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Original Research

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The Association of CHADS-P2A2RC Risk Score With Clinical Outcomes in Patients Taking P2Y12 Inhibitor Monotherapy After 3 Months of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention

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AUTHOR'S SUMMARY

It is unclear whether ischemic risk guides the selection of antiplatelet therapy after percutaneous coronary intervention (PCI). Recently, the CHADS-P2A2RC was developed as an ischemic risk prediction model. There was a stepwise increase in the rates of major adverse cardiac and cerebral events and all-cause death according to increased CHADS-P2A2RC in the study population. No significant interactions were observed between the strata of the CHADS-P2A2RC and the antiplatelet strategies for ischemic and bleeding outcomes; the benefits of P2Y12 inhibitor monotherapy were similar even in patients with high ischemic risk. Randomized studies are needed to evaluate the utility of ischemic risk stratification to guide antiplatelet therapy selection after PCI.

ABSTRACT

Background and Objectives: Concerns remain that early aspirin cessation may be associated with potential harm in subsets at high risk of ischemic events. This study aimed to assess the effects of P2Y12 inhibitor monotherapy after 3-month dual antiplatelet therapy (DAPT) vs. prolonged DAPT (12-month or longer) based on the ischemic risk stratification, the CHADS-P2A2RC, after percutaneous coronary intervention (PCI).

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author(s) upon reasonable request.

Presentation
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Author Contributions
Conceptualization: Song PS, Jeong JO, Hahn JY, Gwon HC, Bae JW, Song YB; Data curation: Song PS, Gwon HC, Song YB; Formal analysis: Song PS, Kim JY, An SY, Kim MJ, Seong SW, Ahn KT, Jin SA, Jeong JO, Yang JH, Hahn JY, Gwon HC, Jang WJ, Yoon HJ, Bae JW, Choi

Methods: This was a sub-study of the SMART-CHOICE trial. The effect of the randomized antiplatelet strategies was assessed across 3 CHADS-P2A2RC risk score categories. The primary outcome was a major adverse cardiac and cerebral event (MACCE), a composite of all-cause death, myocardial infarction, or stroke.
Results: Up to 3 years, the high CHADS-P2A2RC risk score group had the highest incidence of MACCE (105 [12.1%], adjusted hazard ratio [HR], 2.927; 95% confidence interval [CI], 1.358–6.309; p=0.006) followed by moderate-risk (40 [1.4%], adjusted HR, 1.786; 95% CI, 0.868–3.674; p=0.115) and low-risk (9 [0.5%], reference). In secondary analyses, P2Y12 inhibitor monotherapy reduced the Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 bleeding without increasing the risk of MACCE as compared with prolonged DAPT across the 3 CHADS-P2A2RC risk strata without significant interaction term (interaction p for MACCE=0.705 and interaction p for BARC types 2, 3, or 5 bleeding=0.055).
Conclusions: The CHADS-P2A2RC risk score is valuable in discriminating high-ischemic-risk patients. Even in such patients with a high risk of ischemic events, P2Y12 inhibitor monotherapy was associated with a lower incidence of bleeding without increased risk of ischemic events compared with prolonged DAPT.

Trial Registration: ClinicalTrials.gov Identifier: NCT02079194

Keywords: Coronary artery disease; Angioplasty; Dual anti-platelet therapy; Prognosis

INTRODUCTION

Dual antiplatelet therapy (DAPT) is the standard treatment for patients after percutaneous coronary intervention (PCI). DAPT reduces ischemic events but increases the risk of bleeding. Current guidelines recommend that antiplatelet treatment regimens be individualized based on patient-specific risk of ischemia and bleeding.[1)2)] To balance ischemic benefit and bleeding risk, clinical risk assessment tools have been developed to guide decisions regarding antiplatelet treatment regimens.[3)] The observational data indicated that the bleeding risk of an individual patient is a key determinant in defining antiplatelet therapy regimens.[4)] However, many patients are at risk of both increased bleeding and ischemic events.[5)] In some cases, a disproportionate increase was reported in ischemic risk compared with bleeding risk in patients with multiple risk factors.[6)] Aspirin cessation after 1–3 months of DAPT and continuation with P2Y12 inhibitor monotherapy has been shown to favorably affect the balance between bleeding and ischemic risk among unselected patients undergoing PCI.[7)8)] However, concerns remain that early aspirin withdrawal may be associated with potential harm in high ischemic risk patients. It is also unclear whether the use of scores or definitions for ischemic risk stratification to guide the selection of an antiplatelet therapy regimen could identify a balance between the safety and efficacy of alteration to P2Y12 inhibitor monotherapy after short-term DAPT. The present study aimed to analyze the risk-benefit profile of P2Y12 inhibitor monotherapy vs. prolonged DAPT in a contemporary PCI population according to the class of ischemic risk stratified using the CHADS-P2A2RC risk score.[9)]

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METHODS

Ethical statement

The SMART-CHOICE trial was approved by the Institutional Review Board (IRB) at each participating institution (Samsung Medical Center, IRB No. 2014-01-016). All patients provided informed consent. The study complied with the guidelines of the 2013 Declaration of Helsinki and Good Clinical Practices.

