ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2021) **7**, 112–124
doi:10.1093/ehjcvp/pvaa005

**ORIGINAL ARTICLE**
*Acute coronary syndromes*

# Practical guidance for P2Y12 inhibitors in acute myocardial infarction undergoing percutaneous coronary intervention

**Seung Hun Lee [1,2†], Hyun Kuk Kim[3†], Myung Ho Jeong[1*], Satoshi Yasuda[4*], Satoshi Honda [4], Young-Hoon Jeong[5], Joo Myung Lee[2], Joo-Yong Hahn[2], Jeehoon Kang[6], Shung Chull Chae[7], In-Whan Seong[8], Jong-Seon Park [9], Jei Keon Chae[10], Seung-Ho Hur[11], Kwang Soo Cha[12], Hyo-Soo Kim [6], Ki-Bae Seung[13], Seung-Woon Rha[14], Jin-Yong Hwang [15], Dong-Ju Choi [16], Seok Kyu Oh[17], Sung Soo Kim [3], Taek Kyu Park[2], Jeong Hoon Yang[2], Young Bin Song [2], Seung-Hyuk Choi[2], and Hyeon-Cheol Gwon[2]; on the behalf of KAMIR, JAMIR, and SMART-DATE Investigators**

[1]Department of Cardiology, Chonnam National University Hospital, 42 Jaebong-ro, Dong-gu, Gwangju 61469, Korea; [2]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea; [3]Department of Cardiology, Chosun University Hospital, 365 Pilmun-daero Dong-gu, Gwangju 61453, Korea; [4]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1, Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan; [5]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, 11 Samjeongja-ro, Changwon 51472, Korea; [6]Department of Internal Medicine, Cardiovascular Center, Seoul National University Hospital, 101, Daehak-ro Jongno-gu, Seoul 03080, Korea; [7]Department of Internal Medicine, Kyungpook National University Hospital, 680 gukchaebosang-ro, Jung-gu, Daegu 41944, Korea; [8]Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University, College of Medicine, 282 Munhwa-ro, Jung-gu, Daejeon 35015, Korea; [9]Division of Cardiology, Department of Internal Medicine, Yeungnam University Medical Center, Yeungnam University College of Medicine, 170, Hyeonchung-ro, Nam-gu, Daegu 42415, Korea; [10]Division of Cardiology, Department of Internal Medicine, Chonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju 54907, Korea; [11]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, 6 Dalseong-ro, Jung-gu, Daegu 41932, Korea; [12]Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea; [13]Cardiology Division, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea; [14]Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea; [15]Department of Internal Medicine, Gyeonsang National University School of Medicine, Gyeongsang National University Hospital, 79 Gangnam-ro, Jinju 52727, Korea; [16]Department of Internal Medicine, Cardiovascular Center, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea; and [17]Division of Cardiology, Department of Internal Medicine, Wonkwang University School of Medicine, 460 Iksandae-ro, Iksan 54538, Korea

*Received 3 November 2019; revised 15 November 2019; editorial decision 14 January 2020; accepted 17 January 2020; online publish-ahead-of-print 24 January 2020*

**Aims** Potent P2Y12 inhibitors for dual antiplatelet therapy (DAPT) is crucial for managing acute myocardial infarction; however, the selection of drugs is based on limited clinical information such as age and body weight. The current study sought to develop and validate a new risk scoring system that can be used to guide the selection of potent P2Y12 inhibitors by balancing ischaemic benefit and bleeding risk.

**Methods and results** Derivation cohort of 10 687 patients who participated in the Korea Acute Myocardial Infarction Registry-National Institutes of Health study was used to construct a new scoring system. We combined the ischaemic and bleeding models to establish a simple clinical prediction score. Among the low score group ($n = 1764$), the observed bleeding risk (8.7% vs. 4.4%, $P < 0.001$) due to potent P2Y12 inhibitors exceeded ischaemic benefit (1.3% vs. 2.2%, $P = 0.185$) during 12 months. Conversely, the high score group ($n = 1898$) showed an overall benefit from taking potent P2Y12 inhibitors from the standpoint of observed ischaemic (17.1% vs. 8.6%, $P < 0.001$) and bleeding events (10.1% vs. 6.8%, $P = 0.073$). The performance of ischaemic [integrated area under the curve (iAUC) = 0.809] and bleeding model (iAUC = 0.655) was deemed to be acceptable.

* Corresponding authors. Tel: +82 62 220 6243, Fax: +82 62 228 7174, Email: myungho@chollian.net (M.H.J.); Tel: +81 565 8565, Fax: +81 6 6170 1989, Email: yasuda.satoshi.hp@ncvc.go.jp (S.Y.)

† The first two authors contributed equally to this work.

**Conclusion** The new scoring system is a useful clinical tool for guiding DAPT by balancing ischaemic benefit and bleeding risk, especially among Asian populations. Further validation studies with other cohorts will be required to verify that the new system meets the needs of real clinical practice.

**Keywords** Myocardial infarction • Percutaneous coronary intervention • Risk assessment • Platelet aggregation inhibitors • Prognosis

# Introduction

Various scoring systems are available for the evaluation of patients with acute myocardial infarction (AMI); however, it is doubtful whether they will ever be used widely in actual clinical practice.[1] The major limitations of the scoring systems might be attributed to the following factors (i) the derivation cohort failed to reflect the contemporary practice such as percutaneous coronary intervention (PCI) with stents and (ii) most scoring systems were not designed and used for specific treatment decisions. The widely used risk scoring systems such as Thrombolysis In Myocardial Infarction (TIMI) risk scores[2] and the Global Registry of Acute Coronary Events (GRACE) score[3,4] are helpful for stratification of high-risk patients who benefit from early invasive strategy of AMI without ST-segment elevation. Furthermore, the dual antiplatelet therapy (DAPT) score is now used in clinical practice to determine the duration of DAPT beyond 1 year after the PCI.[5]

Based on randomized clinical trials,[6,7] potent P2Y12 inhibitors including ticagrelor and prasugrel are now available for the treatment of patients with AMI and those undergoing PCI. In general, the potential limitations of randomized clinical trials involve exclusion of patients with haemodynamic instability, atrial fibrillation, or anaemia.[8,9] Thus, it is questionable whether the efficacy and safety of potent P2Y12 inhibitors can be guaranteed in various clinical settings. In any case, an appropriate risk-benefit analysis must be conducted when patients are treated with potent P2Y12 inhibitors. However, no practical tools are currently available for the evaluation of benefits and risks of treatment with P2Y12 inhibitors and the decision to use specific inhibitors in DAPT.

In this regard, we sought to develop and validate a new risk scoring system to guide the use of P2Y12 inhibitors in AMI patients.

# Methods

The study population was derived from the nationwide cohort study of patients with AMI in Korea: the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH). KAMIR-NIH is a multicentre, prospective registry used to evaluate the prognostic factors of AMI, and improve the long-term clinical outcomes of patients who have experienced an AMI. The protocols, goals, and details of KAMIR-NIH have been published elsewhere.[10] The details of inclusion and exclusion criteria are summarized in Supplementary material online, *Table S1*. The study design and protocols were approved by the institutional review board of each participating centre, and all participants provided their written informed consent. The attending physicians obtained all clinical data with the assistance of trained clinical research coordinators. Data management was performed via an electronic web-based case report form that was developed using iCReaT, which is an internet-based Clinical Research and Trial management system that was developed by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea.

## Study population

A flow chart with details of the study design is shown in Supplementary material online, *Figure S1*. The patients were enrolled from November 2011 to November 2015 and were followed-up prospectively. Patients who had been diagnosed as AMI and had undergone PCI were eligible for inclusion in the study. Among an initial 11 017 eligible patients, 330 patients were excluded for the following reasons: no follow-up data ($n = 282$); incomplete date regarding the prescribed medications ($n = 48$). Consequently, 10 687 patients were available for constructing our risk scoring system. The 12-month follow-up rate for the patients was 97.4%. The baseline clinical variables and laboratory results were evaluated at presentation. All the included patients received treatment with evidence-based medications, including aspirin, P2Y12 inhibitors, angiotensin-converting enzyme inhibitors, beta-blockers, and statins according to the practical guidelines that were valid at the time of enrolment.[11–15] All patients received an oral dose of aspirin (300 mg) and an oral 300 mg or 600 mg loading dose clopidogrel, unless they had previously received those antiplatelet medications. After the procedure, the patients continued to receive oral maintenance doses of aspirin (100 mg) and clopidogrel (75 mg). More potent P2Y12 inhibitors such as prasugrel (a 60 mg loading dose and 5 mg or 10 mg maintenance doses) or ticagrelor (a 180 mg loading dose and a 90 mg maintenance dose) could be used instead of clopidogrel. The clinical decision for the selection of a P2Y12 inhibitor, including its dose, duration, or switch was made by attending physicians. This study was conducted under the assumption that the initial regimen comprising DAPT was fixed and maintained until the events occurred. All procedures were performed under the guidance of current evidence-based guidelines, while critical decisions were made at the discretion of the operators. The follow-up duration was 1 year after registration, and the follow-up data were collected during interviews conducted by trained clinical research coordinators. If the patient did not visit the hospital, the outcome data were retrieved from hospital electronic medical records and telephone interviews.

