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Cardiac Pharmacology

A HANC Risk Stratification Score for Antiplatelet Therapy Optimization with Low-Dose Prasugrel in Taiwanese Acute Coronary Syndrome Patients from the Switch Study

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Background: A significant proportion of acute coronary syndrome (ACS) patients experience high on-treatment platelet reactivity (HPR) on clopidogrel-based dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI).

Objectives: This study assessed key independent risk factors associated with significant HPR risk on clopidogrel, but not prasugrel, in the Switch Study cohort of 200 Taiwanese ACS patients who switched from clopidogrel to low-dose prasugrel for maintenance DAPT after PCI.

Methods: Univariate analysis and stepwise multivariate logistic regression analysis were conducted to identify key independent risk factors for HPR on clopidogrel, but not prasugrel.

Results: A HANC [H: low hemoglobin (< 13 g/dL for men and < 12 g/dL for women); A: age ≥ 65 years; N: non-ST elevation myocardial infarction; C: chronic kidney disease as defined by estimated glomerular filtration rate < 60 mL/min] risk stratification score was developed, and demonstrated optimal sensitivity and specificity at a cutoff score of ≥ 2. The HANC score compared favorably against the recently validated ABCD score in the full Switch Study cohort (n = 200), and the ABCD-GENE score in a genotyped cohort (n = 102).

Conclusions: The HANC score may serve to alert clinicians to patients at potentially higher HPR risk on clopidogrel, but not prasugrel. Further research to validate this score and assess its correlation with clinical outcomes is warranted.

Key Words: Acute coronary syndrome • Clopidogrel • CYP2C19 • Dual anti-platelet therapy • East Asian paradox • High on-treatment platelet reactivity • Prasugrel • Risk stratification

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INTRODUCTION

In acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) with aspirin and a potent P2Y12 inhibitor such as prasugrel or ticagrelor is currently the standard of care recommended by guidelines[1-6] to reduce thrombotic risk; however, for patients with contraindications, high bleeding risk, or concomitant anticoagulant therapy, clopidogrel is recommended instead. Notably, the European Society of Cardiology (ESC)[1,2] and American College of Cardiology/American Heart Association (ACC/AHA)[3] guidelines recommend the use of prasugrel at a loading dose of 60 mg and daily maintenance dose of 10 mg, or ticagrelor at a loading dose of 180 mg and maintenance dose of 90 mg twice daily. However, increased bleeding risk has been observed with the use of these potent P2Y12 inhibitors at standard doses in East Asian patients,[7] due to the "East Asian paradox," in which East Asian patients demonstrate lower ischemic risk but higher bleeding risk than Western patients at comparable levels of platelet reactivity.[7,8] To reduce the risk of thrombosis without increasing the risk of bleeding in East Asian patients, the use of low-dose prasugrel, at a loading dose of 20 mg and a daily maintenance dose of 3.75 mg, has been proposed. The PRASFIT-ACS study subsequently showed that in Japanese ACS patients, compared to a standard dose of clopidogrel, patients receiving low-dose prasugrel had a numerically lower incidence of major adverse cardiovascular events (MACE) and a lower risk of clinically serious bleeding events.[9] Recent studies have also shown that switching from clopidogrel to reduced-dose (5 mg) or low-dose (3.75 mg) prasugrel can significantly reduce rates of high on-treatment platelet reactivity (HPR) in East Asian ACS patients, but without increasing bleeding risk.[10-15] Therefore, the Japanese Circulation Society (JCS)[4] and the Taiwan Society of Cardiology (TSOC)[5,6] guidelines recommend the use of low-dose prasugrel in ACS patients undergoing PCI, if features associated with increased bleeding risk are present.

A significant proportion (23.5%-59.5%) of ACS patients receiving DAPT with clopidogrel have HPR,[10,16,17] which is associated with an increased risk of periprocedural myonecrosis,[18] major adverse cardiac and cerebrovascular events,[16] and long-term mortality.[17] The high prevalence of *CYP2C19* loss-of-function (LOF) allele carriers among East Asian populations has been cited as a major driver of HPR, as low CYP2C19 enzymatic activity reduces the rate at which clopidogrel is metabolized to its active state.[19] Compared to *CYP2C19* LOF allele prevalence rates of 30-35% in Western populations,[20,21] prevalence rates of 50-60% have been reported in East Asian populations.[11,12,20,19-29] This represents a major concern for clinicians, and efforts to identify patients at high HPR risk on clopidogrel are ongoing[7,30] so as to allow for timely and appropriate P2Y12 inhibitor switching strategies that can pre-empt ischemic and bleeding events.

Recently, the ABCD and ABCD-GENE scores [A: age > 75 years; B: body mass index (BMI) > 30 kg/m^2; C: chronic kidney disease as defined by estimated glomerular filtration rate (eGFR) < 60 ml/min; D: diabetes mellitus (DM); GENE: 1 or 2 *CYP2C19* LOF alleles] were developed and validated in a cohort of over 6,000 international ACS patients, and were shown to correlate with HPR risk, all-cause death, and the composite of all-cause death, stroke, or myocardial infarction (MI) in patients receiving clopidogrel, but not for those receiving prasugrel.[31] The scores do not predict bleeding risk.[31] A 2021 study subsequently validated the ABCD-GENE score in Japanese coronary artery disease (CAD) and ACS patients.[32] However, current guidelines do not recommend the routine use of platelet reactivity testing and *CYP2C19* genotyping, as there is insufficient evidence of clinical benefit.[15,30] Therefore, a risk score composed of easily measurable clinical factors could be useful in alerting clinicians to patients potentially at higher risk of HPR on clopidogrel, and who might be able to benefit from switching, or at least closer monitoring.

The Switch Study was a single-arm, multi-center, open-label, interventional study that assessed the effects of switching from a maintenance dose of clopidogrel (75 mg daily) to low-dose prasugrel (3.75 mg daily) in Taiwanese ACS patients on DAPT after PCI.[10] In this study, we assessed the Switch Study cohort to identify independent factors associated with HPR risk on clopidogrel, but not prasugrel, and sought to develop a risk stratification tool from these factors to inform clinicians.