The current study was a post hoc subgroup analysis of the SMart Angioplasty Research Team: Comparison between P2Y12 antagonist monotHerapy and dual antiplatelet therapy in patients undergOing Implantation of Coronary drug-Eluting stents (SMART-CHOICE) trial. The SMART-CHOICE trial was a multicenter, open-label, randomized controlled trial comparing a novel antiplatelet regimen with P2Y12 inhibitor monotherapy after 3 months of DAPT with prolonged DAPT (12 months or longer) in patients who underwent PCI at 33 study sites in Korea (ClinicalTrials.gov, NCT02079194). The trial design and 3-year results were previously published.[10)11)] In brief, patients undergoing PCI with a drug-eluting stent for chronic coronary syndrome or acute coronary syndrome were randomly assigned (1:1) to either aspirin plus P2Y12 inhibitor for 3 months, followed by P2Y12 inhibitors alone or to prolonged DAPT with aspirin plus P2Y12 inhibitors for at least 12 months. Clinical follow-up was performed at 3, 6, and 12 months and annually thereafter for up to 3 years after the index PCI. The inclusion and exclusion criteria are available in **Supplementary Table 1**. PCI was performed following standard techniques. All patients received 300 mg of aspirin and a loading dose of P2Y12 inhibitor (300–600 mg of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor) orally before PCI unless they had previously received those antiplatelet agents. After the procedure, patients in both groups received DAPT of aspirin (100 mg) once daily plus clopidogrel (75 mg) once daily, prasugrel (10 mg) once daily, or ticagrelor (90 mg) twice daily for 3 months. The administration of aspirin was stopped 3 months after the index procedure in the P2Y12 inhibitor monotherapy group but was continued in the DAPT group. A P2Y12 inhibitor was prescribed continuously in both groups. All patients were advised to receive optimal medical treatment, including statins, beta-blockers, or renin-angiotensin system blockers, as appropriate under current guidelines.[1)2)]

The CHADS-P2A2RC score was developed recently as a risk prediction model for identifying patients without atrial fibrillation at high risk of a first arterial thromboembolic event.[9)] This risk prediction model assigns one point each to congestive heart failure, hypertension, diabetes mellitus, renal disease (estimated glomerular filtration rate <30 mL/min per the Cockcroft-Gault formula and/or renal replacement therapy at the time of screening), age 65–74 years, active smoking, and multi-vessel obstructive coronary artery disease and 2 points each to age ≥75 years and peripheral artery disease. In the present study (**Supplementary Table 2**), the CHADS-P2A2RC risk score was calculated in each patient based on the clinical parameters at hospital admission, and patients were categorized into low-risk (CHADS-P2A2RC score ≤1), moderate-risk (CHADS-P2A2RC score 2–3), and high-risk (CHADSP2A2RC score ≥4) based on results from the validation study, in which a CHADS-P2A2RC score ≥4 was associated with a particularly high risk of major adverse cardiac events (MACEs) and all-cause death.

The primary endpoint was a major adverse cardiac and cerebral event (MACCE), a composite of all-cause death, myocardial infarction (MI), or stroke up to 3 years after the index procedure. Secondary endpoints were the components of the primary endpoint, overall bleeding (Bleeding Academic Research Consortium [BARC] types 2, 3, or 5), and major

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bleeding (BARC types 3 or 5) at 3 years. All clinical events were monitored and verified by an independent clinical event adjudication committee composed of members who did not participate in patient enrollment for this study.

