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ORIGINAL ARTICLE

Risk scoring to guide antiplatelet therapy post-percutaneous coronary intervention for acute coronary syndrome results in improved clinical outcomes

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Aims To use the Global Registry of Acute Coronary Events (GRACE) and Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) scores to risk stratify antiplatelet treatment post-acute coronary syndrome (ACS).

Methods and results This was a prospective registry of 3374 patients undergoing percutaneous coronary intervention for ACS between 2013 and 2015 at a UK cardiac centre. Patients with either low GRACE or high CRUSADE risk scores were stratified either to clopidogrel therapy or ticagrelor was used. The primary endpoint was major adverse cardiac events (MACE) defined as death, non-fatal myocardial infarction, stroke, or target vessel revascularization with bleeding rates as a secondary outcome, assessed at a median follow-up of 1.8 years (interquartile range 0.8–3.4 years). A total of 1723 (51.1%) patients were risk stratified to either clopidogrel ($n = 520$) or ticagrelor treatment ($n = 1203$), with the remaining 1651 not risk scored and treated with clopidogrel therapy. Patients in the risk score stratified group were older than the control group otherwise the groups were similar. Over the follow-up period, a significant reduction in MACE rates between the patients' risk score stratified and control (clopidogrel therapy) (13.7% vs. 19.7%, $P < 0.0001$) was seen [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.31–0.86]. This persisted after adjusting for baseline variables (HR 0.65, 95% CI 0.37–0.89) and propensity matching (HR = 0.63, 95% CI 0.27–0.93; $P = 0.0015$) No significant differences in the rate of major bleeding were seen between the groups (5.3% vs. 5.1%, $P = 0.86$). In the risk-stratified group, no difference in outcome (ischaemic/bleeding) was seen between clopidogrel and ticagrelor.

Conclusion Our registry data suggest that using appropriate risk scoring to guide antiplatelet therapy after ACS is safe and can result in improved clinical outcomes.

Introduction

Newer more potent antiplatelet therapies have improved the medical management of patients with acute coronary syndrome (ACS) as well as those undergoing percutaneous coronary intervention (PCI). Recent guidelines now recommend ticagrelor or prasugrel therapy in combination with aspirin to be taken for up to 12 months in patients presenting with ACS.[1–3] However with more potent antiplatelets, such as ticagrelor, higher non-coronary artery bypass grafting (CABG)-related bleeding rates have been observed over

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clopidogrel.[4] This has led to much debate concerning optimizing or individualizing antiplatelet strategies post-ACS, e.g for patients deemed to be at high risk of bleeding, clopidogrel may be a more appropriate choice. This excess bleeding risk has led to studies looking at downgrading dual antiplatelet therapy (DAPT) therapy after 1 month such as the recent TOPIC study.[5] Prevention of bleeding, while maintaining effective protection against ischaemic events, is therefore an important treatment goal in ACS. The European Society of Cardiology (ESC) guidelines encourage clinicians to manage patients based on their individual risks of bleeding and recurrent ischaemic events. Guidelines provide specific recommendations for patients deemed to be at high or low risk of bleeding, e.g. regarding the duration of DAPT.[3] It is essential to assess ischaemic risk on an individual basis, preferably using quantitative risk-scoring systems such as the Global Registry of Acute Coronary Events (GRACE) model.[6] The use of this model is favoured over other ischaemic risk scores in guidelines and also to balance this against bleeding risk using scores such as the American College of Cardiology/American Heart Association guidelines (CRUSADE) risk score,[7] one of the most popular bleeding risk algorithms.[1,3]

To date, limited data exist to assess combined stratification with these scores. A small observational study showed that the combined risk stratification with GRACE and CRUSADE scores can improve the individual discriminatory power of GRACE and CRUSADE models in the prediction of all-cause mortality and bleeding.[8] This combined assessment provides a more careful treatment approach to maximize the efficacy of therapy to reduce thrombotic risk while reducing the bleeding risk. As bleeding results not only in an immediate threat but also in an increased risk of adverse outcomes during follow-up,[9] it remains to be determined whether ACS risk assessment with combined ischaemic and bleeding risk assessment will prove advantageous. Our aim was to establish the effect of the combined use of GRACE and CRUSADE risk stratification in ACS patients to stratify antiplatelet therapy and to evaluate potential gains in outcomes.