METHODS

Study cohort

The Switch Study included 203 adult ACS patients

maintained with either ticagrelor or clopidogrel DAPT after PCI, all of whom were switched to maintenance with clopidogrel and then switched to low-dose prasugrel. Details of the study design and patient enrollment criteria have previously been reported.[10] In this study, 3 patients withdrew their consent to be included, and thus analysis was only conducted on 200 patients (full Switch Study cohort), with *CYP2C19* genotyping data available for 102 of these patients (genotyped cohort).

Institutional review board statement

The Switch Study and this analysis were conducted according to the guidelines of the Declaration of Helsinki and Good Clinical Practice (GCP), and were approved by the institutional review boards (IRBs) of Cheng Hsin General Hospital, National Taiwan University Hospital, Taipei Veterans General Hospital, MacKay Memorial Hospital, Tri-service General Hospital, Taipei, Taiwan; Chang Gung Memorial Hospital-Linkou, Taoyuan, Taiwan; China Medical University Hospital, Taichung Veterans General Hospital, Taichung, Taiwan; National Cheng Kung University Hospital, Tainan, Taiwan; and Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (Protocol CS747S-B-A4003) prior to September 14, 2018. The Switch Study has been registered at ClinicalTrials.gov (NCT03672097).

Informed consent statement

Written informed consent was provided by all patients prior to enrollment, but 3 of the original 203 enrolled patients in the Switch Study later withdrew their consent to participate, and were therefore not included in this analysis.

Platelet reactivity evaluation

The VerifyNow® (Accumetrics Inc., San Diego, CA, USA) light aggregometry system was used to assess platelet reactivity at baseline on clopidogrel treatment and again at 4 weeks after switching to prasugrel treatment, with platelet reactivity units (PRU) > 208 defined as HPR,[7,30,33,34] and PRU < 85 defined as low on-treatment platelet reactivity (LPR).[7,30]

CYP2C19 genotyping

Blood samples were taken from the 102 patients who voluntarily opted to undergo *CYP2C19* genotyping for LOF alleles, and genomic DNA was extracted for assessment of the *CYP2C19*2* (681G>A; rs4244285) and *CYP2C19*3* (636G>A; rs4986893) LOF alleles, using the TaqMan single nucleotide polymorphism (SNP) genotyping assay (Applied Biosystems, Foster City CA, USA) together with the 7500 Real-Time PCR System (Applied Biosystems). Patients with one or two *CYP2C19* LOF alleles (*2 or *3) were respectively denoted as intermediate metabolizers (IM) or poor metabolizers (PM), while patients with no *CYP2C19* LOF alleles were denoted as extensive metabolizers (EM).

Assessment of factors associated with HPR risk

We assessed 28 demographic factors for their association with HPR risk on clopidogrel or prasugrel, including age ≥ 65 years, male sex, BMI ≥ 25 kg/m^2, BMI ≥ 28 kg/m^2, BMI ≥ 30 kg/m^2, unstable angina (UA), ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), use of bare metal stents (BMS), use of drug-eluting stents (DES), aspartate aminotransferase (AST) > 31 U/L (upper limit of normal, ULN), alanine aminotransferase (ALT) > 41 U/L (ULN), high blood urea nitrogen (BUN > 20 mg/dL), high creatinine (> 1.3 mg/dL), low eGFR (< 60 mL/min), high low density lipoprotein-cholesterol (LDL-C > 100 mg/dL), low hemoglobin (< 13 g/dL for men and < 12 g/dL for women), presence of comorbidities (as defined by a definite diagnosis in electronic medical records) including gastroesophageal reflux disease (GERD), dyslipidemia, hyperuricemia/gout, diabetes mellitus, hypertension, and concomitant use of medications such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers (CCB), oral antiglycemic agents (OA-Gly), statins, and proton pump inhibitors (PPIs; at baseline on clopidogrel or week 4 on prasugrel).

Statistical analysis

Odds ratios (OR) of the 28 demographic factors regarding HPR risk on clopidogrel or prasugrel treatment for the full Switch Study cohort were assessed in univariate analysis using MedCalc statistical software (MedCalc Software, Ostend, Belgium), with significance calculated by two-tailed Fisher's exact test. $p < 0.05$ was deemed to be statistically significant. Stepwise linear regression of the 28 factors was conducted using R software (R Core Team, Vienna, Austria) to identify the strongest correlated vari-

ables, and outcomes were then compared with the univariate analysis results to distill the most important factors associated with HPR risk on clopidogrel treatment. Multivariate logistic regression analysis was then conducted with R software on these factors, and the resulting model was then refined by bootstrapping with 1,000 resamples. The key independent risk factors identified were then tested for their association with HPR risk on prasugrel treatment using multivariate logistic regression analysis.

Development of the HANC score and comparison with the ABCD and ABCD-GENE scores

Independent risk factors associated with HPR on clopidogrel treatment were used to develop a HANC score, with scores for each independent risk factor weighted according to their bootstrapped ORs. The optimal cutoff point, sensitivity, specificity, and significance were calculated using MedCalc software, and compared against the results calculated after 4 weeks of prasugrel treatment. The receiver operating characteristic (ROC) curve, c-statistic, and 95% confidence interval (CI) were calculated using R software. The HANC score was assessed for both the full Switch Study cohort and the genotyped cohort, and compared with the recently validated ABCD and ABCD-GENE scores. ROC curves were compared using the DeLong method. $p < 0.05$ was deemed to be statistically significant.

