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

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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.

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1. 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) [1–3]. The mainstay of pharmacologic treatment for ACS is the use of potent anti-thrombotic 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

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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.

2. Methods

2.1. 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.

2.2. 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 Fig. 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 Fig. 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 <30 g/dL, 30-50 g/dL or >50 g/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).

2.3. 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 <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.

3. 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 = 12,530) 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) whilst 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).

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

Fig. 1. Key to 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
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

3.1. NACE and mortality

The rates of in-hospital NACE and in-hospital mortality are listed according to CRUSADE-GRACE risk combinations in Tables 2a and 2b 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) (Fig. 2a and b). 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 Figs. 2a, 2b and 2d, respectively, $p < 0.001$ for all).

3.2. 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%) (Fig. 2a). There was

no significant difference in the rates of TIMI major bleeding between combined risk groups (Tables 2a and 2b, $p = 0.46$).

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], $p \leq 0.001$ 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 Fig. 2c).

3.3. Treatment strategy

Coronary angiography was performed in the majority (72.3%) of the study cohort (Tables 2a and 2b). 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%) (Tables 2a and 2b, Fig. 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

Table 2a
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	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
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 2b
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.

(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) (Fig. 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.

3.4. Sensitivity analysis

A sensitivity analysis was performed to assess the difference in outcomes between Non-ST Elevation ACS (NSTE-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.

4. 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 >71,000 patients with NSTEMI diagnosis from the NCDR ACTION registry–GWTG™ registry, those at high risk of bleeding and mortality were less likely to receive Clopidogrel
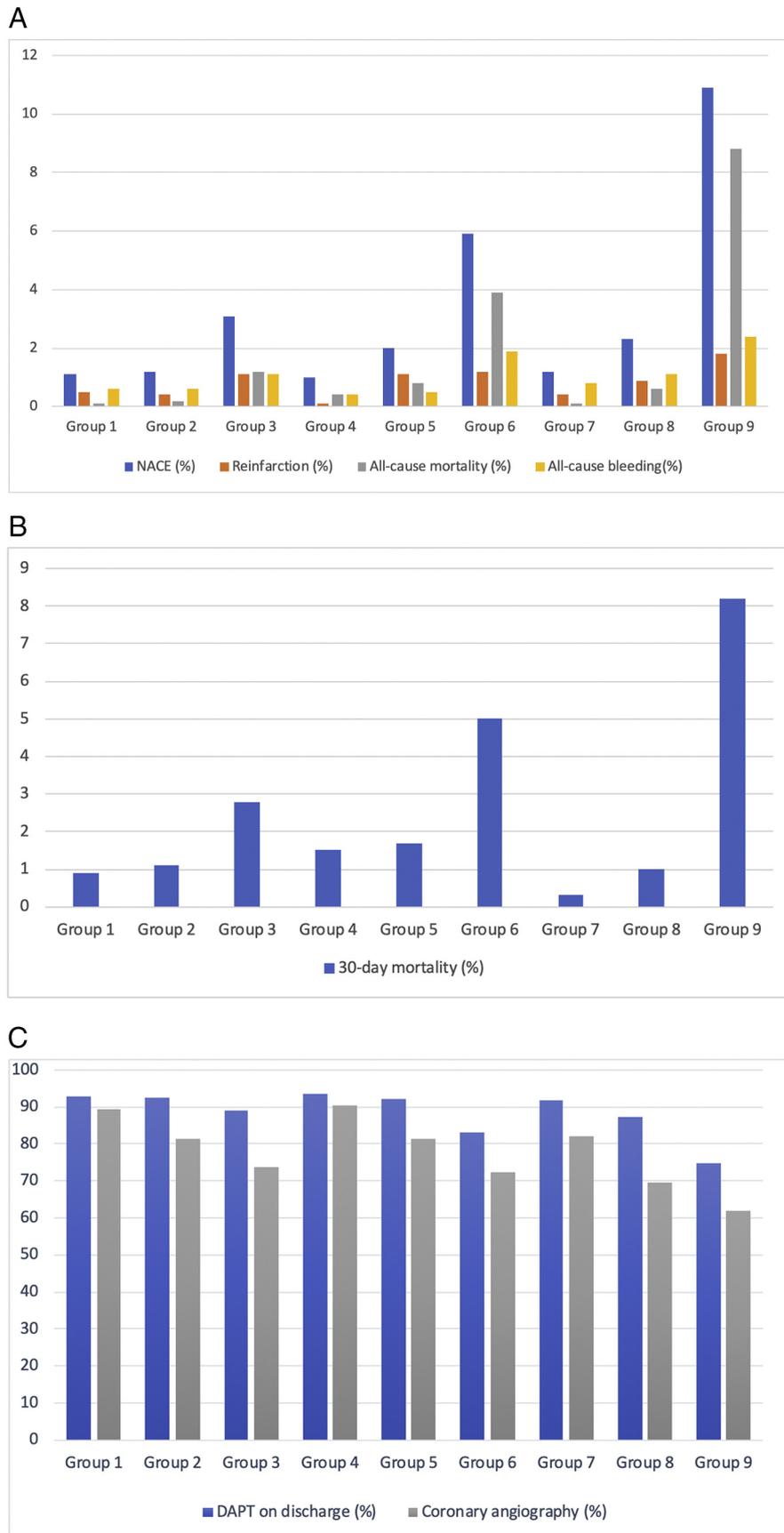
Fig. 2. a. In-hospital adverse events. b. 30-day mortality. c. Receipt of dual antiplatelet therapy (DAPT) and coronary angiography.

(70% vs. 51%), coronary angiography within 48 h (86% vs. 41%) and re-vascularization (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 emphasize 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.

4.1. 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.

5. 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.

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. The manuscript has neither been published (except in

the form of abstract) nor is currently under consideration for publication by any other journal.

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.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.035.

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