Continuous variables are expressed as the median and interquartile range (IQR) and compared using the Kruskal-Wallis H test for multiple comparisons and the Mann-Whitney U test for pairwise comparisons. Categorical variables are presented as counts and percentages and compared using a chi-square test. The prognostic utility of the CHADS-P2A2RC risk score for clinical outcomes was assessed by deriving the C-statistic using receiver operating characteristics curves analysis (MedCalc Version 12.2.1; MedCalc Software, Mariakerke, Belgium). Kaplan-Meier curves were used to show cumulative event rates over time with classification based on the CHADS-P2A2RC risk categories and compared using the log-rank test. Multivariate Cox proportional hazards models were used to evaluate the magnitude of the association between the 3 predefined CHADS-P2A2RC risk categories (low CHADS-P2A2RC risk score was used as the reference group) and each clinical outcome expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). In each model, the CHADS-P2A2RC risk score was adjusted based on baseline clinical and procedural characteristics possibly associated with clinical outcomes: age, sex, hypertension, diabetes mellitus, current active smoking, peripheral vascular disease, previous cerebrovascular injury, previous coronary revascularization, baseline diastolic blood pressure, baseline hemoglobin and estimated glomerular filtration rate, multi-vessel coronary artery disease, anterior ischemia or MI, calcification in the culprit lesion, and the 3 CHADS-P2A2RC risk categories. In addition, the total CHADS-P2A2RC risk scores were entered into separate Cox regression models as continuous variables to evaluate their association with adverse clinical events. Secondary analyses were performed for each clinical outcome, adjusting on consistent covariates as well as the randomized antiplatelet regimens (P2Y12 inhibitor monotherapy vs. prolonged DAPT) by stratifying patients according to the CHADS-P2A2RC risk categories. This included interactions between the CHADS-P2A2RC risk categories and antiplatelet regimens. The proportional hazards assumptions of the HR for P2Y12 inhibitor monotherapy compared with prolonged DAPT in the Cox proportional hazards models were graphically inspected in the log minus log plot and were confirmed with the Schoenfeld residual test. Two-sided p values < 0.05 were considered statistically significant. The statistical analyses were performed in SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Two thousand nine hundred ninety-three patients were randomly assigned to receive P2Y12 inhibitor monotherapy after 3 months of DAPT (1,495 patients) or prolonged DAPT (1,498 patients) after PCI. The median follow-up duration was 1,096 days (IQR, 1,066–1,120). Based on the CHADS-P2A2RC risk score, 661 (22.1%), 1,461 (48.8%), and 871 (29.1%) patients were classified as low-risk, moderate-risk, or high-risk, respectively (**Supplementary Figure 1**). Baseline demographics, lesion and procedural characteristics, and medications at discharge based on the CHADS-P2A2RC risk category are shown in **Supplementary Table 3**. Patients in the high-risk group were older and had higher rates of previous MI, previous coronary revascularization, hypertension, diabetes, established peripheral vascular disease, and known chronic kidney disease compared with subjects in the low- or moderate-risk group. The patients with a high CHADS-P2A2RC risk score had lower hemoglobin levels, estimated glomerular filtration rates, and lower left ventricular ejection fraction levels on 2-dimensional

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echocardiography. Patients with a high-risk score were more likely to have calcification in the culprit lesion, multi-vessel coronary disease, and significantly longer lengths of implanted stents. However, the use of statins, beta-blockers, and renin-angiotensin system blockers was equally distributed among the 3 risk groups.

After the 3-year follow-up, 170 (5.7%) patients experienced MACCE; 101 (3.4%) all-cause death; 45 (1.5%) MI; 37 (1.2%) stroke; 156 (5.2%) BARC 2, 3, or 5 bleeding; and 48 (1.6%) BARC 3 or 5 major bleeding. Up to 3 years, the CHADS-P2A2RC high-risk group had the highest incidence of MACCE (105 [12.1%], adjusted HR, 2.927; 95% CI, 1.358–6.309; p=0.006), followed by moderate-risk (40 [1.4%]; adjusted HR, 1.786; 95% CI, 0.868–3.674; p=0.115) and low-risk groups (9 [0.5%]; reference) (**Figure 1**, **Table 1**). When all-cause death was used as the endpoint, the event rate in the high-score group (72 [8.3%]; adjusted HR, 8.690; 95% CI, 2.019–37.403; p=0.004) was significantly higher than that in the moderate-risk score (27 [1.8%]; adjusted HR, 3.723; 95% CI, 0.869–15.947; p=0.077) and low-risk score groups (2 [0.3%]; reference). The risk of stroke was also higher in patients with high-risk scores (23 [2.6%]; adjusted HR, 7.391; 95% CI, 1.723–31.700; p=0.007) compared with moderate-risk score (12 [0.8%]; adjusted HR, 2.348; 95% CI, 0.523–10.533; p=0.265) and low-risk score (2 [0.3%]; reference). However, the risk of MI, BARC types 2, 3, or 5 bleeding, or BARC types 3 or 5 major bleeding did not significantly differ between the CHADS-P2A2RC risk score groups. At the 3-year follow-up, significant differences were not observed in the occurrence of any of the endpoints (MACCE, all-cause death, MI, or stroke) between the 2

