Supplemental Materials

Validating the Prognostic Utility of the ABCD-GENE score among Asian, ACS Patients on Clopidogrel

Supplemental Figure S1: Histogram of duration of Clopidogrel treatment among patients in the De-escalators group

Supplemental Figure S2: Area Under Curve (AUC) for ABCD-GENE score (as a continuous variable) in discriminating HPR from non-HPR

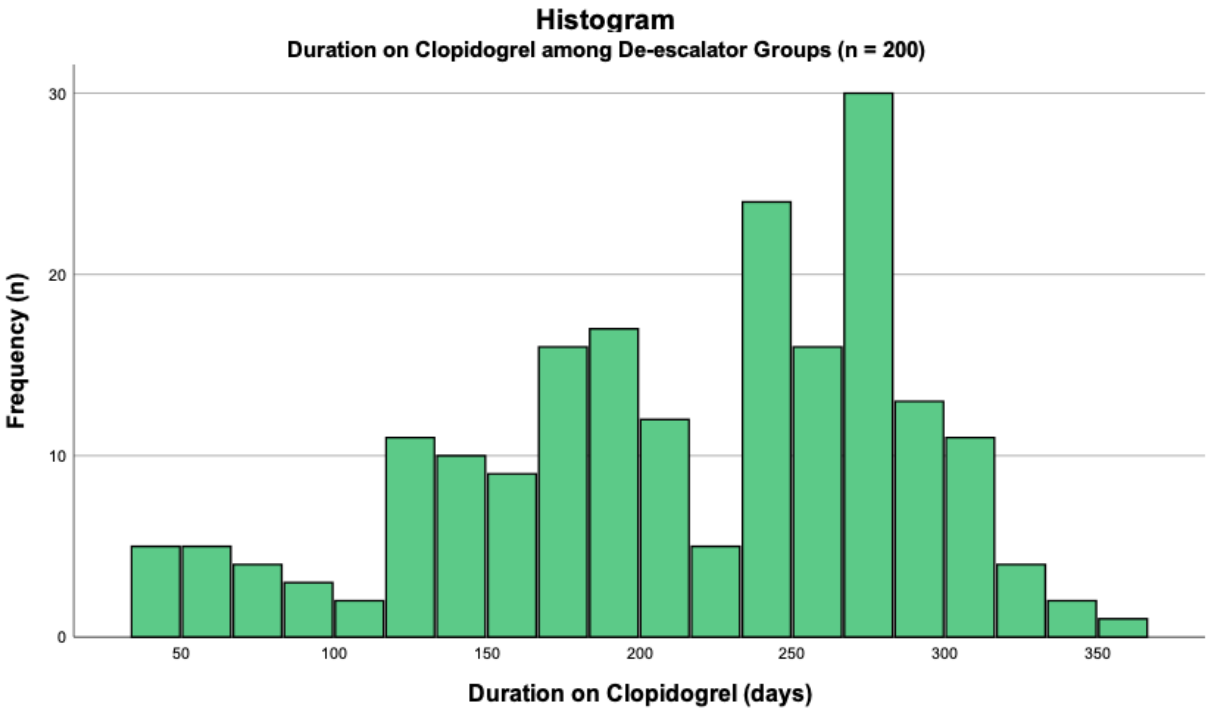
Supplemental Table S1: Rationale of Variable Selection for Sensitivity Analysis

Supplemental Table S2: Baseline Characteristics by Platelet Reactivity Status

Supplemental Table S3: Univariable Cox (Proportional Hazards) Regression Model for MACE at ABCD-GENE Score Cut-off of 10-points.

Supplemental Table S4: Multivariable Cox Regression Model for One-year Risk of MACE at a Cut-Off of 10-points

Supplemental Table S5: Cox (Proportional Hazards) Regression Model for MACE at 10-points in Patients who Received PCI