RESULTS

Patients

Analysis was conducted on 200 patients (full Switch Study cohort), which included a genotyped cohort of 102 patients assessed for *CYP2C19* status. Patient demographics are presented in Table 1. For the full Switch Study cohort, the mean age was 60.1 years, and 35.5% of the patients were aged 65 years or older. The patients were predominantly male (90.5%). There was a relatively even distribution of UA (31.0%), STEMI (35.5%), and NSTEMI (33.5%) patients. Most patients had at least one comorbidity, and were taking at least one concomitant medication, primarily statins (91.0%). There were no significant differences in demographics within the full Switch Study cohort between the genotyped and non-genotyped groups (Table 1).

Univariate analysis and stepwise linear regression identified 4 significant factors associated with HPR risk on clopidogrel

To derive a risk stratification model with a good fit for the full Switch Study cohort, we sought to identify factors associated with HPR on clopidogrel treatment. Univariate analysis was conducted on 28 factors, and age ≥ 65 years, BUN > 20 mg/dL, creatinine > 1.3 mg/dL, low eGFR (< 60 mL/min), low hemoglobin (< 13 g/dL for men and < 12 g/dL for women), and NSTEMI were found to be significantly associated with HPR risk on clopidogrel (Table 2).

Stepwise linear regression, multivariate logistic regression analysis, and bootstrapping

Stepwise linear regression was conducted to identify key independent risk factors of HPR on clopidogrel treatment. Age ≥ 65 years, eGFR < 60 mL/min, low hemoglobin, and NSTEMI were shown to be important independent risk factors of HPR on clopidogrel, and multivariate logistic regression analysis confirmed these 4 factors to be statistically significant independent risk factors (Table 3). The model was further refined by bootstrapping with 1,000 resamples (Table 3).

We also performed univariate analysis of the association between these factors and HPR risk on prasugrel (Supplementary Table 1), and similarly conducted stepwise linear regression and multivariate analyses of significant HPR risk factors on prasugrel identified through univariate analysis, but the results were not significant (Supplementary Table 2). Multivariate logistic regression analysis with bootstrapping further confirmed that the 4 key independent risk factors identified in Table 3 were not significantly associated with HPR risk on prasugrel (Supplementary Table 3).

Development of a HANC risk score for risk stratification of HPR on clopidogrel

The 4 key independent risk factors confirmed through bootstrapped multivariate logistic regression analysis were used to develop a HANC score [H: low hemoglobin (< 13 g/dL for men and < 12 g/dL for women); A: age ≥ 65 years; N: NSTEMI; C: chronic kidney disease as defined by eGFR < 60 mL/min], with weighting for each factor determined according to their bootstrapped ORs (Figure 1A). Scoring results are shown in Figure 1B, and

Table 1. Demographics of the full Switch Study (n = 200) and genotyped (n = 102) cohorts

Characteristics	All (N = 200)	Genotyped (N = 102)	Non-genotyped (N = 98)	p value
Age [years mean (SD)]	60.1 (10.0)	61.8 (9.9)	59.3 (10.1)	0.077
≥ 65 years [n (%)]	71 (35.5%)	42 (41.2%)	31 (31.6%)	0.120
Male [n (%)]	181 (90.5%)	92 (90.2%)	89 (90.8%)	0.827
Asians [n (%)]	200 (100.0%)	102 (100.0%)	98 (100.0%)	N/A
Extensive metabolizers [n (%)]	--	44 (43.1%)	--	
Intermediate metabolizers [n (%)]	--	50 (49.0%)	--	
Poor metabolizers [n (%)]	--	8 (7.8%)	--	
BMI [kg/m^2 mean (SD)]	26.2 (3.5)	25.9 (3.2)	26.4 (3.8)	0.382
BMI ≥ 25 [n (%)]	120 (60.0%)	59 (57.8%)	61 (62.2%)	0.292
BMI ≥ 28 [n (%)]	44 (22.0%)	23 (22.5%)	21 (21.4%)	0.439
BMI ≥ 30 [n (%)]	26 (13.0%)	12 (11.8%)	14 (14.3%)	0.351
SBP [mmHg mean (SD)]	126.9 (16.0)	128.3 (15.3)	125.4 (16.7)	0.296
Heart rate [beat/min mean (SD)]	75.3 (10.8)	75.7 (10.6)	75.6 (11.5)	0.496
Type of ACS [n (%)]				
UA	62 (31.0%)	35 (34.3%)	27 (27.6%)	0.412
NSTEMI	67 (33.5%)	35 (34.3%)	32 (32.7%)	0.423
STEMI	71 (35.5%)	32 (31.4%)	39 (39.8%)	0.417
Use of BA in PCI [n (%)]	20 (10.0%)	7 (6.9%)	13 (13.3%)	0.092
PCI stent types - BMS [n (%)]	21 (10.5%)	8 (7.8%)	13 (13.3%)	0.103
PCI stent types - DES [n (%)]	179 (89.5%)	95 (93.1%)	84 (85.7%)	0.102
Medical history [n (%)]				
Diabetes mellitus	70 (35.0%)	35 (34.3%)	35 (35.7%)	0.959
Dyslipidemia	154 (77.0%)	79 (77.5%)	75 (76.5%)	0.189
Hypertension	119 (59.5%)	58 (56.9%)	61 (62.2%)	0.278
Prior stroke/TIA	5 (2.5%)	3 (2.9%)	2 (2.0%)	0.317
Prior MI	5 (2.5%)	3 (2.9%)	2 (2.0%)	0.317
CKD/ESRD	9 (4.5%)	5 (4.9%)	4 (4.1%)	0.817
Ulcer	8 (4.0%)	3 (2.9%)	5 (5.1%)	0.102
GERD	18 (9.0%)	9 (8.8%)	9 (9.2%)	0.858
Hyperuricemia/Gout	20 (10.0%)	13 (12.7%)	7 (7.14%)	0.652
Concomitant drugs [n (%)]				
Statins	182 (91.0%)	92 (90.2%)	90 (91.8%)	0.448
Beta-blockers	143 (71.5%)	64 (62.7%)	79 (80.6%)	0.586
Proton pump inhibitors (baseline)	93 (46.5%)	48 (47.1%)	45 (45.9%)	0.990
Proton pump inhibitors (week 4)	104 (52.0%)	55 (53.9%)	49 (50.0%)	0.901
Calcium channel blockers	38 (19.0%)	26 (25.5%)	12 (12.2%)	0.084
ACEI/ARB	135 (67.5%)	66 (64.7%)	69 (70.4%)	0.617
Oral antiglycemic agents	50 (25.0%)	27 (26.5%)	23 (23.5%)	0.713
Hematocrit [mean (SD)]	41.9% (3.8%)	41.6% (4.0%)	41.7% (3.8%)	0.892
Hemoglobin [g/dL mean (SD)]	14.1 (1.4)	13.7 (1.3)	14.2 (1.5)	0.188
Distribution [n (%)]				
< 11	4 (2.0%)	2 (2.0%)	2 (2.0%)	0.259
[11-13] (or [11-12] in female)	34 (17.0%)	19 (18.6%)	15 (15.3%)	0.250
≥ 13 (or ≥ 12 in female)	162 (80.0%)	82 (80.4%)	80 (81.6%)	0.307
Platelet count [10^9/L mean (SD)]	264 (79.1)	234.1 (70.8)	224.9 (58.7)	0.636
LDL-C [mg/dL mean (SD)]	80 (28.9)	77 (25.1)	85 (26.2)	0.103
ALT [U/L mean (SD)]	30 (18.6)	28 (16.8)	31 (17.2)	0.202
AST [U/L mean (SD)]	25 (10.2)	24 (9.6)	26 (10.7)	0.252
BUN [mg/dL mean (SD)]	16.9 (5.6)	17.5 (5.8)	16.2 (5.5)	0.273
Creatinine [mg/dL mean (SD)]	1.02 (0.29)	1.05 (0.32)	1.01 (0.46)	0.512
eGFR [mL/min/1.73 m^2 mean (SD)]	81.1 (19.7)	80.1 (20.4)	82.0 (19.4)	0.646
Distribution [n (%)]				
< 30	4 (2.0%)	4 (3.9%)	0 (0.0%)	0.070
[30-60]	28 (14.0%)	11 (10.8%)	17 (17.3%)	0.072
≥ 60	168 (83.0%)	87 (85.3%)	81 (82.7%)	0.214