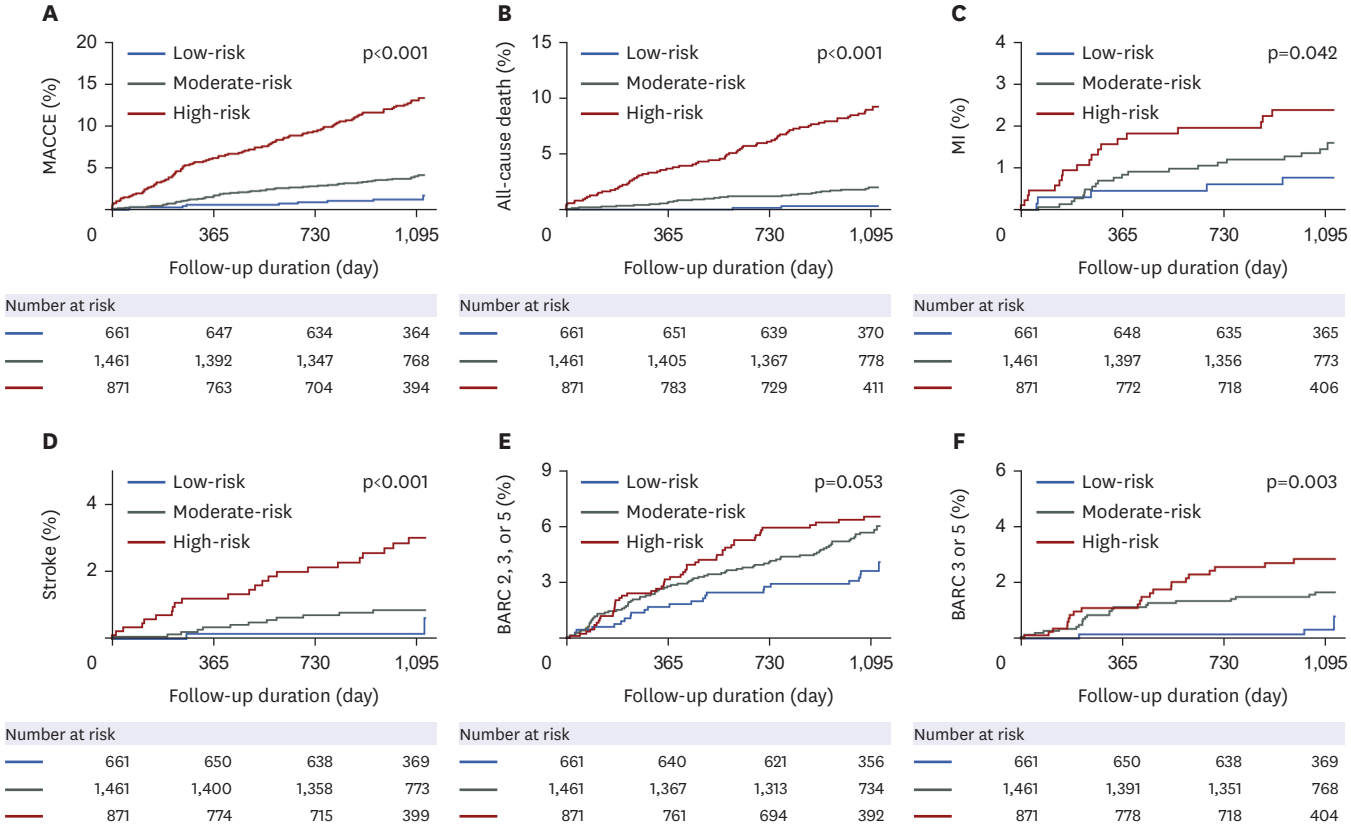

Figure 1. Kaplan-Meier survival curves with Log-rank test of the (A) MACCE, (B) all-cause death, (C) MI, (D) stroke, (E) BARC types 2, 3, or 5, and (F) BARC types 3 or 5. MACCE was defined as a composite of all-cause death, MI, and stroke.
BARC = Bleeding Academic Research Consortium; MACCE = major adverse cardiac cerebral event; MI = myocardial infarction.