Methods

Study design

The study population was derived from a high-volume, single-centre registry of all patients undergoing PCI for ACS [ST-segment elevation myocardial infarction (STEMI), non- segment elevation myocardial infarction (NSTEMI) and unstable angina (UA)] between November 2013 and November 2015. Risk score stratification was introduced in May 2014 with all prior patients treated with clopidogrel therapy (prior to introduction of ticagrelor). During the study period, risk stratification was gradually rolled out to ensure feasibility and effective implementation with all eligible patients bring stratified by the end of study period. Patients with ACS managed medically or by surgical (CABG) intervention were excluded from the study.

For each patient, GRACE[6] and CRUSADE[7] risk scores were calculated. Patients were classified into 3 categories as a function of GRACE risk score (for all-cause mortality from admission to 6 months: low risk ≤108 points, intermediate risk 109–140 points, and high risk >140 points) and 3 categories as a function of CRUSADE risk score (very low/low risk ≤30 points, moderate risk 31–40 points, and high/very high risk >40 points). Patients were treated with clopidogrel therapy with aspirin or stratified by their risk scores to specific antiplatelet therapy (clopidogrel vs. ticagrelor). These stratified by risk score received clopidogrel treatment if either low GRACE or high CRUSADE risk scores or requiring concomitant oral anticoagulant therapy, otherwise ticagrelor was used. Those who were having high GRACE and high CRUSADE scores received clopidogrel therapy (16% of the high GRACE group).

The standard PCI protocol for our institution includes pre-loading with 300 mg aspirin and 600 mg clopidogrel or 180 mg ticagrelor. All patients were prescribed 75 mg aspirin and either 90 mg ticagrelor twice daily or 75 mg clopidogrel daily maintenance therapy. Clopidogrel or ticagrelor maintenance therapy was recommended for 1 year post-PCI. Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors and aspiration thrombectomy was performed at the operator's discretion. Successful PCI result was defined as final thrombolysis in myocardial infarction (TIMI) flow Grade 3 and residual stenosis <20% in all attempted lesions at the end of the procedure.

Data were prospectively entered onto the local database at the time of PCI. Data collected included patient characteristics such as age, gender, history of hypertension, hypercholesterolaemia, diabetes mellitus, smoking status, previous myocardial infarction (MI), previous PCI, previous CABG, left ventricular ejection fraction, and baseline cardiogenic shock. Procedural factors included access site, culprit vessel, number of diseased vessels, number of vessels treated, stent type, TIMI flow pre-procedure, and TIMI flow post-procedure. Procedural complications included MI, emergency CABG, arterial complications, and arrthymias requiring DC cardioversion. Further inpatient complications, post-discharge complications, and further revascularization were documented retrospectively using the electronic patient record.

The primary endpoint was the first major adverse cardiac events (MACE) defined as death, non-fatal MI, stroke, or target vessel revascularization (TVR) assessed at a median follow-up period of 1.8 years (interquartile range 0.8–3.4 years).

Secondary endpoints were bleeding episodes as defined by the BARC classification ≥2 at 1 year after ACS.[10] Each bleeding event was classified separately according to the thrombosis in MI (TIMI) criteria (minimal, minor, or major).[11] A combination of both ischaemic (MACE) and bleeding events (BARC > 2) were used as a composite endpoint defined as overall clinical benefit.

Follow-up all-cause mortality data were obtained via the British Cardiovascular Intervention Society–UK Central Cardiac Audit Database (CCAD). This national database is periodically linked to the UK Office of National Statistics and provides live/death status of treated patients. Only patients who had complete database records and National Health Service unique numbers (allowing live/death status to be assessed) were included in the analysis. Non-mortality outcomes including recurrent MI, stroke, stent thrombosis, TVR, and bleeding events were identified from patient notes and electronic records. Each of these events was adjudicated and substantiated by three independent physicians who were not involved in the procedure and were unaware of the antiplatelet therapy received by the patient.