## Outcome measures

The primary ischaemic endpoint was a composite of ischaemic events, defined as a composite of cardiac death, myocardial infarction, and stent thrombosis (as defined by the Academic Research Consortium).[16] Cardiac death is defined as death from any cardiac cause, including sudden cardiac death, myocardial infarction, heart failure, or cardiac arrhythmias. The primary bleeding endpoint included a composite of type 2, 3, and 5 bleeding events as defined by Bleeding Academic Research Consortium (BARC) criteria.[17] In addition, any major adverse cardiovascular and cerebrovascular event (MACCE), including cardiac death, myocardial infarction, stent thrombosis, any repeat PCI (target lesion, target vessel revascularization, or non-target vessel revascularization), and

cerebrovascular event was also recorded. All clinical events were evaluated by an independent event adjudicating committee.[10,18]

## Statistical analysis

Baseline clinical characteristics, medications, and procedure characteristics were compared between patients who experienced unfavoruable events or not. All discrete or categorical variables are expressed as counts and percentages. The normal distribution of data for continuous variables was assessed by the Shapiro–Wilk test and a visual inspection of the relevant Q–Q plot; data for continuous variables are expressed as the mean and standard deviation. Discrete or categorical variables were analysed using the $\chi^2$ or Fisher's exact test. Continuous variables were analysed using an unpaired *t*-test or the Mann–Whitney rank-sum test according to their distribution.

## Development of ischaemic and bleeding models

To predict the risk of ischaemic and bleeding events after PCI, we constructed a multivariable Cox proportional hazards regression model that included all variables with a *P*-value ≤0.10 in univariate analyses, as well as other variables of potential relevance based on the clinical knowledge. A total of 47 clinical variables was initially identified as potentially relevant to clinical outcomes and are listed in Supplementary material online, *Table S2*. A backward elimination, based on an information criterion, was performed to finally identify significant predictors of clinical events, and the results were used to develop two separate risk models. The hazard ratios (HRs) and 95% confidence intervals (CIs) were identified. The assumptions of proportional hazard were verified using Schoenfeld residual tests. The models were calibrated by examining calibration plots and using the goodness-of-fit test.[19] The discriminant function of each model was quantified by a global concordance probability (integrated area under the curve, iAUC).[20] The iAUC is a weighted average of the AUC values during a follow-up period, and serves as a measure of the model's predictive accuracy during follow-up, with a higher iAUC indicating a better predictive accuracy.[21]

The bootstrap and 10-fold cross-validation methods were used to perform an internal validation. The derived KAMIR-NIH dataset was randomly partitioned into 10 equally sized subsets. Nine subsets were for training, and the remaining subset was for the validation dataset. The iAUC values for the training and validation datasets were calculated using bootstrapping methods with resampling for 1000.[22] This process was repeated 10 times to achieve accurate results, and each of the 10 subsets was only used once for validation. The mean value of these 10 calculations was used to assess reliability. External validations were performed using external datasets: (i) Japan Acute Myocardial Infarction Registry (JAMIR) dataset ($n = 3412$, a prospective and multicentre cohort study)[23] and (ii) Smart Angioplasty Research Team—the safety of 6-month duration of DAPT after PCI in patients with acute coronary syndromes (SMART-DATE) dataset ($n = 2712$, prospective, multicentre, and randomized trial; clinicaltrials.gov identifier, NCT01701453).[24] The study flow charts of external validation are summarized in Supplementary material online, *Figure S2*. The detailed clinical profiles of the SMART-DATE cohort are summarized in Supplementary material online, *Table S3*, and compared with the derivation cohort.

## Assessment of incremental prognostic values of new models

The incremental prognostic value of the new scoring system was evaluated by comparison of Harrell's c-index, category-free net reclassification index, and integrated discrimination index. The R packages 'pROC' and 'PredictABEL' were applied for the analyses.[25,26] The prognostic value of ischaemic model was compared with the GRACE, DAPT, and previous KAMIR scores,[27] and the prognostic value of the bleeding model was compared with the DAPT and National Cardiovascular Data Registry (NCDR) bleeding score.[28]

## Development of a simple prediction scoring system measuring the overall benefit of using potent P2Y12 inhibitors

To simplify the scoring system, we combined the ischaemic and bleeding models by using a method derived from DAPT scores.[5] We calculated the predicted cumulative incidence of ischaemic and bleeding events at 12 months, assuming that DAPT was administered with a potent P2Y12 inhibitor (prasugrel or ticagrelor) or clopdiogrel. The absolute difference between the predicted decrease in ischaemic events (=predicited ischaemic events under clopdiogrel - predicted ischaemic events under potent P2Y12 inhibitors) and increase in bleeding events (=predicted bleeding events under clopidogrel - predicted bleeding events under potent P2Y12 inhibitors) was considered as the 'overall benefit' resulting from the use of a potent P2Y12 inhibitor. A linear regression model was constructed that included 'overall benefit' as a response variable, and all predictors of ischaemic and bleeding events as explanatory variables. The coefficients with greater 'overall benefit' indicated the benefit of reducing ischaemic benefits, wherein those with lesser 'overall benefit' indicated the harm of increasing bleeding events according to treatment with the potent P2Y12 inhibitors. The squared semi-partial correlations indicated the contribution of each variable to the overall change in benefit. Predictors of ≥1% statistically change were significant variables and were included in a simple prediction scoring system. The scores for each variable were derived from their coefficients by multiplying by 10, and then rounding the value to the nearest integer.[29] The total score ranged from -6 to 12.

## Evaluation of effect according to intensity of the P2Y12 inhibitor treatment as stratified by the scoring system

We divided the derived cohort into the following three groups according to quartiles based on the total score: (i) low score group, below the 25th percentile; (ii) intermediate score group, between the 25th–75th percentiles; and (iii) high score group, above the 75th percentile. The patients in each group were compared for the effect of potent P2Y12 inhibitors according to the observed cumulative incidences of outcomes, including ischaemic and bleeding events, MACCEs, and their components, by the Kaplan–Meier analysis, and the log-rank test was performed. The *P*-values for heterogeneity assessed if the absolute reduction in risk observed among treatment groups differed across the subgroups according to the risk score system, as calculated by Cochran's Q statistics for heterogeneity.

Sensitivity analysis was performed to adjust for potential confounders using multivariable-adjusted Cox proportional hazard model, propensity score matching, and inverse probability weighting analysis. A Cox proportional hazard regression was performed in an entire sample using interaction term, and calculated HR and 95% CI. All covariates with a significance of $P < 0.1$ in the univariable models and clinically relevant covariates were included in the multivariable-adjusted Cox proportional hazard modelling. The following variables were finally included: age, sex, diagnosis, atrial fibrillation, hypertension, diabetes mellitus, stroke, smoking, anaemia, renal insufficiency, oral anticoagulants, multivessel disease, left ventricular systolic dysfunction, Killip class, previous history of AMI, and complete revascularization.