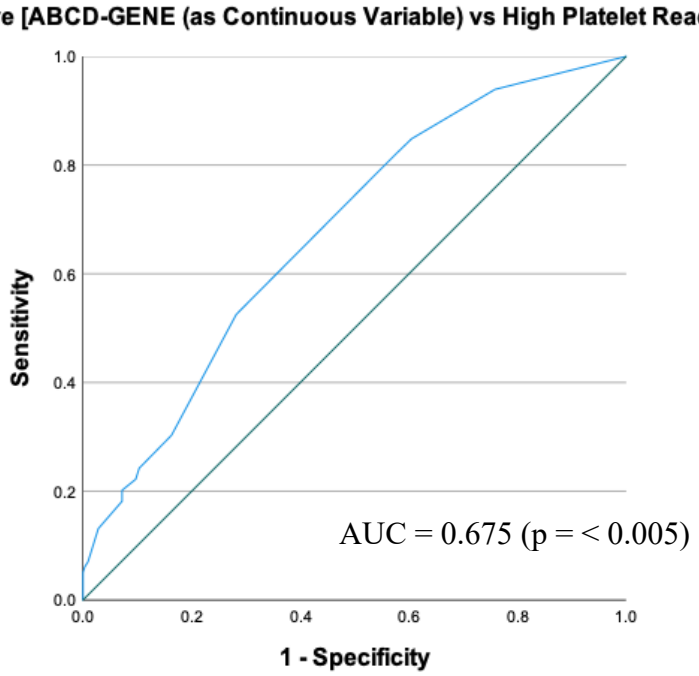


Cumulative Percentile	10	20	30	40	50	60	70	80	90	100
Days	118	149	180	197	236	249	267	275	297	355

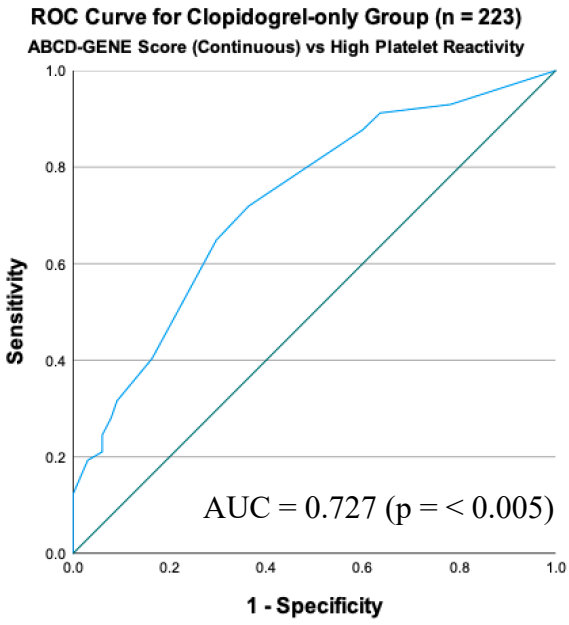
Supplemental Figure S1: Duration of Clopidogrel Received by Patients in the De-escalators Group.

The histogram summarises the duration (in Days) of Clopidogrel treatment received by patients among the De-escalators group. The median duration of Clopidogrel use among the 'De-escalators' was 236 (IQR: 167 – 260) days. The table breakdown the duration on Clopidogrel treatment by cumulative percentiles.

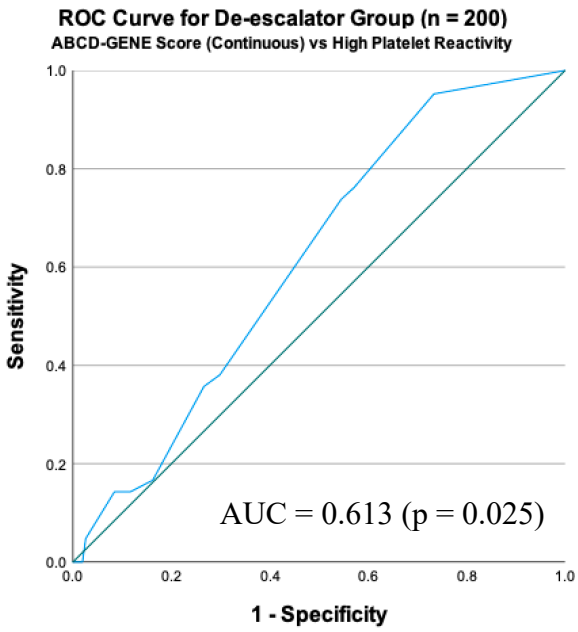
(A)



(B)



(C)



Supplemental Figure S2: The receiver-operating characteristic (ROC) curves for ABCD-GENE score in discriminating on-Clopidogrel HPR

Figure S3(A) visualises the trend when all 423 patients were included in the analysis, while Figure S3(B) and (C) visualises the trend in their corresponding subgroup (i.e.: Clopidogrel-only or De-escalators group). While the discriminatory ability was expectedly poorer in De-escalator group, a moderate discriminatory ability was observed for HPR status in the main and Clopidogrel-only group (AUC = 0.675 and 0.727, $p < 0.005$).