Ethics approval

Data were collected as part of a mandatory national cardiac audit, and all patient identifiable fields were removed prior to analysis. The local ethics committee advised us that formal ethical approval was not required.

Statistical analysis

Clinical characteristics of either risk scored vs. non-risk scored or ticagrelor- vs. clopidogrel-treated patients were compared using the Pearson χ^2 test for categorical variables and the Student's *t* test for continuous variables. Normality of distribution was assessed using the Shapiro–Wilks test. We calculated the Kaplan–Meier product limits for cumulative

Table 1 Baseline characteristics according to treatment group

	Risk score guided ($n = 1723$)	No risk score ($n = 1651$)	*P*-value
Age	67.8 (±14.2)	65.9 (±15.4)	0.005
Gender (female)	451 (26.2%)	447 (27.1%)	0.581
Previous MI	463 (26.9%)	411 (24.9%)	0.204
Previous CABG	162 (9.4%)	147 (8.9%)	0.658
Previous PCI	255 (14.8%)	254 (15.4%)	0.670
Current smoker	582 (33.8%)	548 (33.2%)	0.746
Hypertension	1044 (60.6%)	959 (58.1%)	0.148
Hypercholesterolaemia	1023 (59.4%)	948 (57.4%)	0.265
DM	407 (23.6%)	368 (22.3%)	0.380
Renal disease	93 (5.4%)	86 (5.2%)	0.880
Previous CVA	62 (3.6%)	51 (3.1%)	0.468
PVD	84 (4.9%)	71 (4.3%)	0.475
Cardiogenic shock	91 (5.9%)	94 (5.7%)	0.813
Presentation			0.281
STEMI	780 (45.2%)	716 (43.3%)	
NSTEMI/UA	943 (54.8%)	935 (56.6%)	
GRACE	141 (121–167)	139 (122–158)	0.36
CRUSADE	25 (14–36)	27 (18–38)	0.40

Table 2 Procedural characteristics according to treatment group

	Risk score guided ($n = 1723$)	No risk score ($n = 1651$)	*P*-value
Access			0.405
Radial	1199 (69.6%)	1126 (68.2%)	
Femoral	524 (30.4%)	525 (31.8%)	
Target vessel			0.253
Right coronary artery	743 (43.1%)	695 (42.1%)	
Left main	14 (0.8%)	18 (1.1%)	
Left anterior descending	697 (40.4%)	716 (43.3%)	
Left circumflex	219 (12.7%)	182 (11.1%)	
Saphenous vein graft	50 (2.9%)	40 (2.4%)	
Multivessel intervention	538 (31.2%)	528 (32.0%)	0.664
Thrombectomy use	221 (12.8%)	256 (15.5%)	0.029
Drug-eluting stent use	1319 (75.3%)	1218 (73.5%)	0.067
GPIIb/IIIa inihibitor	305 (17.7%)	350 (21.2%)	0.036
Procedural success	1678 (97.4%)	1592 (96.4%)	0.583

probability of reaching an endpoint and used the log-rank test for evidence of a statistically significant difference between the groups. Time was measured from the first admission for a procedure to outcome (all-cause mortality). Cox regression analysis was used to estimate the hazard ratios (HRs) for the effect of adenosine diphosphate (ADP) receptor antagonist type in age-adjusted and fully adjusted models, based on covariates ($P < 0.05$) associated with the outcome. The proportional hazards assumption was investigated by examining log (-log) survival curves and additionally with Schoenfeld residuals.[12] The proportional hazard assumption was satisfied for all outcomes evaluated.

A propensity score analysis was carried out using a non-parsimonious logistic regression model comparing patient groups pre- and post-introduction of risk scoring and ticagrelor therapy. Multiple variables were included in the model, including age, gender, diabetes, hypertension, hypercholesterolaemia, previous CABG, previous PCI, previous MI, multivessel disease, chronic renal failure, pre-procedure TIMI flow, ejection fraction, and procedural success. C-index was used to measure how well the model discriminated between the high-risk and the low-risk patients. C-index was 0.81 indicating good discrimination.[13,14] After ranking propensity score in an ascending order, a nearest neighbour 1:1 matching algorithm was used with calipers of 0.2 SDs of the logit of the propensity score. Each pre- and post-risk score patient was used in at most one matched pair, to create a matched sample with similar distribution of baseline characteristics between the observed groups. Based on the matched samples, Cox proportional hazard model was used to determine the impact of risk scoring and ticagrelor treatment on mortality over the follow-up period. STATA version 10 and Graphpad Prism version 5 were used for all analysis.