**Table 1 Baseline clinical characteristics of the study population**

| | Ischaemic events (cardiac death, myocardial infarction, or stent thrombosis) | | | Bleeding events (type 2, 3, or 5 BARC bleeding) | | |
|---|---|---|---|---|---|---|
| | Event (*n* = 638) | No event (*n* = 10 049) | *P*-value | Event (*n* = 610) | No event (*n* = 10 077) | *P*-value |
| Age (years) | 71.4 ± 12.4 | 63.0 ± 12.3 | <0.001 | 65.2 ± 12.3 | 63.4 ± 12.5 | 0.001 |
| Age by groups | | | <0.001 | | | 0.027 |
| <55 | 166 (26.0) | 5362 (53.4) | | 289 (47.4) | 5239 (52.0) | |
| 55 to <75 | 171 (26.8) | 2635 (26.2) | | 162 (26.6) | 2644 (26.2) | |
| ≥75 | 301 (47.2) | 2052 (20.4) | | 159 (26.1) | 2194 (21.8) | |
| Male | 412 (64.6) | 7672 (76.3) | <0.001 | 448 (73.4) | 7636 (75.8) | 0.209 |
| Chest pain | 445 (69.7) | 8894 (88.5) | <0.001 | 491 (80.5) | 8848 (87.8) | <0.001 |
| STEMI | 366 (57.4) | 5184 (51.6) | 0.005 | 314 (51.5) | 5236 (52.0) | 0.849 |
| Systolic BP (mmHg) | 112.0 ± 40.6 | 130.8 ± 29.4 | <0.001 | 121.3 ± 36.0 | 130.2 ± 30.1 | <0.001 |
| Diastolic BP (mmHg) | 68.1 ± 25.7 | 79.1 ± 18.1 | <0.001 | 73.4 ± 22.0 | 78.8 ± 18.6 | <0.001 |
| Heart rate (b.p.m.) | 83.5 ± 28.7 | 77.5 ± 18.7 | <0.001 | 78.8 ± 24.1 | 77.8 ± 19.2 | 0.322 |
| LBBB | 16 (2.5) | 85 (0.8) | <0.001 | 8 (1.3) | 93 (0.9) | 0.455 |
| RBBB | 36 (5.6) | 338 (3.4) | 0.003 | 22 (3.6) | 352 (3.5) | 0.972 |
| Atrial fibrillation | 63 (9.9) | 432 (4.3) | <0.001 | 38 (6.2) | 457 (4.5) | 0.067 |
| Killip class | | | <0.001 | | | <0.001 |
| I–II | 369 (57.8) | 8991 (89.5) | | 485 (79.5) | 8875 (88.1) | |
| III | 100 (15.7) | 614 (6.1) | | 59 (9.7) | 655 (6.5) | |
| IV | 169 (26.5) | 444 (4.4) | | 66 (10.8) | 547 (5.4) | |
| GRACE score | 163.1 ± 43.4 | 117.6 ± 36.8 | <0.001 | 131.0 ± 40.7 | 119.6 ± 38.5 | <0.001 |
| GRACE—high risk | 525 (82.3) | 4202 (41.8) | <0.001 | 344 (56.4) | 4383 (43.5) | <0.001 |
| Hypertension | 401 (62.9) | 4949 (49.2) | <0.001 | 339 (55.6) | 5011 (49.7) | 0.006 |
| Diabetes mellitus | 262 (41.1) | 2707 (26.9) | <0.001 | 186 (30.5) | 2783 (27.6) | 0.136 |
| Dyslipidaemia | 48 (7.5) | 1167 (11.6) | 0.002 | 54 (8.9) | 1161 (11.5) | 0.051 |
| Previous MI | 66 (10.3) | 558 (5.6) | <0.001 | 30 (4.9) | 594 (5.9) | 0.363 |
| Previous heart failure | 22 (3.4) | 96 (1.0) | <0.001 | 12 (2.0) | 106 (1.1) | 0.057 |
| Stroke or TIA | 61 (9.6) | 533 (5.3) | <0.001 | 35 (5.7) | 559 (5.5) | 0.914 |
| Cigarette smoking | 182 (28.5) | 4126 (41.1) | <0.001 | 214 (35.1) | 4094 (40.6) | 0.008 |
| Familial history | 27 (4.2) | 678 (6.7) | 0.016 | 35 (5.7) | 670 (6.6) | 0.426 |
| Anaemia[a] | 310 (48.6) | 2075 (20.6) | <0.001 | 174 (28.5) | 2211 (21.9) | <0.001 |
| Renal insufficiency (Cr > 2.0 mg/dL) | 127 (19.9) | 389 (3.9) | <0.001 | 58 (9.5) | 458 (4.5) | <0.001 |
| LV systolic dysfunction (LVEF < 30%) | 78 (12.2) | 244 (2.4) | <0.001 | 24 (3.9) | 298 (3.0) | 0.212 |
| Troponin-I (ng/mL) | 79.2 ± 144.0 | 48.8 ± 109.8 | <0.001 | 50.8 ± 113.2 | 50.6 ± 101.8 | 0.965 |
| NT-proBNP (pg/mL) | 8281.4 ± 12 987.1 | 1863.9 ± 7223.7 | <0.001 | 3437.6 ± 7756.0 | 2208.1 ± 7893.8 | 0.003 |
| hsCRP (mg/dL) | 3.3 ± 6.6 | 1.3 ± 5.9 | <0.001 | 2.2 ± 9.9 | 1.4 ± 5.6 | 0.090 |

Data are expressed as number (%), mean ± standard deviation.
BARC, Bleeding Academic Research Consortium; BP, blood pressure; Cr, creatinine; GRACE, Global Registry of Acute Coronary Event; hsCRP, high-sensitivity C-reactive protein; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RBBB, right bundle branch block; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack.
[a]Anaemia was defined as haemoglobin <13.0 g/dL for men, and <12.0 g/dL for women.

For propensity score matching and inverse probability weighting analysis, logistic regression model for using of a potent P2Y12 inhibitor was applied to calculate propensity scores in each subgroup according to the risk score. Patients in treatment with the potent P2Y12 were matched 1:1 with patients in treatment with clopidogrel by 'nearest neighbour matching' (a greedy match) without replacement and a caliper size predefined as 0.2. The inverse probability weighting analyses were performed based on propensity scores. Residual differences in characteristics between matched cohorts were assessed by calculating the absolute standardized mean differences. Standardized mean differences for each variable between the comparator groups were summarized in Supplementary material online, *Table S4* and *Figure S3*. Standardized mean differences were less than 0.1 across all matched covariates, indicating a good balance. All CIs for the inverse probability weighting analyses were assessed with the bootstrapping methods with 1000 iterations.[22,30]

All analyses were two-tailed, and statistical significance was defined as a *P*-value ≤0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY, USA) and R version 3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria).