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; BA, balloon angioplasty; BMI, body mass index; BMS, bare metal stent; BUN, blood urea nitrogen; CKD, chronic kidney disease; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GERD, gastroesophageal reflux disease; LDL-C, low density lipoprotein-cholesterol; MI, myocardial infarction; N/A, not applicable; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina. The p value was derived from comparison between genotyped and non-genotyped cohorts.

Table 2. Univariate analysis of risk factors associated with HPR on clopidogrel

Factor	Risk of HPR on clopidogrel treatment	
	Odds ratio [95% confidence interval (CI)]	p value
Age ≥ 65 yrs	3.345 [1.685-6.641]	< 0.001*
Male	0.276 [0.104-0.729]	0.017*
BMI ≥ 25 kg/m^2	0.947 [0.481-1.867]	0.876
BMI ≥ 28 kg/m^2	1.196 [0.548-2.612]	0.653
BMI ≥ 30 kg/m^2	1.319 [0.516-3.370]	0.564
UA	0.566 [0.260-1.232]	0.200
STEMI	0.679 [0.330-1.399]	0.377
NSTEMI	2.084 [1.050-4.134]	0.036*
PCI stent - BMS	1.436 [0.522-3.947]	0.580
PCI stent - DES	0.696 [0.253-1.914]	0.580
Diabetes mellitus	1.169 [0.587-2.325]	0.657
Dyslipidemia	0.576 [0.275-1.209]	0.145
Hypertension	1.158 [0.586-2.292]	0.732
GERD	0.404 [0.089-1.828]	0.374
Hyperuricemia/Gout	0.848 [0.268-2.676]	> 0.999
ACEI/ARB	0.653 [0.328-1.299]	0.278
Statins	0.415 [0.151-1.142]	0.134
Beta-blockers	0.743 [0.364-1.518]	0.455
Proton pump inhibitors (baseline)	1.269 [0.653-2.468]	0.502
Calcium channel blockers	1.560 [0.682-3.564]	0.366
Oral antiglycemic agents	1.120 [0.526-2.383]	0.845
LDL-C > 100 mg/dL	1.056 [0.474-2.353]	> 0.999
Low hemoglobin (< 13 g/dL for men and < 12 g/dL for women)	4.500 [2.106-9.614]	< 0.001*
ALT > 41 U/L (ULN)	0.554 [0.119-2.573]	0.740
AST > 31 U/L (ULN)	0.756 [0.269-2.124]	0.805
BUN > 20 mg/dL	2.737 [1.304-5.747]	0.012*
Creatinine > 1.3 mg/dL	2.979 [1.166-7.614]	0.026*
eGFR < 60 mL/min	4.199 [1.918-9.194]	< 0.001*

ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; BMS, bare metal stent; BUN, blood urea nitrogen; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; LDL-C, low density lipoprotein-cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; ULN, upper limit of normal. * p < 0.05.