Supplemental Table S1: Rationale of Variable Selection for Sensitivity Analysis

Variable	Rationale
Age > 75, BMI > 30, Chronic Kidney Disease, Diabetes, CYP2C19 LoF Allele	Components of the ABCD-GENE Score[9]
BMI ≥ 27.5	Compared to the Eurasian cut-off of obesity at 30, the Asian cut-off is lowered to BMI ≥ 27.5[17].
Age ≥ 60	Due to small sample size in Age > 75, the sample size is expanded by including subjects aged 60 and above.
Gender, Ethnic (Chinese, Malay, Indian & Others)	According to National Registry of Diseases Office (NRDO), there is a disparity in incidence of ACS between gender and across ethnicity[i]. Baseline difference was also observed between ABCD-GENE < 10 and ≥ 10.
History of ACS	History of ACS is a known variable that is associated with Clopidogrel response[9].
PCI	Angiolillo et al.[11] and Saito et al.[14] included ACS patients on Clopidogrel with PCI-only, whereas this study focused on ACS patients with and without PCI. Parameters introduced to ascertain whether those without PCI influenced the overall discriminability of HPR.
DHP CCBs, Insulin, Haemoglobin, Level, Type of Stents	Baseline Difference (**Table 1**).

Abbreviation: ACS = Acute Coronary Syndrome, BMI = Body Mass Index, DHP CCBs = Dihydropyridine Calcium Channel Blockers, HPR = High Platelet Reactivity, LoF = Loss-of-Function, PCI = Percutaneous Coronary Intervention.

[i] Singapore Myocardial Infarction Registry Annual Report 2019. [Internet]. Health Promotion Board; 31 Jul 2021 [cited 27 Feb 2022]. Available from https://www.nrdo.gov.sg/docs/librariesprovider3/ default-document-library/smir-web-report-2019.pdf.

Supplemental Table S2: Baseline Characteristics (by Platelet Reactivity Status)

Parameters[†]	Total (n = 423)	Platelet Reactivity Status[‡]		*p* value
		Non-HPR (n = 319)	HPR (n = 99)	
Age	55.9 ± 9.41	55.5 ± 9.48	57.1 ± 9.18	0.120
> 75	16 (3.8)	13 (4.1)	3 (3.0)	0.772
Gender (Male)	366 (86.5)	286 (89.7)	76 (76.8)	**< 0.005***
Ethnicity				
Chinese	208 (49.2)	161 (50.5)	43 (43.4)	
Malay	129 (30.5)	95 (29.8)	33 (33.3)	0.476
Indian and Others	86 (20.3)	63 (19.7)	23 (23.2)	
Body Mass Index [BMI (kg/m^2)]	25.8 (22.9 – 28.9)	25.5 (22.9 – 28.7)	26.7 (23.8 – 29.4)	**0.022**
Non-Obese (≤ 22.99)	106 (25.1)	82 (25.7)	21 (21.2)	
Overweight (23.00 – 26.99)	157 (37.1)	122 (38.2)	33 (33.3)	0.114
Obese (≥ 27.0)	160 (37.8)	115 (36.1)	45 (45.5)	
Smoking Status (Smoker)	188 (44.4)	150 (47.0)	37 (37.4)	0.105
Co-morbidities				
Hypertension	234 (55.3)	172 (53.9)	58 (58.6)	0.421
Hyperlipidaemia	420 (99.3)	317 (99.4)	98 (99.0)	0.557
Diabetes	175 (41.4)	111 (36.1)	58 (58.6)	**< 0.005***
Chronic Kidney Disease (CKD)	17 (4.0)	13 (4.1)	4 (4.0)	1.000
Stage 1 – 2 CKD[§]	379 (89.6)	293 (91.8)	82 (82.8)	
Stage 3 – 4 CKD	34 (8.0)	21 (6.6)	13 (13.1)	**0.033***
ESRD	10 (2.4)	5 (1.6)	4 (4.0)	
History of ACS	77 (18.2)	56 (17.9)	19 (19.4)	0.765
History of Bleeding	7 (1.7)	4 (1.3)	3 (3.0)	0.364
Type of ACS				0.727
STEMI	234 (55.3)	180 (56.4)	52 (52.5)	
NSTEMI	157 (37.1)	115 (36.1)	40 (40.4)	
Unstable Angina	32 (7.6)	24 (7.5)	7 (7.1)	
Percutaneous Coronary Intervention (PCI)[¶]	408 (96.5)	313 (98.1)	95 (96.0)	0.257
Type of Stents				**0.049***
Bare Metal Stent (BMS)	22 (6.9)	18 (5.8)	4 (4.3)	
Drug-Eluting Stent (DES)	357 (84.4)	275 (88.7)	77 (82.8)	
PCI without Stents[¶]	29 (5.2)	17 (5.5)	12 (12.9)	
Number of Stents				0.201
0	26 (6.1)	14 (4.5)	12 (12.9)	
1	281 (66.4)	218 (70.3)	58 (62.4)	
2	82 (19.4)	62 (20.0)	20 (21.5)	
≥ 3	19 (4.5)	16 (5.2)	3 (3.2)	
Medication at Discharge				
ACEI	217 (51.3)	164 (51.4)	49 (50.5)	0.909
ARB	54 (12.8)	37 (11.6)	17 (17.2)	0.170