**Table 2 Medications and procedure characteristics**

| | Ischaemic events (cardiac death, myocardial infarction, or stent thrombosis) | | | Bleeding events (type 2, 3, or 5 BARC bleeding) | | |
|---|---|---|---|---|---|---|
| | Event ($n = 638$) | No event ($n = 10\,049$) | *P*-value | Event ($n = 610$) | No event ($n = 10\,077$) | *P*-value |
| DAPT with prasugrel or ticagrelor | 101 (15.8) | 3124 (31.1) | <0.001 | 273 (44.8) | 2952 (29.3) | <0.001 |
| P2Y12 inhibitors | | | <0.001 | | | <0.001 |
| Clopidogrel | 537 (84.2) | 6925 (68.9) | | 337 (55.2) | 7125 (70.7) | |
| Prasugrel | 31 (4.9) | 1098 (10.9) | | 96 (15.7) | 1033 (10.3) | |
| Ticagrelor | 70 (11.0) | 2026 (20.2) | | 177 (29.0) | 1919 (19.0) | |
| CCBs | 27 (4.2) | 586 (5.8) | 0.110 | 40 (6.6) | 573 (5.7) | 0.419 |
| Beta-blockers | 297 (46.6) | 8696 (86.5) | <0.001 | 478 (78.4) | 8515 (84.5) | <0.001 |
| ACE inhibitors | 139 (21.8) | 5078 (50.5) | <0.001 | 250 (41.0) | 4967 (49.3) | <0.001 |
| ARBs | 146 (22.9) | 3254 (32.4) | <0.001 | 231 (37.9) | 3169 (31.4) | 0.001 |
| Statins | 352 (55.2) | 9544 (95.0) | <0.001 | 529 (86.7) | 9367 (93.0) | <0.001 |
| Oral anticoagulants | 17 (2.7) | 249 (2.5) | 0.871 | 236 (2.3) | 30 (4.9) | <0.001 |
| Multivessel disease | 414 (64.9) | 5092 (50.7) | <0.001 | 325 (53.3) | 5181 (51.4) | 0.394 |
| Target-LM | 64 (10.0) | 194 (1.9) | <0.001 | 31 (5.1) | 227 (2.3) | <0.001 |
| Target-LAD | 307 (48.1) | 4730 (47.1) | 0.635 | 268 (43.9) | 4769 (47.3) | 0.112 |
| Target-RCA | 185 (29.0) | 3409 (33.9) | 0.012 | 190 (31.1) | 3404 (33.8) | 0.196 |
| Target-LCX | 82 (12.9) | 1716 (17.1) | 0.007 | 121 (19.8) | 1677 (16.6) | 0.046 |
| ACC/AHA Type A | 6 (0.9) | 132 (1.3) | 0.530 | 9 (1.5) | 129 (1.3) | 0.818 |
| ACC/AHA Type B1/B2 | 330 (51.7) | 4942 (49.2) | 0.228 | 338 (55.4) | 4934 (49.0) | 0.002 |
| ACC/AHA Type C | 302 (47.3) | 4975 (49.5) | 0.306 | 263 (43.1) | 5014 (49.8) | 0.002 |
| Bare metal stents | 80 (12.5) | 271 (2.7) | <0.001 | 45 (7.4) | 306 (3.0) | <0.001 |
| 1st generation DES | 5 (0.8) | 154 (1.5) | 0.178 | 3 (0.5) | 156 (1.5) | 0.055 |
| 2nd generation DES | 433 (67.9) | 7189 (71.5) | 0.052 | 448 (73.4) | 7174 (71.2) | 0.251 |
| Stent diameter ≥3 mm | 219 (34.3) | 2929 (29.1) | 0.006 | 163 (26.7) | 2985 (29.6) | 0.139 |
| Number of stents ≥2 | 106 (16.6) | 1654 (16.5) | 0.962 | 94 (15.4) | 1666 (16.5) | 0.503 |
| Pre-procedure TIMI 0 | 316 (49.5) | 4628 (46.1) | 0.096 | 286 (46.9) | 4658 (46.2) | 0.782 |
| Post-procedure TIMI 3 | 586 (91.8) | 9794 (97.5) | <0.001 | 585 (95.9) | 9795 (97.2) | 0.082 |
| Complete revascularization[a] | 621 (97.3) | 10 000 (99.5) | <0.001 | 607 (99.5) | 10 014 (99.4) | 0.887 |

Data are expressed as number (%).
ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.
[a]Minimum stenosis diameter reduction to less than 20%.

# Results

## Clinical profile of the study population

Among 10 687 patients, 638 (5.9%) patients experienced cardiac death, myocardial infarction, or stent thrombosis; 610 (5.7%) patients experienced type 2, 3, or 5 BARC bleeding events. Patients with an ischaemic event were more likely to be female, of an older age, have a diagnosis of ST-segment elevation myocardial infarction, Killip III or IV and had higher rates of hypertension, diabetes mellitus, previous myocardial infarction, previous heart failure, stroke or transient ischaemic attack, anaemia, renal insufficiency, and left ventricular systolic dysfunction (*Table 1*). Those patients had lower rates of treatment with potent P2Y12 inhibitors, beta-blockers, renin–angiotensin–aldosterone system blockers, and statins, deployment of drug-eluting stents, restoration of post-procedure TIMI 3 flow, and angiographic complete revascularization (*Table 2*). The patients with a bleeding event showed somewhat similar trends in differences; however, the differences for some variables were not statistically significant. Moreover, there were significant differences in the rates of cigarette smoking and use of oral anticoagulants. The incidence of the use of potent P2Y12 inhibitors was higher among patients with a bleeding event than among patients without a bleeding event.

## Predictors of ischaemic and bleeding events

The results of the final multivariable Cox proportional hazard models predicting ischaemic and bleeding events are shown in *Table 3*. The significant predictors in both models were DAPT with potent P2Y12 inhibitors, age, Killip III or IV, and renal insufficiency. The variables of

**Table 3 Predictors of ischaemic and bleeding events**

| Predictors of events | Ischaemic model | | | Bleeding model | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P*-value | Hazard ratio | 95% CI | *P*-value |
| Prasugrel or ticagrelor vs. clopidogrel | 0.60 | 0.48–0.75 | <0.001 | 2.13 | 1.81–2.52 | <0.001 |
| Age (55 to <75 vs. age <55) | 1.44 | 1.10–1.87 | 0.013 | 1.20 | 0.98–1.47 | 0.083 |
| Age (≥75 vs. age <55) | 3.21 | 2.45–4.21 | <0.001 | 1.64 | 1.30–2.08 | <0.001 |
| STEMI vs. NTSE-ACS | 1.35 | 1.14–1.60 | <0.001 | | | |
| Killip III vs. Killip I–II | 2.04 | 1.62–2.58 | <0.001 | 1.53 | 1.16–2.02 | 0.003 |
| Killip IV vs. Killip I–II | 5.44 | 4.48–6.61 | <0.001 | 2.59 | 2.00–3.35 | <0.001 |
| Renal insufficiency (Cr > 2.0 mg/dL) | 2.77 | 2.23–3.43 | <0.001 | 2.31 | 1.75–3.05 | <0.001 |
| LV systolic dysfunction (LVEF < 30%) | 2.34 | 1.83–2.99 | <0.001 | | | |
| Anaemia[a] | 1.48 | 1.23–1.77 | <0.001 | | | |
| Angiographic complete revascularization[b] | 0.26 | 0.16–0.43 | <0.001 | | | |
| Multivessel disease | 1.31 | 1.11–1.55 | 0.001 | | | |
| Atrial fibrillation | 1.50 | 1.16–1.95 | 0.002 | | | |
| Previous myocardial infarction | 1.51 | 1.17–1.95 | 0.002 | | | |
| Use of oral anticoagulants | | | | 2.05 | 1.42–2.97 | <0.001 |

Cr, creatinine; LVEF, left ventricular ejection fraction; NSTE-ACS, non ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.
[a]Anaemia was defined as haemoglobin <13.0 g/dL for men, and <12.0 g/dL for women.
[b]Minimum stenosis diameter reduction to less than 20%.

diagnosis, low ejection fraction, anaemia, angiographic complete revascularization, atrial fibrillation, and previous myocardial infarction were independent predictors for ischaemic events. The variable of use of oral anticoagulants was a predictor for bleeding events. The ischaemic model displayed a moderate discriminant function (iAUC = 0.809) with an acceptable calibration (goodness-of-fit $P = 0.298$). The bleeding model displayed an acceptable discriminant function (iAUC = 0.655) with an acceptable calibration (goodness-of-fit $P = 0.343$). After a k-fold cross-validation was performed with the bootstrapping method, the mean iAUC values for both the ischaemic (iAUC = 0.791) and bleeding model (iAUC = 0.650) were found to be similar (Supplementary material online, *Table S5*).

External validations were performed using the JAMIR and SMART-DATE datasets. The discriminant function of the JAMIR was acceptable in both ischaemic (iAUC = 0.702) and bleeding models (iAUC = 0.671). In the SMART-DATE dataset, the discriminant function of the ischaemic (iAUC = 0.774) and bleeding models (iAUC = 0.692) was consistent and acceptable, after excluding 836 patients with unstable angina.

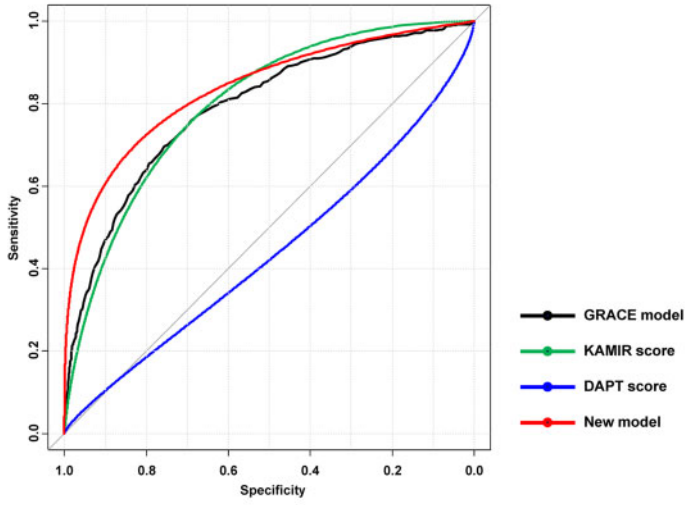
## Comparison of discriminant and reclassification ability of new scoring system

The discriminant and reclassification abilities of new scoring system are shown in *Figure 1*. For predicting ischaemic events, the new ischaemic model showed good discriminant function, and significantly increased Harrell's c-index (GRACE 0.794 vs. new model 0.837, $P$ for difference ≤ 0.001) and reclassification abilities (net reclassification index 0.086, $P \leq 0.001$; integrated discrimination index 0.019, $P = 0.001$), compared with the GRACE model. For predicting bleeding events, the new bleeding model showed modest discriminant function, and significantly increased Harrell's c-index (DAPT 0.541 vs. new model 0.631, $P$ for difference ≤ 0.001) and reclassification abilities (net reclassification index 0.178, $P \leq 0.001$; integrated discrimination index 0.011, $P \leq 0.001$) compared with the DAPT score.