Results

The cohort included 3374 patients undergoing PCI for ACS with a mean age of 67.4 ± 12.3 years (range 31–92 years). In all, 75.5% of patients were male. A total of 1496 (44.3%) patients presented with STEMI and underwent primary PCI with the remainder presenting following NSTEMI/UA. A total of 1723 (51.1%) patients were risk stratified to either clopidogrel ($n = 520$) or ticagrelor treatment ($n = 1203$), with the remaining 1651 not risk scored and treated with clopidogrel therapy.

Patient characteristics

Patients in the risk score stratified group were older than the control group, otherwise the groups were similar. The majority of the patients were male in both groups (73.9% in the risk score stratified group and 72.8% in the control group). The numbers of STEMI and NSTEMI/UA were similar in each group (*Table 1*). Procedural characteristics were similar aside from lower rates of manual thrombectomy catheter use and GPIIb/IIIa inhibitor use in the risk score stratified group (*Table 2*).

Follow-up

Unadjusted Kaplan–Meier analysis revealed a significant reduction in MACE rates over the follow-up period between the patients risk score stratified and the control group (clopidogrel therapy) (13.7% vs. 19.7%, $P < 0.0001$) (*Figure 1*). The pattern was similar for all MACE components including all-cause mortality, recurrent MI, and TVR (*Table 3*).

In the risk scored group, there were 12 crossovers from clopidogrel to ticagrelor (for STEMI occurring on clopidogrel therapy, or unknown cause) and 44 crossovers from ticagrelor to clopidogrel (dyspnoea, low patient compliance, bleeding, and unknown cause).

Unadjusted and multivariate analysis

Age-adjusted Cox analysis demonstrated a persistent reduction in outcome over the Follow-up period between the risk score stratified

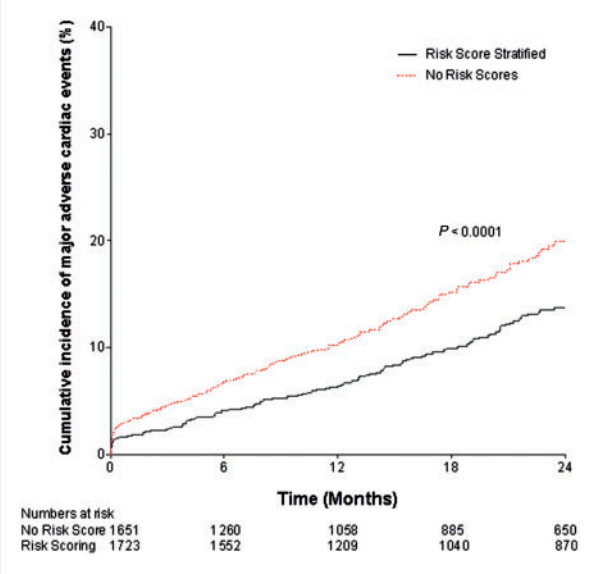

Figure 1 The Kaplan–Meier curves showing cumulative probability of major adverse cardiac events comparing the risk score stratified vs. control (no risk score stratification).

Table 3 Endpoints during follow-up according to treatment group

	Risk score guided ($n = 1723$)	No risk score ($n = 1651$)	*P*-value
MACE	236 (13.7%)	325 (19.7%)	<0.0001
All-cause death	103 (6.0%)	147 (8.9%)	0.0015
Stroke	22 (1.3%)	37 (2.2%)	0.045
Target vessel revascularization	57 (3.3%)	79 (4.8%)	0.036
Recurrent MI	110 (6.4%)	140 (8.5%)	0.024
Stent thrombosis	18 (1.1%)	32 (1.9%)	0.020
Bleeding BARC ≥ 2	91 (5.3%)	84 (5.1%)	0.860
TIMI major	20 (1.2%)	13 (0.8%)	0.370
TIMI minor	65 (3.8%)	56 (3.4%)	0.616
TIMI minimal	126 (7.3%)	102 (6.2%)	0.213
Overall clinical benefit	327 (19.0%)	409 (24.8%)	<0.0001

and control groups (HR 0.61, 95% CI 0.31–0.86). This persisted after multivariate adjustment (HR 0.65, 95% CI 0.37–0.89).