Table 3. Multivariate logistic regression analysis of key HPR risk factors on clopidogrel

Factor	Clopidogrel			
	Odds ratio [95% CI]	p	Bootstrapped odds ratio [95% CI]	p
Age ≥ 65 yrs	2.909 [1.335-6.338]	0.007*	2.876 [1.302-6.305]	0.007*
eGFR < 60 mL/min	3.066 [1.309-7.181]	0.010*	3.033 [1.276-7.148]	0.006*
Low hemoglobin	2.554 [1.107-5.890]	0.028*	2.528 [1.081-5.864]	0.029*
NSTEMI	2.967 [1.366-6.443]	0.006*	2.927 [1.326-6.403]	0.009*

CI, confidence interval; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-segment elevation myocardial infarction.
* p < 0.05.

three cutoff scores of ≥ 1, ≥ 2, and ≥ 3 were tested for sensitivity and specificity (Figure 1A), as well as significance of predicting HPR risk on clopidogrel and prasugrel. In light of the East Asian paradox, in which East Asian ACS patients on DAPT have higher bleeding risk but lower ischemic risk, it would make sense

for a predictive score to have greater specificity (to ensure that patients with a greater chance of benefitting from switching to prasugrel are selected) and lower sensitivity (so as to avoid the potential risk of bleeding in patients who may not need more potent treatment). By these criteria, a cutoff score of ≥ 2 was selected as having the best statistical significance, as well as optimal balance between sensitivity and specificity (Figure 1A). The ROC curve was subsequently plotted for the HANC score, and a c-statistic of 0.745 with 95% CI of 0.656-0.835 was noted (Figure 2A and 2C).

Comparison of the HANC score with the ABCD score and ABCD-GENE score

We applied the recently validated ABCD score to the full Switch Study cohort, and a cutoff score of ≥ 6 was found to be statistically significant (p = 0.015; Figure 2C) for predicting HPR risk on clopidogrel, but not on prasugrel, with 26.70% sensitivity and 88.40% sensitivity (Figure 2C). These results were less balanced or significant when compared to the performance of the HANC score in the Switch Study cohort (Figure 2C), and this is borne out by the ROC curve analysis (Figure 2B), which showed a c-statistic of just 0.627 (95% CI: 0.526-0.758) for the ABCD score in the Switch Study cohort, lower than that achieved by the HANC score (Figure 2A). The two ROC curves were then compared using the DeLong method, and the results showed that the HANC score was statistically superior to the ABCD score in the full Switch Study cohort, indicative of a much better fit with the data (Figure 3).

A

Factors Odds Ratio [95% CI], P value	Score
Low Hemoglobin Hemoglobin < 13 g/dL (men)/ < 12 g/dL (women) **2.528** [1.081-5.864], P = 0.029	+1
Aged Age ≥ 65 yrs **2.876** [1.302-6.305], P = 0.007	+1
NSTEMI NSTEMI (+) **2.927** [1.326-6.403], P = 0.009	+1
Chronic Kidney Disease eGFR < 60 mL/min **3.033** [1.276-7.148], P = 0.006	+1

Cutoff	Sensitivity	Specificity	P value: Clopidogrel	P value: Prasugrel
≥ 1	88.89%	42.58%	< 0.001	0.055
≥ 2	**57.78%**	**81.29%**	**< 0.001**	**0.192**
≥ 3	28.89%	96.77%	< 0.001	0.331

B

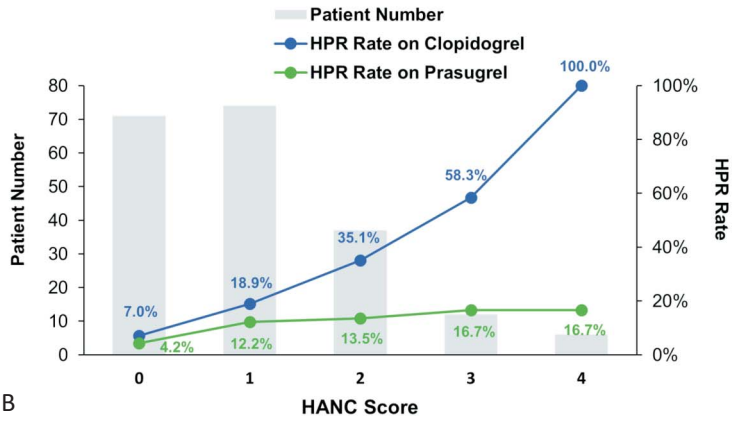
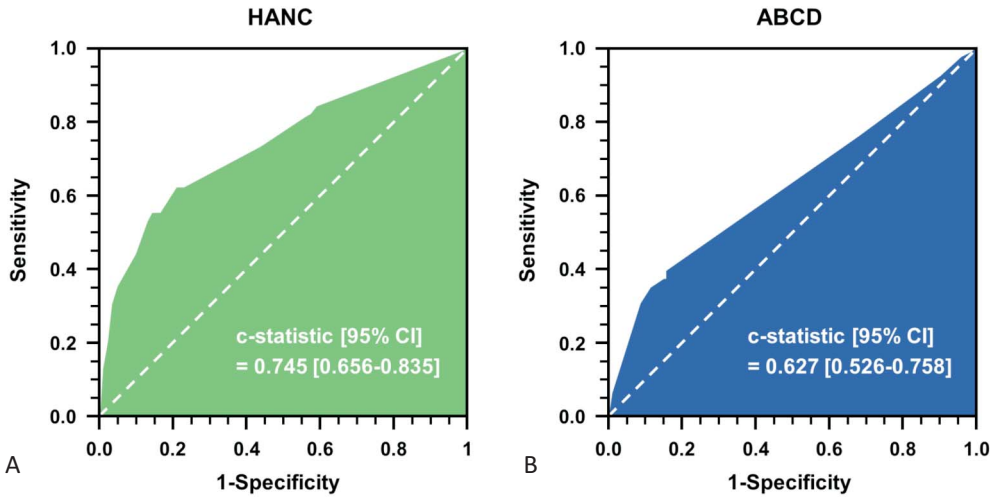


Figure 1. *Development of a HANC score to assess HPR risk on clopidogrel. (A) Weighted scores for each factor as calculated from the bootstrapped ORs derived through multivariate logistic regression analysis. Sensitivity, specificity, and significance on clopidogrel and prasugrel as calculated for the three cutoff points assessed. (B) Distribution of scores in the Switch Study cohort (n = 200), stratified by HPR at baseline on clopidogrel and after 4 weeks of prasugrel treatment; note the significant reduction in HPR for patients with scores of 2 or above following the switch to prasugrel. HPR, high on-treatment platelet reactivity.*