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Table 1. Comparison of clinical outcomes based on the CHADS-P2A2RC risk categories

	Overall	Low-risk (CHADS-P2A2RC score ≤1; n=661)	Moderate-risk (CHADS-P2A2RC score 2–3; n=1,461)	High-risk (CHADS-P2A2RC score ≥4; n=871)
MACCE*				
Incidence	170 (5.7)	9 (1.4)	56 (3.8)	105 (12.1)
Unadjusted HR (95% CI)		Reference	2.892 (1.431–5.847); p=0.003	9.994 (5.059–19.743); p<0.001
Adjusted HR (95% CI)		Reference	1.786 (0.868–3.674); p=0.115	2.927 (1.358–6.309); p=0.006
All-cause death				
Incidence	101 (3.4)	2 (0.3)	27 (1.8)	72 (8.3)
Unadjusted HR (95% CI)		Reference	6.258 (1.488–26.316); p=0.012	30.413 (7.462–123.957); p<0.001
Adjusted HR (95% CI)		Reference	3.723 (0.869–15.947); p=0.077	8.690 (2.019–37.403); p=0.004
MI				
Incidence	45 (1.5)	5 (0.8)	21 (1.4)	19 (2.2)
Unadjusted HR (95% CI)		Reference	1.983 (0.731–5.141); p=0.183	3.164 (1.181–8.476); p=0.022
Adjusted HR (95% CI)		Reference	1.570 (0.586–4.204); p=0.369	1.578 (0.531–4.689); p=0.412
Stroke				
Incidence	37 (1.2)	2 (0.3)	12 (0.8)	23 (2.6)
Unadjusted HR (95% CI)		Reference	2.795 (0.625–12.487); p=0.178	9.844 (2.320–41.760); p=0.002
Adjusted HR (95% CI)		Reference	2.348 (0.523–10.533); p=0.265	7.391 (1.723–31.700); p=0.007
BARC type 2,3 or 5				
Incidence	156 (5.2)	24 (3.6)	81 (5.5)	51 (5.9)
Unadjusted HR (95% CI)		Reference	1.578 (1.001–2.488); p=0.050	1.789 (1.106–2.920); p=0.018
Adjusted HR (95% CI)		Reference	1.062 (0.532–2.119); p=0.865	1.259 (0.800–1.979); p=0.320
BARC type 3 or 5				
Incidence	48 (1.6)	3 (0.5)	23 (1.6)	22 (2.5)
Unadjusted HR (95% CI)		Reference	3.572 (1.073–11.898); p=0.038	6.165 (1.845–20.602); p=0.003
Adjusted HR (95% CI)		Reference	2.352 (0.684–8.088); p=0.175	2.288 (0.586–8.936); p=0.234

BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac cerebral event; MI = myocardial infarction.
*MACCE was defined as a composite of all-cause death, MI, and stroke.

antiplatelet strategies, P2Y12 inhibitor monotherapy and prolonged DAPT. However, P2Y12 inhibitor monotherapy was associated with significantly lower risk of overall bleeding (BARC types 2, 3, or 5 bleeding, 3.2% vs. 8.2%, HR, 0.39; 95% CI, 0.28–0.55; p<0.001) and major bleeding (BARC types 3 or 5 bleeding, 1.2% vs. 2.4%, HR, 0.56; 95% CI, 0.31–0.99; p=0.048) compared with prolonged DAPT (**Supplementary Table 4**). In secondary analyses using multivariable Cox proportional hazard models, evidence was not found of an interaction between the 2 antiplatelet strategies and CHADS-P2A2RC risk score categories throughout the strata on any ischemic and bleeding outcomes up to 3 years. Within each CHADS-P2A2RC risk stratum, the 2 antiplatelet groups did not significantly differ in the occurrence of any endpoint (MACCE, all-cause death, MI, or stroke), and the interaction term did not reach statistical significance. Consistent with analyses in the overall cohort, the P2Y12 inhibitor monotherapy compared with the prolonged DAPT was associated with a reduction of BARC types 2, 3, or 5 overall bleeding, and BARC types 3 or 5 major bleeding across the CHADS-P2A2RC risk score categories (**Figure 2**, **Table 2**).

The CHADS-P2A2RC risk score showed good discrimination (C-statistic value=0.728; 95% CI, 0.712–0.744) for MACCE. The overall discriminative and calibration abilities of the CHADS-P2A2RC risk score for all-cause death, MI, stroke, BARC types 2, 3, or 5 overall bleeding, and BARC types 3 or 5 major bleeding are shown in **Supplementary Figure 2** and **Supplementary Table 5**. These results were not different from randomized treatment assignments (P2Y12 inhibitor monotherapy or prolonged DAPT) (**Supplementary Tables 6** and **7**).