Bleeding

The cumulative probability of bleeding (BARC > 2) was similar between patients risk score stratified and the control group [5.3% (95% CI 4.5–6.6) vs. 5.1% (95% CI 4.3–6.3)] ($P = 0.86$), respectively. No difference was seen in rates of TIMI major, minor, or minimal bleeding. The adjusted HR (BARC > 2) was 1.10 (95% CI 0.78–1.20), indicating no difference in bleeding rates after correcting for confounders. Mortality rates were higher in patients who had major bleeding events (22.1% vs. 8.2%, $P < 0.0001$) compared to those who did not with bleeding events an independent predictor of mortality [HR 1.58 (1.15–1.95)]. A composite endpoint of overall clinical benefit (MACE + BARC > 2 bleeding) was significantly reduced in the risk score stratified group compared with the control (19.0% vs. 24.8%, $P < 0.0001$) (*Table 3*).

Propensity-matched analysis

To further account for confounding variables and bias, propensity score matching was performed to adjust for differences in demographic and procedural variables to assess the introduction of risk scoring compared with the control, producing a total of 3004 patients (1502 matched procedures). The baseline demographics and procedural variables were well balanced in the propensity-matched cohorts. In the propensity-matched cohorts, there was a significant reduction in the incidence of MACE, following the introduction of risk scoring and ticagrelor treatment (13.3% vs. 18.4%, $P = 0.001$). Applying Cox multivariate regression analysis to adjust for baseline clinical and procedural characteristics risk scoring was an independent predictor for survival (HR = 0.63, 95% CI 0.27–0.93, $P = 0.0015$) compared with the control.

Subgroup analysis of clopidogrel vs. ticagrelor in the risk stratified cohort

Patients in the ticagrelor group were older (69.88± 14.1 vs. 64.90±16.1) and more likely to have had previous MI (16.9% vs. 12.8%) and have undergone previous PCI compared with patients receiving clopidogrel. Patients on clopidogrel treatment were more likely to have undergone PCI for an NSTEMI with higher rates of primary PCI for STEMI seen in the ticagrelor group. As expected, mean GRACE scores were significantly higher in the ticagrelor treated group with higher CRUSADE scores in the clopiodgrel group (*Table 4*).

Follow-up

Unadjusted Kaplan–Meier analysis revealed no significant difference in MACE rates over the follow-up period between patients given ticagrelor vs. clopidogrel (11.2% vs. 12.7%, $P = 0.45$) (*Figure 2*). The pattern was similar for all MACE components including all cause mortality, recurrent MI and TVR. Age-adjusted Cox analysis demonstrated no difference in outcome between the ticagrelor and clopidogrel groups [HR 0.91, 95% confidence interval (CI) 0.61–1.36]. This persisted after multivariate adjustment (HR 0.85, 95% CI 0.64–1.45). In addition, after regression adjustment incorporating a propensity score into the hazards model as a covariate, no difference in outcome emerged (HR 0.88, 95% CI 0.71–1.44).

Bleeding

The cumulative probability of bleeding (BARC > 2) was similar between patients treated with ticagrelor compared with clopiodgrel [5.5% (95% CI 4.8–6.6) vs. 5.1% (95% CI 4.2–6.4] ($P = 0.86$),

Table 4 Baseline characteristics according to treatment in the risk score stratified group