C

Cutoff	Sensitivity	Specificity	P value Clopidogrel	P value Prasugrel
HANC ≥ 2	57.78%	81.29%	< 0.001	0.192
ABCD ≥ 6	26.70%	88.40%	0.015	0.195

Figure 2. *Comparison of the HANC score with the ABCD score. (A) ROC curve results for the HANC score. (B) ROC curve results for the ABCD score. (C) Comparison of sensitivity, specificity, and significance for predicting HPR risk on clopidogrel and prasugrel at the optimal cutoff scores for the HANC score and ABCD score. ROC, receiver operating characteristic.*

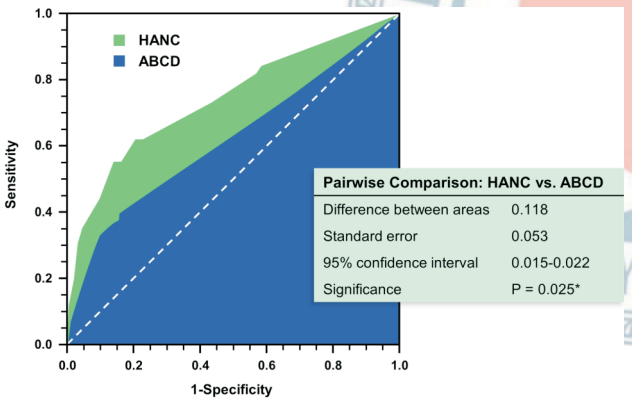


Figure 3. *DeLong analysis of the HANC and ABCD scores. Statistical significance is indicated for pairwise comparison. * p < 0.05.*

Comparison of the HANC and ABCD-GENE scores in the genotyped cohort

We also examined how the ABCD-GENE score would perform in the Switch Study cohort. However, only 102 patients out of the full Switch Study cohort were genotyped for *CYP2C19*, and therefore we proceeded to conduct a validation of the ABCD-GENE score in the genotyped cohort of 102 patients. The results showed that at a cutoff score of ≥ 9 (p = 0.024), the sensitivity was 53.8% and specificity was 71.1%, comparable to the validation results of the ABCD-GENE score in East Asian[32] and other populations.[31] The ROC curve was found to be significant (p = 0.018), but with a c-statistic of 0.648 (Figure 4B).

We then sought to compare the HANC score with the ABCD-GENE score in the genotyped cohort. At the same cutoff score of ≥ 2 as the full Switch Study cohort (p = 0.003), 75.0% sensitivity and 72.2% specificity were noted, and these were also the optimal sensitivity and specificity values for the genotyped cohort. The ROC curve for the HANC score in the genotyped cohort was also significant (p < 0.001), with a c-statistic of 0.780, indicative of a good fit with the data (Figure 4A). We proceeded to compare the ROC curve of the HANC score with that of the ABCD-GENE score in the genotyped cohort, using the DeLong method, but the results showed no significant difference between the curves (Figure 4C).