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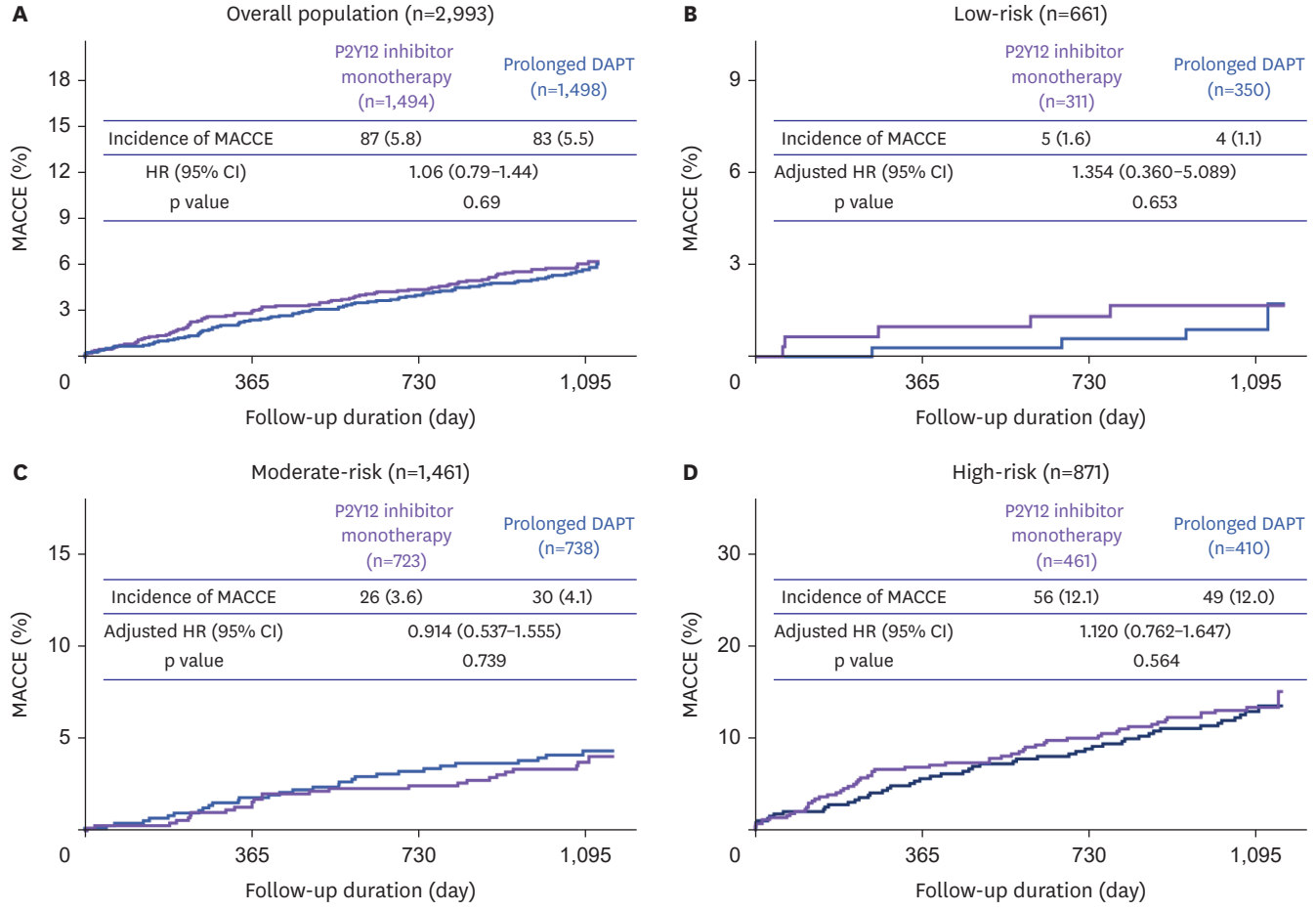

Figure 2. Risk stratification strategies to guide antiplatelet therapy by the CHADS-P2A2RC risk criteria. MACCE was defined as a composite of all-cause death, recurrent myocardial infarction, and stroke.
CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiac cerebral event.

DISCUSSION

The principal findings of this study were that 1) the CHADS-P2A2RC risk score had good clinical value for long-term ischemic events in patients who underwent PCI. 2) Subjects in the high CHADS-P2A2RC risk score group had a substantially higher risk of MACCE, all-cause death, and stroke than subjects in the moderate and low CHADS-P2A2RC risk score groups at follow-up. 3) Evidence was not found in the interactions between CHADS-P2A2RC risk stratification and the effects of 2 antiplatelet treatment regimens on ischemic and bleeding outcomes for up to 3 years, as shown by a negative p-value for interactions. Even when patients were stratified into high ischemic risk using the CHADS-P2A2RC score, P2Y12 inhibitor monotherapy after 3 months of DAPT was associated with a similar rate of ischemic events compared with prolonged DAPT. Furthermore, P2Y12 inhibitor monotherapy compared with prolonged DAPT showed reduced BARC types 2, 3, or 5 bleeding throughout the strata of CHADS-P2A2RC risk score categories.