	Ticagrelor (n = 1203)	Clopidogrel (n = 520)	P-Value
Age	69.8 (±14.1)	64.9 (±16.1)	<0.0001
Gender (female)	905 (75.2%)	396 (76.1%)	0.654
Previous MI	203 (16.9%)	67 (12.9%)	0.022
Previous CABG	109 (9.1%)	37 (7.2%)	0.186
Previous PCI	116 (12.8%)	77 (9.4%)	0.026
Current smoker	215 (23.8%)	272 (33.2%)	<0.001
Hypertension	556 (61.6%)	444 (54.1%)	0.002
Hypercholesterolaemia	538 (59.6%)	389 (47.4%)	<0.001
DM	231 (25.6%)	166 (20.3%)	0.010
Renal disease	53 (5.9%)	39 (4.8%)	0.335
Previous CVA	33 (3.6%)	17 (2.1%)	0.062
PVD	44 (4.9%)	27 (3.3%)	0.115
Cardiogenic shock	53 (5.9%)	46 (5.6%)	0.837
Presentation			0.020
STEMI	567 (47.1%)	213 (41.0%)	
NSTEMI/UA	636 (52.9%)	307 (59.0%)	
GRACE	145 (126–167)	121 (105–142)	<0.001
CRUSADE	23 (14–36)	35 (18–38)	<0.001

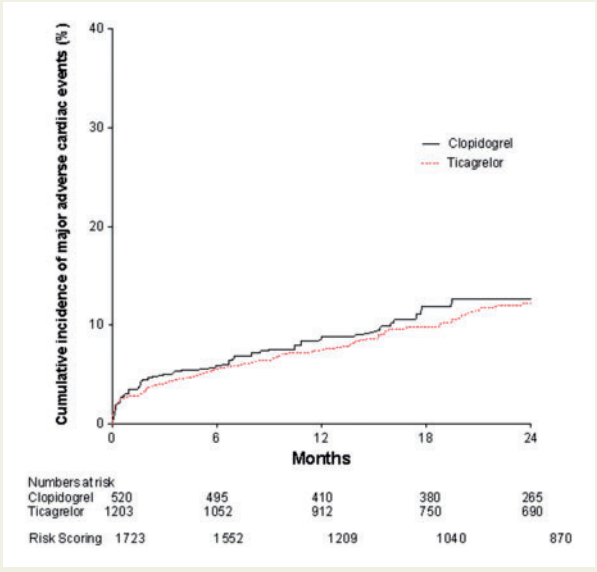

Figure 2 The Kaplan–Meier curves showing cumulative probability of major adverse cardiac events comparing ticagrelor and clopidogrel groups in the risk-stratified cohort (n = 1723).

respectively. No difference was seen in the rates of TIMI major, minor, or minimal bleeding.

Discussion

This study, using data from a large PCI registry, is the largest observational study performed to date specifically to assess the effect of risk scoring to guide antiplatelet therapy after ACS. This study demonstrated that simple clinical risk scores such as GRACE and CRUSADE can be used to identity high-risk patients likely to receive the greatest absolute benefit from ticagrelor therapy while limiting patients at high risk of bleeding to less potent agents. This resulted in improved MACE outcomes with risk scoring to guide antiplatelet therapy compared with no risk scoring. Within the risk score-stratified group similar improved outcomes were seen with both ticagrelor and clopidogrel treatment with equivalent bleeding rates. Stratifying ADP receptor antagonist therapy post-ACS to optimize patient management and clinical outcomes is crucial in view of the newer more potent antiplatelet drugs with their increased predisposition to bleeding complications.

Ticagrelor is recommended by the current ACS guidelines based on a single large randomized controlled trial, the PLATO trial[3,2] with analysis from this demonstrating both clinical and cost-effectiveness.[15] However, it should be noted that an exclusion criteria listed within the study are patients at high risk of bleeding including patients receiving oral anticoagulation, active bleeding or bleeding history, or major surgery within 30 days.[16] This has led to some suggestions that further study and real-world data are needed. Recent observational data from 45 073 ACS patients from the SWEDEHEART registry[17] demonstrated that outcomes in an ACS registry of patients treated with ticagrelor vs. clopidogrel appeared similar to that achieved in the PLATO trial. Patients discharged on ticagrelor had a lower incidence of the composite endpoint (death, MI, or stroke) as well as lower mortality alone. However, patients prescribed ticagrelor were also at higher risk of bleeding, as evidenced both by more readmissions with bleeding and more PCI-related in-hospital bleeding events,[17] suggesting that further risk stratification may be needed. Interestingly, further analysis from this cohort demonstrated that patients discharged on ticagrelor constituted a subset of ACS cases with a more benign risk factor profile and therefore a lower risk of bleeding than would be expected.