DISCUSSION

HPR on DAPT is a serious concern for ACS patients,

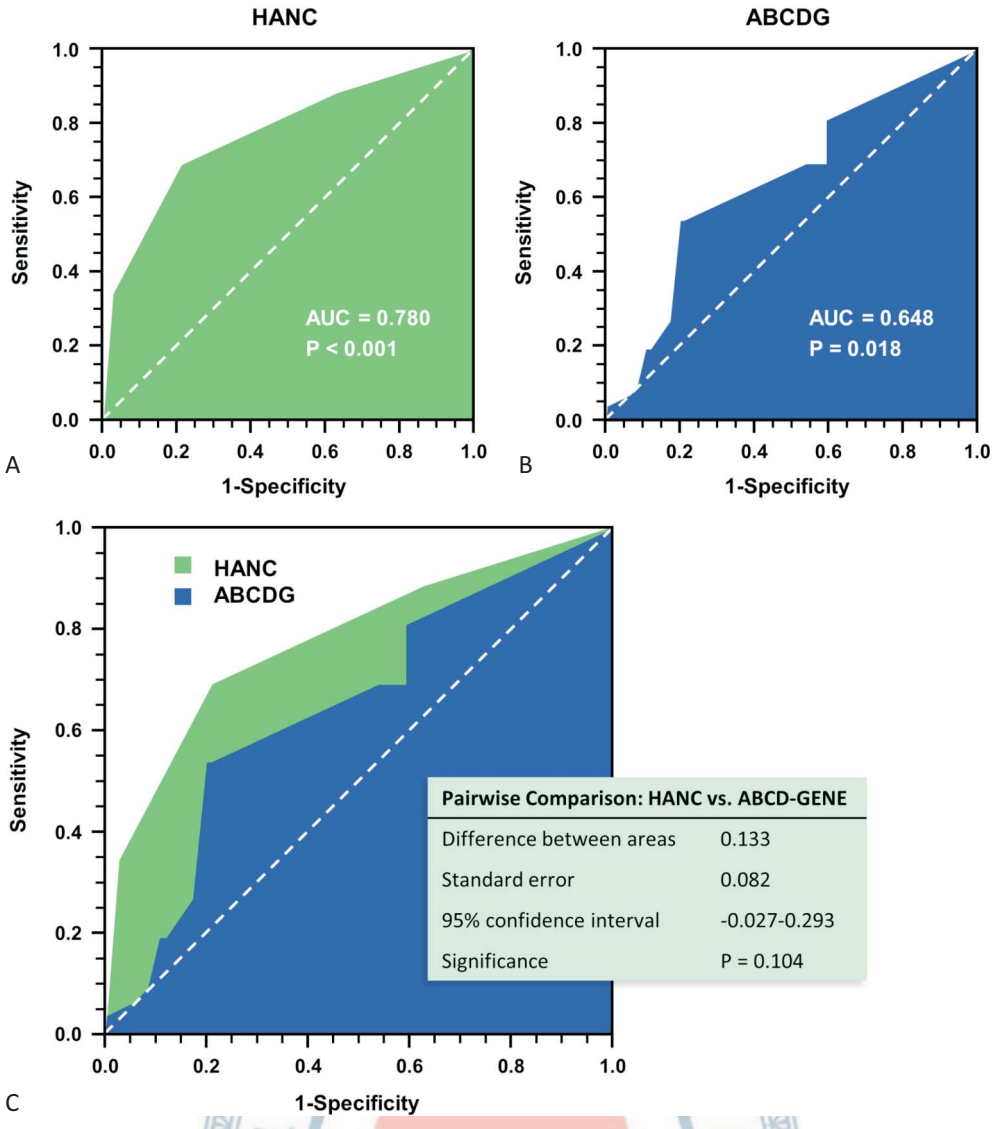


Figure 4. *Comparison of the HANC and ABCD-GENE (ABCDG) scores in the genotyped cohort. (A) ROC curve results for the HANC score in the genotyped cohort. (B) ROC curve results for the ABCD-GENE (ABCDG) score in the genotyped cohort. (C) Pairwise comparison of the HANC and ABCD-GENE (ABCDG) ROC curves using the DeLong method. ROC, receiver operating characteristic.*

and has been associated with increased risk of unfavorable outcomes.[16-18] The recently validated ABCD-GENE and ABCD scores were shown to be associated with HPR risk on clopidogrel, and correlated with clinical outcomes such as MACE and bleeding as well.[31] These scores could potentially be useful as risk stratification tools, but current guidelines do not recommend routine platelet function testing or *CYP2C19* genotyping, as these tests have not been shown to have a significant correlation with improved outcomes.[15,30] We therefore sought to develop a risk stratification tool that would not require genotyping, using a cohort of 200 Taiwanese ACS patients from the Switch Study.[10]

A comparison of the Switch Study cohort and the derivation dataset for the ABCD-GENE and ABCD scores[31] showed that the Switch Study cohort was younger (60.1 ± 10.0 vs. 65.1 ± 10.3 years), predominantly male (90.5% vs. 68.9%), had lower BMI (26.2 ± 3.5 vs. 31.1 ± 6.1 kg/m^2) and had lower prevalence of comorbidities and previous cardiovascular events. Prevalence of eGFR < 60 mL/min was much lower for the Switch Study cohort (16.0% vs. 40.4%). However, usage rates of beta-blockers, ACEIs, ARBs, and PPIs were higher in the Switch Study cohort, and there was also a greater prevalence of

patients with 1 or 2 *CYP2C19* LOF alleles (56.8% vs. 35.5%). Overall, HPR risk factor (with the exception of *CYP2C19* LOF allele carrier rates) and comorbidity prevalence rates were lower, but concomitant medication use was higher in the Switch Study cohort, as compared to the derivation dataset for the ABCD-GENE and ABCD scores. These differences in the cohorts can likely explain the differing univariate analysis results observed; for example, analysis of the derivation dataset for the ABCD-GENE and ABCD scores found that female sex, hypertension, hyperlipidemia, and diabetes were risk factors for HPR on clopidogrel, but this was not seen in the Switch Study cohort. The effect of *CYP2C19* LOF alleles on HPR risk was also not as strong for the Switch Study cohort.

CYP2C19 LOF alleles may reduce the rate at which clopidogrel is converted into its active form;[19] however, *CYP2C19* genotyping has not been convincingly correlated with clinical benefit in studies conducted to date,[15,30] and this suggests that other factors may have stronger roles in determining HPR on clopidogrel. The ABCD-GENE score is heavily weighted for *CYP2C19* LOF status, but in the original study,[31] the authors acknowledged that the contribution of *CYP2C19* genotype to HPR was fractional, suggesting that antiplatelet treatment strategies should not be determined on the basis of *CYP2C19* genotype alone.[31] In this study, the ABCD-GENE and ABCD scores performed comparably in the genotyped cohort, and this may be explained by the fact that the proportion of patients with homozygous LOF alleles was not high, and one LOF allele alone may not have sufficient discriminative capability.[31] The HANC score performed well in both the genotyped cohort and full Switch Study cohort, and although validation in a larger ACS population is necessary, this allows for the possibility of an HPR risk stratification tool that is based on readily available clinical parameters, without requiring platelet reactivity testing or *CYP2C19* genotyping.

The HANC score presented in this study was developed from 4 independent factors associated with risk of HPR on clopidogrel (Table 3), but not on prasugrel treatment (Supplementary Table 3). Optimal sensitivity and specificity were noted at a cutoff score ≥ 2, and this was also the point at which a clear reduction in HPR rates was noted after switching to low-dose prasugrel, indicating that a majority of patients with a HANC score ≥ 2 benefited from reduced platelet reactivity after switching from clopidogrel to prasugrel (Figure 1B). To the best of our understanding, this is the first such risk score to be developed in Taiwanese ACS patients. Although the HANC score still needs to be validated in a larger patient population, it may help to alert clinicians to patients at high risk of HPR on clopidogrel, so that mitigation strategies such as closer monitoring or switching to low-dose prasugrel can be implemented. This would be particularly applicable to patients with 3 or 4 of the risk factors in the HANC score (i.e., HANC score = 3 or 4).

The HANC score compared favorably to the recently validated ABCD and ABCD-GENE scores (Figures 3 and 4). Both the HANC score and the ABCD-GENE score include chronic kidney disease (CKD)/low eGFR (< 60 mL/min) and old age (HANC: $\geq$ 65 years; ABCD-GENE: > 75 years), which are known to be associated with increased HPR risk,[35-37] ischemic risk,[35-38] and bleeding risk[38] in ACS patients. The increased inflammation, heightened platelet reactivity, and endothelial dysfunction in patients with CKD, and to a lesser extent in the elderly, creates a toxic cascade that heightens risk for ACS, thrombotic events, and bleeding.[35,37] It would certainly be helpful to stay vigilant and employ strategies to reduce risk when treating such patients. Low hemoglobin is also strongly associated with increased HPR and thrombotic risk for both clopidogrel[39,40] and ticagrelor,[41] and can increase bleeding risk as well.[40] Previously, such patients were primarily treated with clopidogrel to avoid increased bleeding risk with more potent P2Y12 inhibitors,[40,41] but a low-dose prasugrel strategy may offer more balanced control of ischemic and bleeding risk. In NSTEMI patients, higher thrombotic platelet activity[42,43] and poor response to clopidogrel[44] have also been observed.