Parameters†	Total (n = 423)	Platelet Reactivity Status‡		*p* value
		Non-HPR (n = 319)	HPR (n = 99)	
Beta-Blockers (BB)	349 (82.5)	261 (81.8)	83 (83.8)	0.657
Calcium Channel Blockers (CCB)				
Non-DHP CCB	3 (0.7)	3 (0.9)	0 (0)	1.000
DHP CCB	64 (15.1)	39 (12.2)	25 (25.3)	**< 0.005***
Insulin	131 (31.0)	86 (27.0)	44 (44.4)	**< 0.005***
Statins	418 (98.8)	316 (99.1)	97 (98.0)	0.339
Ticagrelor (at Initiation)	200 (47.3)	154 (48.3)	42 (42.4)	0.357
Proton Pump Inhibitors (PPI)	126 (29.8)	97 (30.4)	26 (26.3)	0.452
Vitals & Laboratory Parameters				
Baseline HbA1c (%)	6.00 (5.60 – 7.40)	6.00 (5.60 – 7.30)	6.10 (5.60 – 8.15)	0.719
Baseline Haemoglobin (g/dL)	14.3 (13.2 – 15.2)	14.4 (13.3 – 15.3)	13.8 (12.8 – 15.1)	**0.013***
Baseline LDL (mmol/L)	3.49 (2.63 – 4.37)	3.55 (2.67 – 4.33)	3.30 (2.49 – 4.41)	0.350
Estimated GFR ($mL/min/1.73m^2$) §	90 (73 – 101)	92 (74 – 101)	82 (68 – 97)	**< 0.005***
Systolic Blood Pressure (mmHg)	135 ± 25.0	134 ± 25.4	137 ± 28.5	0.346
Others				
Days to MEA Measurement	24 (19 – 24)	24 (19 – 29)	24 (18 – 30)	0.408
Days on Clopidogrel	365 (238 – 365)	365 (217 – 365)	365 (262 – 365)	0.116
CYP2C19*2/*3 Allele				
No LoF Allele	193 (45.6)	161 (50.5)	30 (30.3)	**< 0.005***
1 LoF Allele	187 (44.2)	135 (42.3)	51 (51.5)	0.132
2 LoF Alleles	43 (10.2)	23 (7.2)	18 (18.2)	**< 0.005***

Abbreviation: ACEI = Angiotensin Converter Enzyme Inhibitor, ACS = Acute Coronary Syndrome, ARB = Angiotensin Receptor Blocker, CVA = Cerebrovascular Accident, DHP = Dihydropyridine, ESRD = End-Stage Renal Disease, GFR = Glomerular Filtration Rate, LDL = Low Density Lipoprotein, LoF = Loss-of-Function, MEA = Multiple Electrode Aggregometry, NSTEMI = Non-ST Elevated Myocardial Infarction, PCI = Percutaneous Coronary Intervention, STEMI = ST-Elevated Myocardial Infarction.