A major obstacle to the implementation of evidence-based therapies is the perceived greater complexity and co-morbidities of real-world patients than those enrolled in clinical trials.[18] Therefore, the use of risk scores such as GRACE and CRUSADE can help identify those patients most likely to benefit from these therapies. This study demonstrates that these scores can be implemented in real-world practice to guide antiplatelet treatment, with reassuring low rates of drug crossover post-stratification.

Although several ACS risk prediction tools have been proposed in recent years, the GRACE and CRUSADE scores have been shown to be the most robust for evaluating ischaemic and bleeding risk.[19] These risk algorithms are recommended by contemporary guidelines and have been incorporated into clinical practice with potential improvements in decision-making.[1,2] However, there are no other studies evaluating the impact of ACS risk scores in choice of antithrombotic therapy post-ACS, despite data supporting their use in other strategies such as early vs. delayed angiography[20] and their use in prediction of events post NSTEMI.[6] An observational study supports the combined risk stratification strategy with both GRACE and CRUSADE models to enable a more accurate prediction of all-cause

mortality and bleeding risk in patients with NSTEMI.[8] They showed that the two scores complement each other in the prognostication of patients. This would potentially allow more accurate identification of patients who will benefit from more aggressive therapies and those who are suited to a more conservative approach. Our study builds on this work showing that these scores can be used to select appropriate antiplatelet therapies.

Major bleeding is one of the commonest serious adverse events in patients admitted with ACS[21] with a strong relationship demonstrated between bleeding and mortality, even when the haemorrhage is not considered to be severe. In this study, we demonstrated higher mortality rates in individuals who suffered major bleeding events. This finding is consistent with previous studies which have shown 60% increase in hospital death[22,23] and a five-fold increase in 1-year mortality[9] associated with major bleeding. This confirms the importance of antiplatelet risk stratification post-ACS, especially with the increasingly complex and higher risk patients (e.g. the elderly, those with co-morbidities) presenting with ACS. These concerns over bleeding risk are the reason for the recent TOPIC study,[5] which evaluated the benefit of switching from aspirin plus a newer P2Y12 blocker to aspirin plus clopidogrel 1 month after ACS. In this study, no significant differences were reported on ischaemic endpoints between the groups but a significant reduction in bleeding was observed (BARC $\geq$ 2 bleeding occurred in 4.0% patients in the switched DAPT vs. 14.9% in the unchanged DAPT group) (HR 0.30, 95% CI 0.18–0.50; $P < 0.01$).[5] As agreed by the accompanying editorial,[24] this study adds 'fuels to the debate on individualizing and optimizing post-ACS treatment', and we propose that an alternative to 'downgrading' DAPT is to use these simple readily available risk scores to ensure the correct patients receive the correct therapy for them.

Guidelines recommend formal risk stratification for ACS management, enabling estimation of patient prognosis, a key issue for therapeutic decision-making and selection of antiplatelet treatments. However, treatment selection in clinical practice must balance the risk of ischaemic events with bleeding risk, which is difficult in patients with multiple risk factors. Many risk factors for ischaemic events are the same as for bleeding events, complicating decision-making. Our goal in risk stratification is to identify modifiable risk, i.e. those patients who have the most to gain from effective therapies but also in whom that therapy can provide a favourable outcome. Using the GRACE and CRUSADE scores to clearly identify these patients appears a unique and novel way of improving outcomes after ACS.

Limitations

This study has all the limitations of a registry and all the potential bias and unmeasured confounding associated with non-randomized studies. In addition, we cannot exclude the possibility of under-reporting of complications although the tracking of mortality is robust.

Conclusion

Our registry data suggest that using appropriate risk scoring to guide antiplatelet therapy after ACS is safe and can result in improved clinical outcomes.

Conflict of interest: none declared.