This study has a number of limitations. Firstly, the limited number of patients (n = 200) means that overfitting is a possibility, and biases and artifacts stemming from the cohort could have been introduced. Therefore, validation in a larger patient population is needed. Secondly, HPR is only an intermediary endpoint, and further research is needed to ascertain whether the strategy of switching to low-dose prasugrel in response to high HPR risk in clopidogrel can indeed decrease ischemic and bleeding events over the long term. The significantly reduced HPR rates and absence of increased bleeding risk after switching to prasugrel shows promise in this regard, suggesting that this may be a viable strategy

for high-risk patients who have traditionally been undertreated. Future research to confirm this in a larger ACS patient population is warranted.

CONCLUSIONS

This study utilized the Switch Study cohort to identify 4 key independent factors associated with HPR risk on clopidogrel, and developed these into a HANC score that demonstrated good sensitivity and specificity in predicting patients potentially at high risk of HPR on clopidogrel, but not on prasugrel treatment.

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DECLARATION OF CONFLICT OF INTEREST

Shuji Tsukiyama, Wei-Cheng Yang, and Li-Chung Cheng are employees of Daiichi Sankyo. I-Chih Wang, Feng-Yu Kuo, Ping-Yen Liu, Tze-Min Lu, Yen-Hung Lin, and Wei-Hsien Yin served as chairs of meetings sponsored by Daiichi Sankyo. Wen-Lieng Lee, Yi-Chih Wang, Chieh-Shou Su, Hsin-Fu Lee, Ying-Chang Tung, Ping-Yen Liu, Cheng-Huang Su, Feng-Yu Kuo, Wei-Shiang Lin, Pao-Hsien Chu, Tse-Min Lu, Ping-Han Lo, Wei-Hsian Yin, and Yen-Hung Lin received study funding from Daiichi Sankyo.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Univariate analysis of risk factors associated with HPR on prasugrel

Factor	Risk of HPR on prasugrel treatment	
	Odds ratio [95% confidence interval (CI)]	p value
Age ≥ 65 yrs	3.906 [1.480-10.311]	0.006*
Male	0.553 [0.146-2.091]	0.413
BMI ≥ 25 kg/m^2	2.793 [0.897-8.690]	0.076
BMI ≥ 28 kg/m^2	2.154 [0.801-5.790]	0.128
BMI ≥ 30 kg/m^2	1.205 [0.327-4.434]	0.780
UA	0.719 [0.249-2.076]	0.619
STEMI	0.976 [0.371-2.570]	> 0.999
NSTEMI	0.898 [0.302-2.668]	0.846
PCI stent - BMS	0.421 [0.053-3.317]	0.701
PCI stent - DES	1.062 [0.229-4.936]	> 0.999
Diabetes mellitus	0.777 [0.285-2.120]	0.622
Dyslipidemia	0.316 [0.122-0.820]	0.018*
Hypertension	1.667 [0.612-4.536]	0.348
GERD	0.505 [0.064-4.007]	> 0.999
Hyperuricemia/Gout	0.446 [0.056-3.521]	0.700
ACEI/ARB	0.883 [0.335-2.330]	0.805
Statins	0.515 [0.135-1.960]	0.399
Beta-blockers	0.714 [0.269-1.894]	0.602
Proton pump inhibitors (week 4)	2.983 [1.097-8.114]	0.033*
Calcium channel blockers	0.514 [0.114-2.326]	0.537
Oral antiglycemic agents	1.325 [0.480-3.655]	0.591
High LDL-C	0.904 [0.286-2.859]	> 0.999
Low hemoglobin	4.260 [1.621-11.198]	0.003*
High ALT	0.676 [0.084-5.459]	> 0.999
High AST	1.147 [0.312-4.211]	0.738
High BUN	2.231 [0.829-6.005]	0.144
High creatinine	3.417 [1.098-10.628]	0.042*
eGFR < 60 mL/min	3.949 [1.473-10.589]	0.006*

ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; BMS, bare metal stent; BUN, blood urea nitrogen; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; LDL-C, low density lipoprotein-cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina. * $p < 0.05$.

Supplementary Table 2. Multivariate logistic regression analysis of significant HPR risk factors on prasugrel derived from univariate analysis

Factor	Prasugrel	
	Odds ratio	p
Age ≥ 65 yrs	2.855 [0.986-8.264]	0.053
eGFR < 60 mL/min	2.235 [0.489-10.203]	0.299
Low hemoglobin	2.615 [0.917-7.460]	0.072
High creatinine	1.237 [0.206-7.412]	0.816
Proton pump inhibitors (week 4)	0.687 [0.072-6.573]	0.744

eGFR, estimated glomerular filtration rate.

Supplementary Table 3. Multivariate analysis test of association between key HPR risk factors on clopidogrel and HPR risk on prasugrel

Factor	Prasugrel			
	Odds ratio	p	Bootstrapped odds ratio	p
Age ≥ 65 yrs	2.951 [0.982-8.356]	0.051	2.858 [0.949-8.263]	0.052
eGFR < 60 mL/min	2.662 [0.940-7.537]	0.065	2.703 [0.981-7.578]	0.067
Low hemoglobin	2.471 [0.873-6.988]	0.088	2.473 [0.875-6.990]	0.075
NSTEMI	1.542 [0.548-4.333]	0.412	1.554 [0.560-4.345]	0.429

eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-segment elevation myocardial infarction.