*Statistical significance

†All variables are reported either as mean ± S.D., median (interquartile range) or n (%).

‡ The MEA reading for 5 of the 423 subjects were not available.

§CKD is staged in accordance with the eGFR classification listed on the KDIGO guideline. eGFR is calculated using the CKD-EPI equation.

¶ Only 408 received PCI. The remaining 15 subjects received DAPT for medical management of ACS, and did not received PCI. PCI without Stents refer to subjects who received Thrombectomy, Percutaneous Old Balloon Angioplasty or Drug-Eluting Balloon.

Supplemental Table S3: Univariable Cox Regression Model for MACE at ABCD-GENE Score Cut-off of 10-points.

Parameters	Crude Hazard Ratio (HR) (p = 0.05)	*p* value
Age	1.016 (0.962 – 1.073)	0.578
> 75	0.047 (0.000 – 8174)	0.619
Gender (Male)	3.716 (1.245 – 11.089)	**0.019***
Ethnicity		0.502
Chinese	Ref	Ref
Malay	1.880 (0.574 – 6.160)	0.297
Indian and Others	0.931 (0.181 – 4.802)	0.932
Body Mass Index [BMI (kg/m^2)]	1.139 (1.066 – 1.217)	**< 0.005***
Non-Obese (≤ 22.99)	Ref	
Overweight (23.00 – 26.99)	0.668 (0.135 – 3.308)	0.346
Obese (≥ 27.0)	1.713 (0.454 – 6.460)	
Smoking Status (Smoker)	1.068 (0.359 – 3.177)	0.906
Co-morbidities		
Hypertension	2.015 (0.632 – 6.425)	0.236
Hyperlipidaemia	20.276 (0 – 5.50 x 10^{14})	0.849
Diabetes	2.506 (0.840 – 7.481)	0.100
Chronic Kidney Disease (CKD)	9.604 (3.011 – 30.634)	**< 0.005***
Stage 1 – 2 CKD†	Ref	
Stage 3 – 4 CKD	4.594 (1.187 – 17.777)	**< 0.005***
ESRD	22.686 (6.635 – 77.559)	
History of ACS	5.501 (1.906 – 15.877)	**< 0.005***
History of Bleeding	0.049 (0 – 9841526)	0.757
Type of ACS		0.558
STEMI	0.439 (0.084 – 2.279)	0.327
NSTEMI	0.712 (0.148 – 3.429)	0.672
Unstable Angina	Ref	Ref
Percutaneous Coronary Intervention (PCI)	0.510 (0.066 – 3.933)	0.519
Type of Stents		
Bare Metal Stent (BMS)	0 (0)	0.982
Drug-Eluting Stent (DES)	0.955 (0.123 – 7.400)	0.965
PCI without Stents‡	Ref	Ref
Number of Stents		0.725
0	Ref	Ref
1	1.016 (0.130 – 7.944)	0.988
2	0.334 (0.021 – 5.337)	0.438
≥ 3	1.443 (0.090 – 23.077)	0.795
Medication at Discharge		
ACEI	0.279 (0.077 – 1.014)	0.053
ARB	4.175 (1.364 – 12.774)	**0.012***
Beta-Blockers (BB)	1.328 (0.297 – 5.937)	0.710
Calcium Channel Blockers (CCB)		
Non-Dihydropyridine (DHP) CCB	0.049 (0 – 7.752 x 10^9)	0.819