In retrospective studies, several clinical, procedural, and laboratory factors have been found to be associated with increased ischemic or bleeding risk and have been included in the scores and definitions for risk assessment.[7)8)12)] The most commonly adopted ischemic scores

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Table 2. HRs for antiplatelet therapy regimens

Stratification	P2Y12 Inhibitor monotherapy (n=1,495)	Prolonged DAPT (n=1,498)	Unadjusted HR (95% CI) p value	Interaction p value	Adjusted HR (95% CI) p value	Interaction p value
MACCE*				0.702		0.705
Low-risk (n=661)	5/311 (1.6)	4/350 (1.1)	1.457 (0.391–5.428) p=0.575		1.354 (0.360–5.089) p=0.653	
Moderate-risk (n=1,461)	26/723 (3.6)	30/738 (4.1)	0.883 (0.522–1.493) p=0.643		0.914 (0.537–1.555) p=0.739	
High-risk (n=871)	56/461 (12.1)	49/410 (12.0)	1.039 (0.708–1.525) p=0.845		1.120 (0.762–1.647) p=0.564	
All-cause death				0.710		0.620
Low-risk (n=661)	2/311 (0.6)	0/350 (0.0)	- p=0.459		- p=0.499	
Moderate-risk (n=1,461)	11/723 (1.5)	16/738 (2.2)	0.699 (0.325–1.507) p=0.361		0.653 (0.283–1.509) p=0.318	
High-risk (n=871)	38/461 (8.2)	34/410 (8.3)	1.007 (0.634–1.599) p=0.976		1.139 (0.681–1.903) p=0.620	
MI				0.865		0.841
Low-risk (n=661)	2/311 (0.6)	3/350 (0.9)	0.758 (0.127–4.536) p=0.761		0.758 (0.123–4.655) p=0.765	
Moderate-risk (n=1,461)	10/723 (1.4)	11/738 (1.5)	0.925 (0.393–2.179) p=0.859		0.987 (0.416–2.337) p=0.975	
High-risk (n=871)	8/461 (1.7)	11/410 (2.7)	0.658 (0.265–1.635) p=0.367		0.666 (0.267–1.658) p=0.382	
Stroke				0.962		0.985
Low-risk (n=661)	1/311 (0.3)	1/350 (0.3)	1.264 (0.079–20.292) p=0.869		2.172 (0.094–50.238) p=0.628	
Moderate-risk (n=1,461)	7/723 (1.0)	5/738 (0.7)	1.430 (0.454–4.507) p=0.541		1.395 (0.439–4.435) p=0.572	
High-risk (n=871)	13/461 (2.8)	10/410 (2.4)	1.182 (0.518–2.696) p=0.691		1.399 (0.602–3.251) p=0.434	
BARC types 2, 3, or 5				0.086		0.055
Low-risk (n=661)	2/311 (0.6)	22/350 (6.3)	0.101 (0.024–0.429) p=0.002		0.107 (0.025–0.455) p=0.003	
Moderate-risk (n=1,461)	27/723 (3.7)	54/738 (7.3)	0.503 (0.317–0.798) p=0.004		0.541 (0.336–0.869) p=0.011	
High-risk (n=871)	15/461 (3.3)	36/410 (8.8)	0.371 (0.203–0.678) p=0.001		0.370 (0.199–0.691) p=0.002	
BARC types 3 or 5				0.603		0.628
Low-risk (n=661)	0/311 (0.0)	3/350 (0.9)	0.018 (0.000–212.660) p=0.402		- p=0.960	
Moderate-risk (n=1,461)	10/723 (1.4)	13/738 (1.8)	0.784 (0.344–1.788) p=0.563		0.771 (0.338–1.761) p=0.537	
High-risk (n=871)	7/461 (1.5)	15/410 (3.7)	0.422 (0.172–1.036) p=0.060		0.438 (0.178–1.074) p=0.071	

BARC = Bleeding Academic Research Consortium; CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiac cerebral event; MI = myocardial infarction.
*MACCE was defined as a composite of all-cause death, MI, and stroke.