References

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe A, Jneid SH, Kelly RF, Kontos MC, Levine GN, Liebson P, Mukherjee RD, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;**130**:e344–e426.
2. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack M, Mauri J, Mehran L, Mukherjee RD, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 2016;**134**:e123–e155.
3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
4. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Plato I, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
5. Cuisset T, Deharo Quilici PJ, Johnson T, Deffarges W, Bassez S, Bonnet C, Fourcade GL, Mouret J, Lambert P, Verdier MV, Morange PE, Alessi MC, Bonnet JL. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017;**38**:3070–3078.
6. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van Werf FD, Avezum A, Goodman SG, Flather MD, Fox KA; Global, Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–2353.
7. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV, Peterson ED, Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score. *Circulation* 2009;**119**:1873–1882.
8. Paiva L, Providência R, Barra SN, Dinis P, Faustino AC, Costa M, Gonçalves L. Improving risk stratification in non-ST-segment elevation myocardial infarction with combined assessment of GRACE and CRUSADE risk scores. *Arch Cardiovasc Dis* 2014;**107**:681–689.
9. Segev A, Strauss BH, Tan M, Constance C, Langer A, Goodman SG; Canadian Acute Coronary Syndromes Registries Investigators. Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome Registries. *Am Heart J* 2005;**150**:690–694.
10. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**:2736–2747.
11. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–154.

12. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;**69**:239–241.
13. Royston P, Sauerbrei W. A new measure of prognostic separation in survival data. *Stat Med* 2004;**23**:723–748.
14. Gönen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. *Biometrika* 2005;**92**:965–970.
15. Wisløff T, Atar D. Cost-effectiveness of antiplatelet drugs after percutaneous coronary intervention. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:52–57.
16. James S, Åkerblom A, Cannon CP, Emanuelsson H. Comparison of ticagrelor, the first reversible oral P2Y 12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* 2009;**157**:599–605.
17. Sahlén A, Varenhorst Lagerqvist C, Renlund B, Omerovic H, Erlinge E, Wallentin DL, James SK, Jernberg T. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. *Eur Heart J* 2016;**37**:3335–3342.
18. Sahlén A, Varenhorst C, Lagerqvist B, Renlund H, Wallentin L, James SK, Jernberg T. Contemporary use of ticagrelor in patients with acute coronary syndrome: insights from Swedish web system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Eur Heart J Cardiovasc Pharmacother* 2016;**2**:5–12.
19. Costa F, Tijssen J, Ariotti G, Giatti S, Moscarella S, Guastaroba EP, Palma R, Andò D, Oreto G, Zijlstra GF, Valgimigli M. Incremental value of the CRUSADE, ACUITY, and HAS-BLED risk scores for the prediction of hemorrhagic events after coronary stent implantation in patients undergoing long or short duration of dual antiplatelet therapy. *J Am Heart Assoc* 2015;**12** pii: e002524.
20. Fox KA, Anderson FA, Dabbous OH, Steg PG, López-Sendón J, Van de Werf F, Budaj A, Gurfinkel EP, Goodman SG, Brieger D; on behalf of GRACE investigators. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The global registry of acute coronary events (GRACE). *Heart* 2007;**93**:177–182.
21. Hoekstra JW, Pollack CV, Roe MT, Peterson ED, Brindis R, Harrington RA, Christenson RH, Smith SC, Ohman EM, Gibler WB. Improving the care of patients with non-ST-elevation acute coronary syndromes in the emergency department: the CRUSADE initiative. *Acad Emergency Med* 2002;**9**:1146–1155.
22. Moscucci M, Fox KA, Cannon CP, Klein W, López-Sendón J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the global registry of acute coronary events (GRACE). *Eur Heart J* 2003;**24**:1815–1823.
23. Brieger D, Fox KA, Fitzgerald G, Eagle KA, Budaj A, Avezum A, Granger CB, Costa B, Anderson FA, Steg PG, Global ROACEI. Predicting freedom from clinical events in non-ST-elevation acute coronary syndromes: the global registry of acute coronary events. *Heart* 2009;**95**:888–894.
24. Sinnaeve PR, Van de Werf F. Clopidogrel instead of prasugrel or ticagrelor after 1 month in stabilized ACS patients: back to square one for DAPT. *Eur Heart J* 2017;**38**:3079–3081.