Parameters	Crude Hazard Ratio (HR) (p = 0.05)	*p* value
DHP CCB	2.014 (0.630 – 6.434)	0.237
Insulin	2.891 (1.003 – 8.334)	**0.049***
Statins	20.454 (0 – 4.863 x 10^{10})	0.784
Proton Pump Inhibitors (PPI)	1.393 (0.467 – 4.158)	0.552
Laboratory Parameters		
Baseline HbA1C (%)	0.839 (0.590 – 1.194)	0.329
Baseline Haemoglobin (g/dL)	0.756 (0.610 – 0.936)	**0.010***
Baseline LDL (mmol/L)	1.290 (0.872 – 1.909)	0.202
Estimated GFR (mL/min/1.73m^2)	0.964 (0.948 – 0.980)	**< 0.005***
Systolic Blood Pressure (mmHg)	0.991 (0.969 – 1.012)	0.397
Platelet Reactivity		
Days to MEA Measurement	1.003 (0.983 – 1.022)	0.792
Days on Clopidogrel	1.000 (0.993 – 1.007)	0.974
Platelet Reactivity (U)	1.015 (0.992 – 1.039)	0.197
Platelet Reactivity Status	2.247 (0.713 – 7.082)	0.167
CYP2C19*2/*3 Allele		
No LoF Allele	2.147 (0.720 – 6.407)	0.171
1 LoF Allele	0.339 (0.095 – 1.215)	0.097
2 LoF Alleles	1.532 (0.343 – 6.844)	0.577
Score		
ABCD-GENE (Continuous)	1.034 (0.975 – 1.096)	0.264
ABCD-GENE (Dichotomised)	3.544 (1.191 – 10.546)	**0.023***

Abbreviation: ACEI = Angiotensin Converter Enzyme Inhibitor, ACS = Acute Coronary Syndrome, ARB = Angiotensin Receptor Blocker, CVA = Cerebrovascular Accident, ESRD = End-Stage Renal Disease, GFR = Glomerular Filtration Rate, LDL = Low Density Lipoprotein, LoF = Loss-of-Function, MEA = Multiple Electrode Aggregometry, NSTEMI = Non-ST Elevated Myocardial Infarction, STEMI = ST-Elevated Myocardial Infarction.

* Statistical Significance
† CKD is staged in accordance to the eGFR classification listed on the KDIGO guideline. eGFR is calculated using the CKD-EPI equation.
‡ PCI without Stents = Thrombectomy, Percutaneous Old Balloon Angioplasty (POBA) & Drug-Eluting Balloon (DEB).

Supplemental Table S4: Multivariable Cox Regression Model for One-year Risk of MACE at a Cut-Off of 10-points

Predictors	Adjusted Hazard Ratio (HR) (95% CI)	*p* value
Model 1: Unadjusted Model		
ABCD-GENE Score	3.544 (1.191 – 10.546)	**0.023***
Model 2: Adjusted Model		
ABCD-GENE Score	3.771 (1.041 – 13.661)	**0.043***
Gender (Female)	10.892 (2.516 – 47.143)	**< 0.005***
Type of Revascularisation		
PCI without Stents	Ref	0.997
Bare Metal Stents (BMS)	3×10^{-6} (0.000 -)	0.990
Drug Eluting Stents (DES)	1.118 (0.114 – 10.950)	0.924
Smoking Status (Smoker)	4.103 (0.868 – 19.395)	0.075
Systolic Blood Pressure	1.006 (0.978 – 1.035)	0.686
History of ACS	4.749 (1.083 – 20.825)	**0.039***
Baseline LDL Level	1.894 (1.201 – 2.987)	**0.006***
Angiotensin Receptor Blocker (ARB)	15.793 (3.011 – 82.831)	**< 0.005***
Days to MEA Measurement	1.002 (0.972 – 1.032)	0.902

Abbreviation: MEA = Multiple Electrode Aggregometry
* Statistical Significance

Supplemental Table S5: Cox Regression Model for MACE at 10-points in Patients who Received PCI.

Predictors	Adjusted HR (95% CI)	*p* value
ABCD-GENE Score (Dichotomised)	3.696 (1.007 – 13.569)	**0.049***
Gender (Female)	11.476 (2.529 – 52.078)	**< 0.005***
History of ACS	4.933 (1.075 – 22.638)	**0.040***
Systolic Blood Pressure	1.005 (0.976 – 1.036)	0.728
Baseline LDL Level	1.891 (1.200 – 2.979)	**0.006***
Days to MEA Measurement	1.002 (0.972 – 1.032)	0.902
Angiotensin Receptor Blocker (ARB)	15.144 (2.867 – 79.994)	**< 0.005***
Smoking Status (Smoker)	3.735 (0.742 – 18.789)	0.110

Abbreviation: ACS = Acute Coronary Syndrome
* Statistical Significance