## Constructing a clinical prediction scoring system: KAMIR-DAPT score

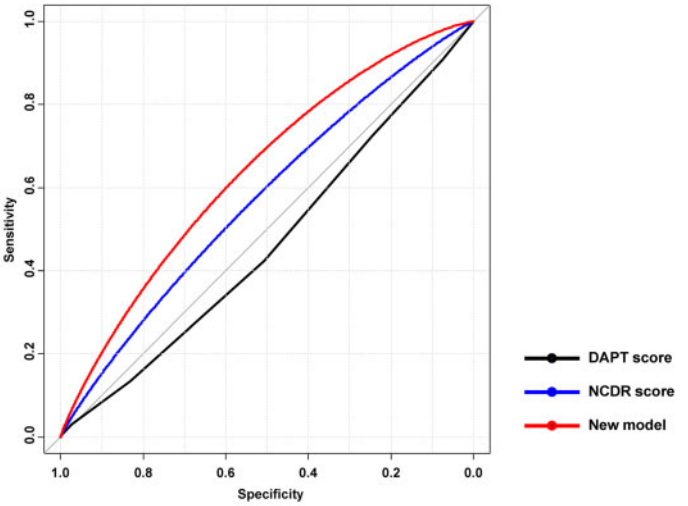
We combined the ischaemic and bleeding models to establish a simple clinical prediction score that measures the overall benefit obtained from using a potent P2Y12 inhibitor: Korea Acute Myocardial Infarction-Dual Antiplatelet Therapy (KAMIR-DAPT) score. Supplementary material online, *Table S6* shows a result obtained when using a linear regression model for predicting overall benefit, which was the difference between the benefit of reducing ischaemic events and the risk of increasing bleeding events. By using the coefficients of those variables, we assigned the scores as follows: 4 points for cardiogenic shock (Killip IV); 3 points for an ejection fraction <30%; 3 points for anaemia at presentation; 2 points for acute pulmonary oedema or decompensated heart failure (Killip III); 2 points for diagnosis of ST-segment elevation myocardial infarction; 2 points for atrial fibrillation; 1 point for a previous myocardial infarction; 1 point for multivessel disease; -2 points for angiographic complete revascularization; -2 points for a creatinine level >2.0 mg/dL; and -4 points for use of oral anticoagulants. Illustrations of the clinical prediction score and the distribution of the derivation cohort according to score are shown in *Figure 2*. The patients were divided into the following three groups based on the distribution of the derived cohort by score: ≤-2 points for the low score group ($n = 1764$); -1 to 2 points for the intermediate score group ($n = 7025$); and ≥3 points for the high score group ($n = 1898$).

**A** Comparison of Discriminant and Reclassification Ability of Predictive Models for Ischemic Events



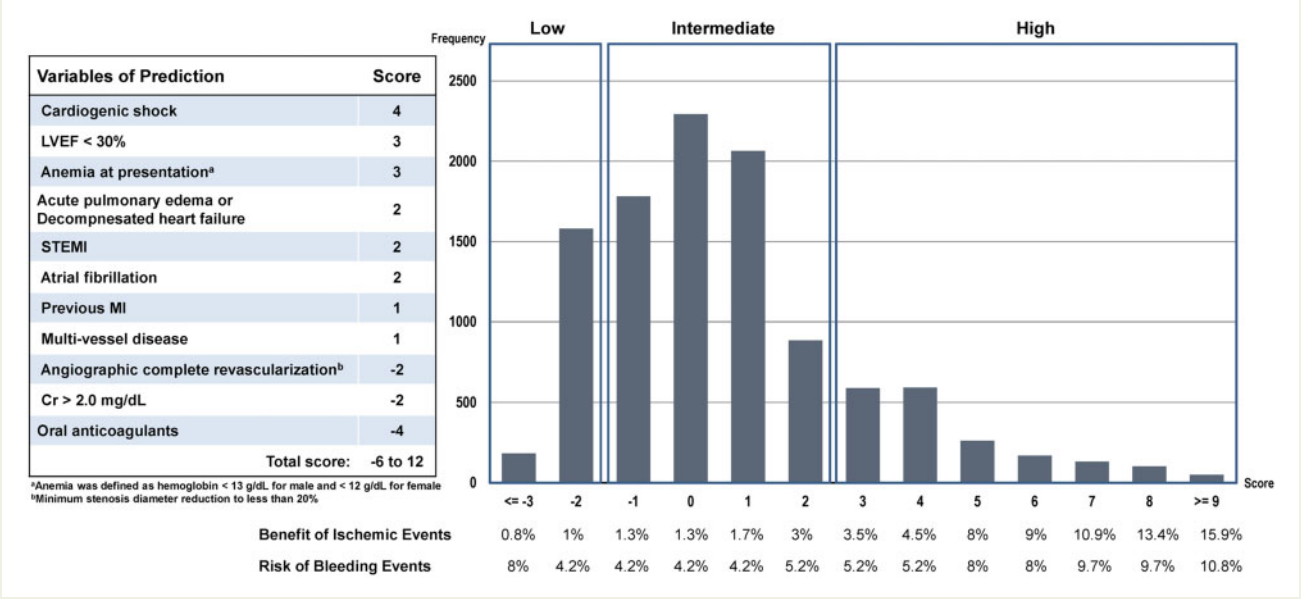

| Prediction Model | Harrell's C-index | Increment versus GRACE | | | | | |
|---|---|---|---|---|---|---|---|
| | | C-Index | P value | NRI | P value | IDI | P value |
| GRACE model | 0.794 | Reference | | Reference | | Reference | |
| KAMIR score | 0.794 | 0.001 | 0.989 | -0.013 | 0.584 | -0.007 | 0.214 |
| DAPT score | 0.580 | -0.215 | <0.001 | -0.674 | <0.001 | -0.105 | <0.001 |
| New model | 0.837 | 0.043 | <0.001 | 0.086 | <0.001 | 0.019 | 0.001 |

**B** Comparison of Discriminant and Reclassification Ability of Predictive Models for Bleeding Events




| Prediction Model | Harrell's C-index | Increment versus DAPT score | | | | | |
|---|---|---|---|---|---|---|---|
| | | C-Index | P value | NRI | P value | IDI | P value |
| DAPT score | 0.541 | Reference | | Reference | | Reference | |
| NCDR score | 0.571 | 0.030 | 0.035 | 0.063 | 0.012 | 0.002 | <0.001 |
| New model | 0.631 | 0.090 | <0.001 | 0.178 | <0.001 | 0.011 | <0.001 |

**Figure 1** Comparison of discriminant and reclassification ability of new scoring system. Discriminant and reclassification abilities of the new scoring system for (*A*) ischaemic and (*B*) bleeding events were compared with previously established prediction models. (*A*) The new ischaemic model showed significantly increased Harrell's c-index (0.794 vs. 0.837, *P* for difference ≤ 0.001) and reclassification abilities (NRI 0.086, *P* ≤ 0.001; IDI 0.019, *P* = 0.001) compared with the GRACE model. (*B*) The new bleeding model showed significantly increased Harrell's c-index (0.541 vs. 0.631, *P* for difference ≤ 0.001) and reclassification abilities (NRI 0.178, *P* ≤ 0.001; IDI 0.011, *P* ≤ 0.001) compared with the DAPT score. DAPT, dual antiplatelet therapy; GRACE, Global Registry of Acute Coronary Event; IDI, integrated discrimination index; KAMIR, Korea Acute Myocardial Infarction Registry; NCDR, National Cardiovascular Data Registry; NRI, net reclassification index.




