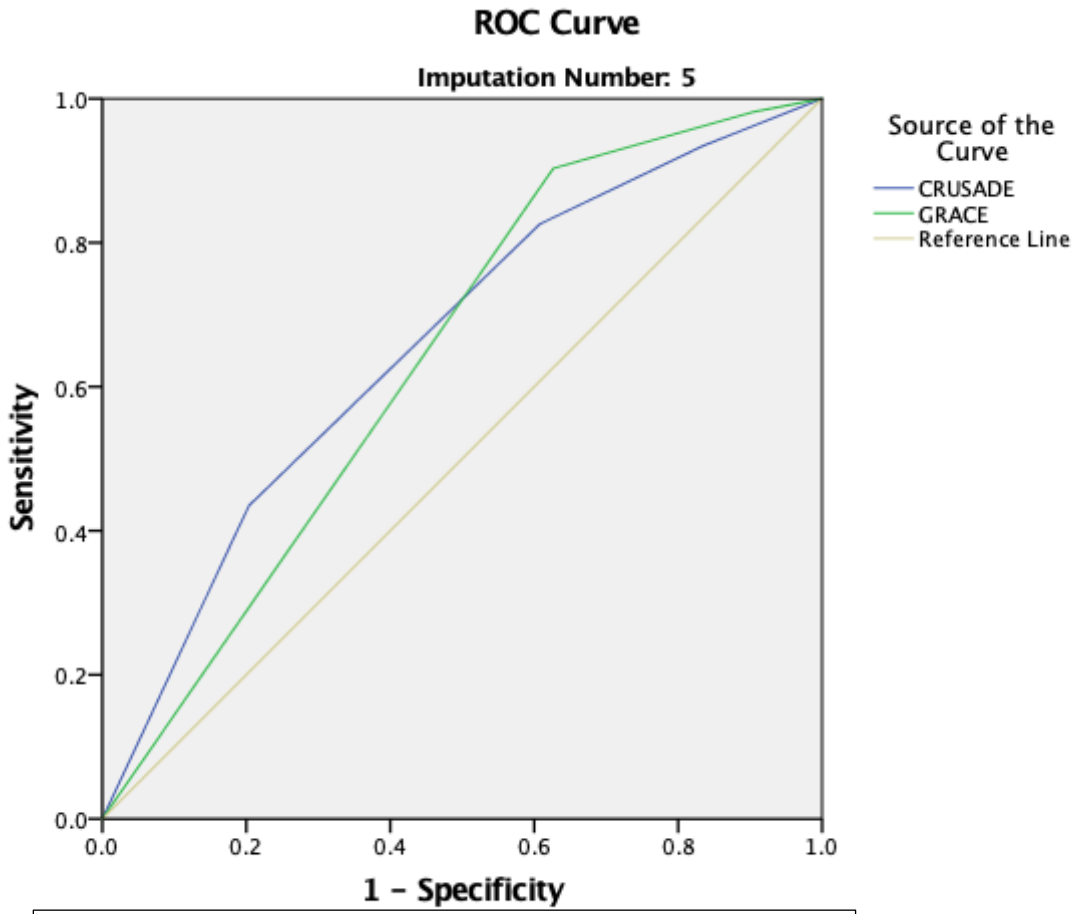
Score	AUC	95% CI UL		p-value
		UL	LL	
CRUSADE	0.738	0.721	0.755	<0.001
GRACE	0.664	0.647	0.680	<0.001

Supplementary Figure 2c. ROC of CRUSADE and GRACE scores as predictors of all-cause bleeding



Score	AUC	95% CI UL		p-value
		UL	LL	
CRUSADE	0.623	0.589	0.657	<0.001
GRACE	0.603	0.571	0.634	<0.001

Supplementary Figure 2d. ROC of CRUSADE and GRACE scores as predictors of 30-day mortality



Score	AUC	95% CI UL		p-value
		UL	LL	
CRUSADE	0.659	0.639	0.678	<0.001
GRACE	0.640	0.623	0.656	<0.001