| Variables of Prediction | Score |
|---|---|
| Cardiogenic shock | 4 |
| LVEF < 30% | 3 |
| Anemia at presentation[a] | 3 |
| Acute pulmonary edema or Decompnesated heart failure | 2 |
| STEMI | 2 |
| Atrial fibrillation | 2 |
| Previous MI | 1 |
| Multi-vessel disease | 1 |
| Angiographic complete revascularization[b] | -2 |
| Cr > 2.0 mg/dL | -2 |
| Oral anticoagulants | -4 |
| Total score: | -6 to 12 |

[a]Anemia was defined as hemoglobin < 13 g/dL for male and < 12 g/dL for female
[b]Minimum stenosis diameter reduction to less than 20%

**Figure 2** Scoring system for predicting overall benefit from the use of potent P2Y12 inhibitors and score distribution of derivation cohort. The derivation cohort was divided into three groups according to quartile based on the score. The high score group showed an overall benefit from taking potent P2Y12 inhibitors (benefit from reducing ischaemic events was greater than the harm caused by increasing the number of bleeding events). Cr, creatinine; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

## Clinical outcomes by intensity of P2Y12 inhibitor treatment as stratified by the scoring system

The high score group was associated with a larger observed reduction in risk for ischaemic events (risk difference -10.54%, *P* for heterogeneity ≤ 0.001), while the low score group was associated with a greater observed risk increase for bleeding events (risk difference 4.25%, *P* for heterogeneity ≤ 0.001, *Table 4*). There were no significant changes in the variation of risk for myocardial infarction and stent thrombosis (without myocardial infarction). The reduced risk for MACCEs (caused by using potent P2Y12 inhibitors) was greatest in the high score group (risk difference -10.86%, *P* for heterogeneity ≤ 0.001). Patients in the low score group received no significant clinical benefit from using a potent P2Y12 inhibitor, from the standpoint of ischaemic events and MACCEs (*Figure 3*). On the contrary, the use of potent P2Y12 inhibitors was associated with a higher incidence of bleeding events (HR 2.01, log-rank $P < 0.001$). Patients in the high score group had lower incidences of ischaemic events (HR 0.40, log-rank $P < 0.001$) and MACCEs (HR 0.58, log-rank $P < 0.001$) without any significant increase in bleeding events (HR 1.38, log-rank $P = 0.073$). Among patients in the intermediate score group, the use of potent P2Y12 inhibitors was associated with reductions in ischaemic events (HR 0.52, log-rank $P < 0.001$) and MACCEs (HR 0.65, log-rank $P < 0.001$); however, at the same time, it was associated with an increase in bleeding events (HR 2.11, log-rank $P < 0.001$). These trends were consistent even after adjusted for potential confounders by multivariable Cox proportional hazard modelling using the interaction term (*Table 5*), propensity score matching, and inverse probability weighting analyses (Supplementary material online, *Table S7*).

For convenient use of the new scoring system, the KAMIR investigators provided a paper copy of the system (Supplementary material online, *Figure S4*) and created a web-based calculator: https://kamirscore.com (Supplementary material online, *Figure S5*).

# Discussion

The current study developed a risk scoring system designed to balance the benefit obtained from avoiding ischaemia and the risk for bleeding events during a 12 month period in patients who received DAPT after PCI. Our major findings can be summarized as follows. First, each ischaemic and bleeding model had a good discriminant function, which was confirmed by both internal and external validation studies. Second, the KAMIR-DAPT score for determining the use of potent P2Y12 inhibitors includes the variables of cardiogenic shock (Killip IV), impaired left ventricular ejection fraction, anaemia, acute pulmonary oedema or decompensated heart failure (Killip III), ST-segment elevation myocardial infarction, atrial fibrillation, previous history of myocardial infarction, multivessel disease, angiographic complete revascularization, renal insufficiency, and the use of oral anticoagulants. Third, a low score group indicates a greater risk for bleeding events, while a high score group indicates that the patients will more likely to benefit from avoiding ischaemic events when they are treated with potent P2Y12 inhibitors. Fourth, the new risk scoring system is also helpful for predicting MACCEs for a period of 12 months. Fifth, this scoring system has the advantage of being applicable in real clinical practice, because the derivation cohort included clinically and haemodynamically unstable patients, as well as patients with atrial fibrillation.

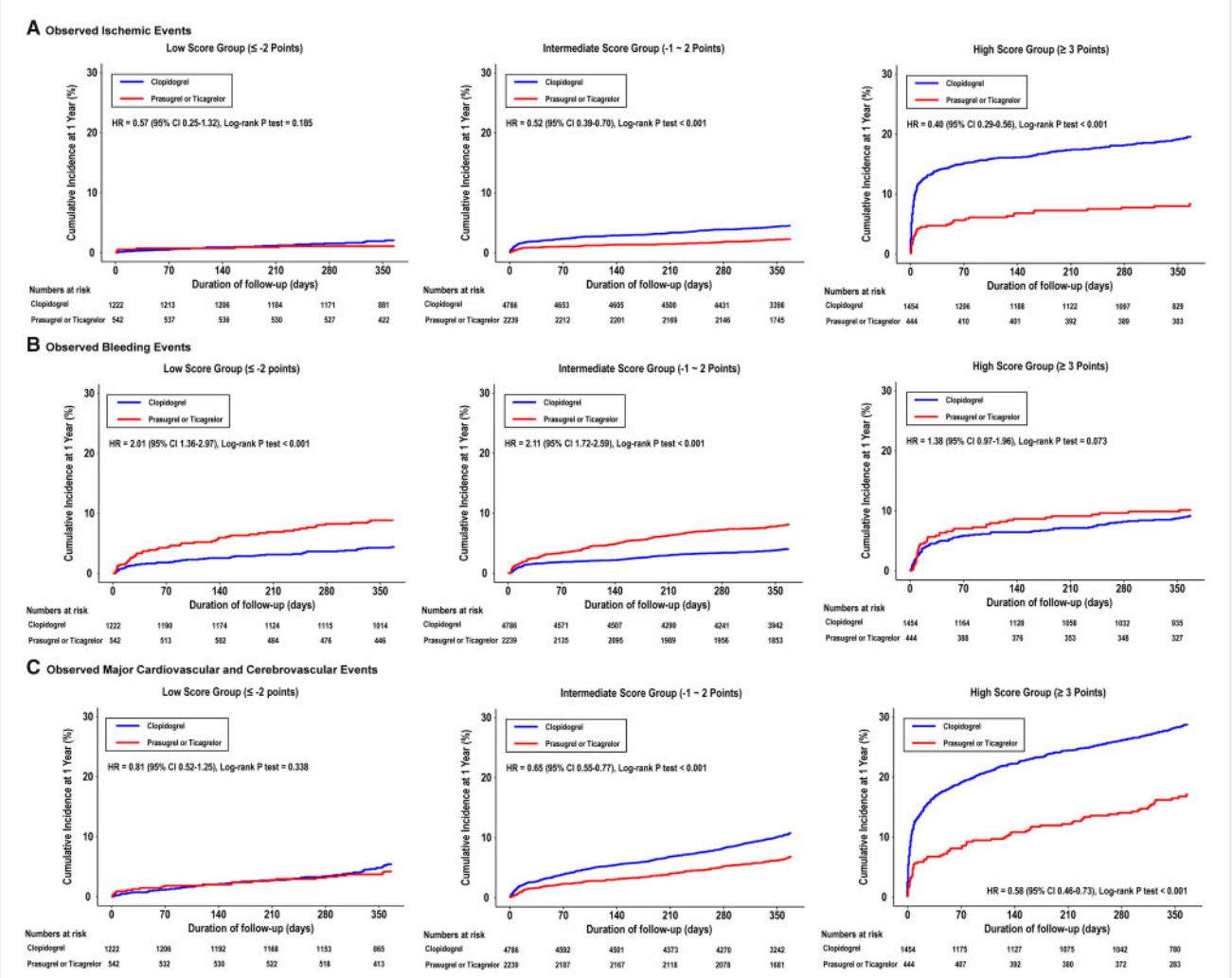



**Figure 3** Observed cumulative incidences of outcomes as determined by clinical prediction scores measuring the overall benefit of potent P2Y12 inhibitors. Survival analyses using Kaplan–Meier curves demonstrated the effect of using potent P2Y12 inhibitors within each group, as stratified by the prediction score.

## Risk scoring systems as assistance for personalized medicine

DAPT study investigators have developed a new scoring system for determining the appropriate duration of DAPT after PCI.[5] By balancing the overall benefit obtained from avoiding ischaemic events and the risk for bleeding events, the DAPT score is valuable for optimizing patient care in the drug-eluting stent era. We believe that a scoring system should present a blueprint for determining the optimal treatment strategy that will improve a patient's prognosis. The KAMIR study group has already established a scoring system for predicting clinical outcomes after AMI.[27] In real clinical practice, however, it is not enough to just improve patient care by assessing and stratifying patients into different risk groups. In this respect, the KAMIR-DAPT score represents a novel scoring system that predicts ischaemic and bleeding events, simultaneously, and finally determines the type of P2Y12 inhibitor that could be used when DPAT is required (e.g. aspirin plus ticagrelor or prasugrel vs. aspirin plus clopidogrel).

It is well known that ticagrelor and prasugrel can reduce ischaemic events; however, the risk for bleeding can be presented.[6,7] It remains uncertain as to which DAPT regimen can be more beneficial for AMI patients, in terms of their efficacy and safety. We suggest that the KAMIR-DAPT score can assist in guiding the choice of P2Y12 inhibitors. The variables are included and reflected net effect between ischaemic and bleeding events, simultaneously. In the new scoring system, a positive number signifies an increased risk for ischaemic events, and a negative number signifies an increased risk for bleeding events related to the DAPT provided with potent P2Y12 inhibitors. For example, the variable of cardiogenic shock (4 points) is related to the probability of ischaemic events; conversely, the variable of oral anticoagulants (-4 points) is related to the probability of bleeding

**Table 4 Observed outcomes during 12 months according to the use of antiplatelet therapy**

| | Number of patients | | Number of events | | | Risk difference % (95% CI) | *P* for heterogeneity[a] |
|---|---|---|---|---|---|---|---|
| | Prasugrel or ticagrelor | Clopidogrel | All patients (*n* = 10 687) | Prasugrel or ticagrelor (*n* = 3225) | Clopidogrel (*n* = 7462) | | |
| Cardiac death | | | | | | | <0.001 |
| Low (≤-2) | 542 | 1222 | 21 (1.2) | 4 (0.7) | 17 (1.4) | -0.65 (-1.15 to -0.16) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 204 (2.9) | 32 (1.4) | 172 (3.6) | -2.16 (-2.53 to -1.80) | |
| High (≥3) | 444 | 1454 | 290 (15.3) | 32 (7.2) | 258 (17.7) | -10.54 (-12.12 to -8.95) | |
| Myocardial infarction | | | | | | | 0.421 |
| Low (≤-2) | 542 | 1222 | 20 (1.1) | 6 (1.1) | 14 (1.1) | -0.04 (-0.58 to 0.50) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 123 (1.8) | 39 (1.7) | 84 (1.8) | -0.01 (-0.35 to 0.32) | |
| High (≥3) | 444 | 1454 | 41 (2.2) | 5 (1.1) | 36 (2.5) | -1.35 (-2.00 to -0.70) | |
| Stent thrombosis | | | | | | | 0.692 |
| Low (≤-2) | 542 | 1222 | 4 (0.2) | 0 (0) | 4 (0.3) | -0.33 (-0.49 to -0.16) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 24 (0.3) | 6 (0.3) | 18 (0.4) | -0.11 (-0.25 to 0.03) | |
| High (≥3) | 444 | 1454 | 14 (0.7) | 5 (1.1) | 9 (0.6) | 0.51 (-0.03 to 1.05) | |
| Any repeat revascularization | | | | | | | 0.785 |
| Low (≤-2) | 542 | 1222 | 56 (3.2) | 16 (3.0) | 40 (3.3) | -0.32 (-1.21 to 0.57) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 384 (5.5) | 117 (5.2) | 267 (5.6) | -0.35 (-0.93 to 0.22) | |
| High (≥3) | 444 | 1454 | 110 (5.8) | 27 (6.1) | 83 (5.7) | 0.37 (-0.91 to 1.66) | |
| Cerebrovascular events | | | | | | | 0.055 |
| Low (≤-2) | 542 | 1222 | 10 (0.6) | 2 (0.4) | 8 (0.7) | -0.29 (-0.63 to 0.06) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 53 (0.8) | 9 (0.4) | 44 (0.9) | -0.52 (-0.71 to -0.33) | |
| High (≥3) | 444 | 1454 | 23 (1.2) | 8 (1.8) | 15 (1.0) | 0.77 (0.09 to 1.45) | |
| Ischaemic events | | | | | | | <0.001 |
| Low (≤-2) | 542 | 1222 | 34 (1.9) | 7 (1.3) | 27 (2.2) | -0.92 (-1.56 to -0.28) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 280 (4.0) | 56 (2.5) | 224 (4.7) | -2.18 (-2.63 to -1.73) | |
| High (≥3) | 444 | 1454 | 324 (17.1) | 38 (8.6) | 286 (19.7) | -11.11 (-12.80 to -9.42) | |
| Major adverse cardiovascular and cerebrovascular events | | | | | | | <0.001 |
| Low (≤-2) | 542 | 1222 | 104 (5.9) | 28 (5.2) | 76 (6.2) | -1.05 (-2.23 to 0.12) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 728 (10.4) | 176 (7.9) | 552 (11.5) | -3.67 (-4.41 to -2.94) | |
| High (≥3) | 444 | 1454 | 517 (27.2) | 84 (18.9) | 433 (29.8) | -10.86 (-13.07 to -8.65) | |
| Bleeding events | | | | | | | <0.001 |
| Low (≤-2) | 542 | 1222 | 101 (5.7) | 47 (8.7) | 54 (4.4) | 4.25 (2.91 to 5.60) | |
| Intermediate (-1 to 2) | 2239 | 4786 | 365 (5.2) | 181 (8.1) | 184 (3.8) | 4.24 (3.60 to 4.88) | |
| High (≥3) | 444 | 1454 | 610 (5.7) | 45 (10.1) | 99 (6.8) | 3.33 (1.75 to 4.90) | |

Data are expressed as a number (%).
[a]The *P*-values for heterogeneity assessed if the absolute reduction in risk observed among treatment groups differed across the subgroups according to the risk score system, as calculated by Cochran's Q statistics for heterogeneity.

events. In other words, if the score is higher, the use of potent P2Y12 inhibitors would be better; and if the score is lower, the use of potent P2Y12 inhibitors may be prohibited because of high bleeding risk.

Although the KAMIR-DAPT score can be used to calculate each ischaemic benefit and increase in bleeding risk related to the use of potent P2Y12 inhibitors, we divided the patients into three groups for simplification. The observed cumulative incidence of outcomes showed that patients in the high score group would benefit from reducing the risk for ischaemic events without increasing the risk for bleeding events during a 12-month period. Conversely, when the low score group was treated with potent P2Y12 inhibitors, only the bleeding events increased, and no reduction in ischaemic events was found. The intermediate score group showed a reduction in ischaemic events and an increase in bleeding events due to the use of potent P2Y12 inhibitors. Therefore, the final decision to use P2Y12 inhibitors in the intermediate group rests with the physician.

## Clinical application of the KAMIR-DAPT score

The originality of the KAMIR-DAPT score is based on the characteristics of the derived cohort. The score takes into consideration recent trends in the treatment of AMI, in terms of therapeutic approaches. Acute myocardial infarction patients with cardiogenic shock, atrial fibrillation, renal insufficiency, or heart failure are included in the derived cohort. The atrial fibrillation is common

**Table 5 Cox-regression analysis for the potent P2Y12 inhibitors on clinical outcomes stratified according to risk score group**

| | Univariate | | | Multivariable adjusted[a] | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P*-value | *P*-value for interaction | HR (95% CI) | *P*-value | *P*-value for interaction |
| Cardiac death | | | | | | |
| Low (≤-2) | 0.59 (0.22–1.57) | 0.290 | 0.384 | 1.24 (0.43–3.60) | 0.689 | 0.336 |
| Intermediate (-1 to 2) | 0.42 (0.29–0.60) | <0.001 | | 0.69 (0.48–0.99) | 0.048 | |
| High (≥3) | 0.38 (0.26–0.54) | <0.001 | | 0.45 (0.31–0.65) | <0.001 | |
| Myocardial infarction | | | | | | |
| Low (≤-2) | 0.93 (0.36–2.41) | 0.874 | 0.156 | 1.33 (0.47–3.71) | 0.591 | 0.161 |
| Intermediate (-1 to 2) | 0.92 (0.63–1.34) | 0.649 | | 1.20 (0.81–1.78) | 0.359 | |
| High (≥3) | 0.39 (0.15–0.99) | 0.049 | | 0.44 (0.17–1.13) | 0.087 | |
| Stent thrombosis | | | | | | |
| Low (≤-2) | 0 (0–inf) | 0.998 | 0.065 | 0 (0–inf) | 0.998 | 0.065 |
| Intermediate (-1 to 2) | 0.68 (0.27–1.72) | 0.418 | | 0.74 (0.29–1.90) | 0.534 | |
| High (≥3) | 1.62 (0.54–4.83) | 0.388 | | 1.33 (0.43–4.17) | 0.622 | |
| Any repeat revascularization | | | | | | |
| Low (≤-2) | 0.86 (0.48–1.54) | 0.615 | 0.785 | 0.92 (0.51–1.68) | 0.796 | 0.891 |
| Intermediate (-1 to 2) | 0.88 (0.71–1.10) | 0.262 | | 0.91 (0.73–1.13) | 0.381 | |
| High (≥3) | 0.94 (0.61–1.45) | 0.768 | | 0.81 (0.52–1.27) | 0.361 | |
| Cerebrovascular events | | | | | | |
| Low (≤-2) | 0.55 (0.12–2.57) | 0.444 | 0.055 | 0.73 (0.14–3.66) | 0.697 | 0.058 |
| Intermediate (-1 to 2) | 0.42 (0.21–0.86) | 0.018 | | 0.60 (0.29–1.25) | 0.173 | |
| High (≥3) | 1.57 (0.67–3.70) | 0.304 | | 2.15 (0.88–5.28) | 0.093 | |
| Ischaemic events | | | | | | |
| Low (≤-2) | 0.57 (0.25–1.32) | 0.191 | 0.156 | 0.95 (0.40–2.28) | 0.911 | 0.172 |
| Intermediate (-1 to 2) | 0.52 (0.39–0.70) | <0.001 | | 0.78 (0.58–1.06) | 0.113 | |
| High (≥3) | 0.40 (0.29–0.56) | <0.001 | | 0.47 (0.33–0.67) | <0.001 | |
| Major adverse cardiovascular and cerebrovascular events | | | | | | |
| Low (≤-2) | 0.81 (0.52–1.25) | 0.338 | 0.096 | 1.01 (0.64–1.59) | 0.970 | 0.132 |
| Intermediate (-1 to 2) | 0.65 (0.55–0.77) | <0.001 | | 0.81 (0.68–0.97) | 0.021 | |
| High (≥3) | 0.58 (0.46–0.73) | <0.001 | | 0.66 (0.52–0.84) | 0.001 | |
| Bleeding events | | | | | | |
| Low (≤-2) | 2.01 (1.36–2.97) | <0.001 | 0.053 | 2.33 (1.55–3.52) | <0.001 | 0.057 |
| Intermediate (-1 to 2) | 2.11 (1.72–2.59) | <0.001 | | 2.45 (1.98–3.03) | <0.001 | |
| High (≥3) | 1.38 (0.97–1.96) | 0.073 | | 1.42 (0.98–2.04) | 0.060 | |

[a]The variables of age, sex, diagnosis; atrial fibrillation, hypertension, diabetes mellitus, stroke, smoking, anaemia, renal insufficiency, oral anticoagulants, multivessel disease, left ventricular systolic dysfunction, Killip class, previous history of AMI, and complete revascularization were included.

among patients undergoing PCI, and it is independently associated with mortality.[31] Therefore, we believe that this new scoring system is more suitable for use in real clinical practice, particularly because it can be used to evaluate AMI patients with atrial fibrillation. The recent guideline for the management of atrial fibrillation accompanied by acute coronary syndrome recommends clopidogrel, rather than prasugrel as the preferred agent for triple therapy.[32] Consistent with that recommendation, the KAMIR-DAPT score also indicated that AMI patients with atrial fibrillation and prescribed an oral anticoagulation agent were at risk for bleeding when they used a potent P2Y12 inhibitor. In the guideline, the ischaemic risk assessment was based on the CAHDS2-VASc risk score. Our new scoring system is useful because it provides additional evidence for selecting P2Y12 inhibitors. Moreover, the KAMIR-DAPT score showed incremental prognostic values compared with the previously established models for predicting both ischaemic and bleeding events. These results confirmed that the KAMIR-DAPT score could be used for clinical applications.

Any scoring system designed for use in routine clinical practice should be easy to utilize with supporting of auxiliary tools. Use of the GRACE model is facilitated by a web-based calculator. Similar to the GRACE model, the KAMIR investigators created a web-based calculator that can be used on mobile phones. We hope that this ease of use will contribute to increasing the daily use of the scoring system.

## Limitations

This study has some limitations that should be mentioned. First, although data obtained from >10 000 AMI patients were used to construct our final scoring system, a larger number of patients may have

increased the predictive ability of the new system. To overcome this issue, we trained and validated the scoring system by using statistical methods, bootstrapping, and k-fold cross-validation methods. Furthermore, the external validation that was performed using an independent cohort provided additional evidence of accuracy. The external validations were independently and separately performed in JAMIR and SMART-DATA datasets. Although the sample size of these datasets was relatively smaller than the KAMIR-NIH dataset, the external validations yielded modest discriminant function of ischaemic and bleeding models. A few analyses were only conducted in the derived cohort due to data access. Second, although the KAMIR-NIH was designed to register all AMI patients in a blinded fashion for procedural data and medications, there remains the potential for selection bias. Third, although the KAMIR-DAPT scoring system is comprised of only essential variables; it still contains more than 10 variables, which might inhibit its intuitive use in clinical practice. The authors have attempted to facilitate the use of the new scoring system by providing a web-based calculator and a paper copy of the scoring system. Fourth, the appropriate dose of DAPTs and the duration of dosing are disputed. Our new scoring system has been developed to guide decisions regarding the choice of P2Y12 inhibitors used for treatment during 12 months. The current study included only patients who were treated with the usual dose of a potent P2Y12 inhibitor. Compliance with DAPT is a critical issue related to ischaemic events during the first month after PCI; however, in this analysis, no compliance data were available. Moreover, potent P2Y12 inhibitors might be switched to clopidogrel during the 1 year; however, the underlying reasons and patient numbers associated with the switch were not clearly defined. Fifth, although the use of proton pump inhibitors can affect both ischaemic and bleeding events, no data were available for assessment of their effect. Sixth, this analysis was based on East Asian population in both derived and validated cohorts. In the East Asian population, despite the higher CYP2C19 loss-of-function than in the Western population, the prevalence of ischaemic events was lower and bleeding events were higher compared with non-East Asians.[33] Therefore, it is more important and the pattern of trade-off between ischaemic events and bleeding risk can differ according to the race. It is doubtable if the new scoring system can overcome the racial difference and be adopted in other cohorts. Further validation studies involving other cohorts are needed to establish the appropriate KAMIR-DAPT score under various clinical circumstances. Although the inclusion of CYP2C19 polymorphism or platelet function test in the risk scoring model may improve the discriminant function, it was not available due to the lack of data.

# Conclusions

The KAMIR-DAPT score is the first scoring system developed to guide the use of specific P2Y12 inhibitors in real clinical practice. This system was constructed by evaluating the balance between ischaemic benefit and bleeding risk when potent P2Y12 inhibitors were prescribed for AMI patients who underwent PCI. A web-based version of the risk calculator (https://www.kamirscore.com) was created to promote its ease of use in daily practice. Our model showed that potent P2Y12 inhibitors were indicated for patients with a high score because they reduced the risk of ischaemic events and MACCEs associated without a significant increase in bleeding events. Our model also showed that patients with a low score may use clopidogrel, as it reduces the risk of bleeding events. The KAMIR-DAPT score is worth using in daily clinical practice of East Asians because it is also applicable to clinically and haemodynamically unstable patients. Further validation in other racial cohorts is needed to expand its use.

# Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.


## Acknowledgements

The authors would like to thank the clinical investigators of the Korea Acute Myocardial Infarction Registry, Japan Acute Myocardial Infarction Registry, and Smart Angioplasty Research Team who contributed their time and effort to this study.

## Funding

This research was supported by the Research of Korea Centers for Disease Control and Prevention (2016-ER6304-01).

**Conflict of interest:** none declared.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