(i.e., Global Registry of Acute Coronary Events or thrombolysis in myocardial infarction) are mainly used for prognostic stratification. Regarding the use of scores or definitions for ischemic risk stratification to guide the selection of antiplatelet therapy, the recent European Society of Cardiology (ESC) guidelines provide a thrombotic risk stratification for intensified antithrombotic treatment after the standard DAPT duration by defining patients at high or moderate thrombotic risk.[13] However, the ESC criteria could classify more individuals as having high ischemic risk. Recently, Würtz and colleagues[14] developed the CHADS-P2A2RC score as a risk prediction model for the identification of patients without atrial fibrillation at high risk of a first arterial thromboembolic event[9] and reported that the CHADS-P2A2RC score provides better prognostic precision and improved selection

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of at-risk patients compared with the 2019 ESC guideline criteria. Consistent with the previous study, the results of the present study indicate that the CHADS-P2A2RC risk score has a good performance for ischemic risk discrimination in patients who underwent PCI (C-statistic value=0.728 for MACCE). Therefore, the CHADS-P2A2RC score could be used as an immediate, simple, and convenient method of ischemic risk stratification even without using results of procedural and/or cardiac biomarkers. However, the CHADS-P2A2RC risk score did not adequately discriminate BARC types 2, 3, and 5 overall bleeding risk (C-statistic value=0.564). Therefore, a prospective evaluation of the CHADS-P2A2RC-guided approach to antiplatelet decision-making is warranted to confirm its effectiveness.

Although the strategy of P2Y12 inhibitor monotherapy and discontinuing aspirin after a brief period of DAPT was shown to reduce bleeding complications without any trade-off in ischemic events, some concerns may exist regarding the increased risk of thrombotic or ischemic events for some patients with higher ischemic risks. Because some patients with very high ischemic risk might benefit from more intensive antithrombotic therapy.[15)16)] However, the influence of the ischemic scoring system remains unclear regarding the strategy of short DAPT (3 months) followed by P2Y12 inhibitor monotherapy. Therefore, the current study investigated the effect of P2Y12 inhibitor monotherapy vs. prolonged DAPT in patients who underwent PCI across 3 CHADS-P2A2RC risk strata. Consistent with the results of the main SMART-CHOICE trial, a regimen of P2Y12 inhibitor monotherapy compared with continuing DAPT was not associated with increased ischemic risk across the ischemic risk stratum of patients. Furthermore, regarding bleeding endpoints, a regimen of P2Y12 inhibitor monotherapy was associated with a significant and sustained reduction in clinically relevant overall bleeding, irrespective of patient ischemic risk. There are several possible explanations for these observations. First, aspirin might have provided minimal additional inhibition of platelet aggregation, even for patients with higher ischemic features. Antagonism of platelet P2Y12 receptors can inhibit platelet activation and aggregation mediated by thromboxane A2-dependent pathways by reducing platelet production of thromboxane A2 and inhibiting responses following thromboxane A2/prostaglandin H2 receptor activation.[17)18)] In a previous in vitro study, P2Y12 receptor blockade alone caused inhibition of platelet aggregation, which aspirin minimally enhanced.[19)] Second, an increase in bleeding risk needs to be considered due to its negative effect on treatment adherence, potentially leading to higher rates of ischemic events.[20)] Notably, It is well known that the risk factors for bleeding and ischemic events overlap.[5)] In the present study, the high-risk CHADS-P2A2RC group had the highest incidence of BARC types 3 or 5 (2.5%), followed by moderate-risk (1.6%) and low-risk (0.5%) groups (log-rank p=0.003). The cause of ischemic events in these patients may be patient-related factors that trigger transient interruptions in DAPT due to bleeding events that could subsequently lead to ischemic events. Third, individual patient risk using appropriate ischemic risk scoring systems, such as the CHADS-P2A2RC score, may have a limited role in deciding the application of de-escalation or abbreviation of DAPT. The findings in this study are in agreement with recent secondary analyses from large, randomized trials. In the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, irrespective of the presence of diabetes, chronic kidney disease, and their combination, ticagrelor monotherapy reduced the risk of bleeding without a significant increase in ischemic events compared with ticagrelor plus aspirin.[21)] As a general principle, short DAPT may be associated with an increased incidence of MACEs among patients at high thrombotic risk, such as those undergoing complex PCI.[22)] Yet, recently, Gragnano et al.[23)] reported that P2Y12 inhibitor monotherapy after 1-month to 3-month DAPT was associated with similar rates of fatal and ischemic events and lower risk of major bleeding compared

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with standard DAPT, irrespective of PCI complexity. These findings provide reassurance regarding the anti-ischemic efficacy of P2Y12 inhibitor monotherapy; a P2Y12 inhibitor monotherapy after an appropriate DAPT period could be considered even in patients at high risk of ischemic events.[24)25)] Yet, Further studies are warranted to establish the optimal antithrombotic monotherapy after stopping DAPT in patients with high ischemic risk.

The present study had several limitations. First, this was a post-hoc analysis of the SMART-CHOICE study; thus, the results should be interpreted with caution. In addition, the sample size was relatively small, and the clinical event rate was too low to guarantee the conclusion. Therefore, this analysis was underpowered to detect differences in ischemic events and should be viewed strictly as hypothesis-generating. Second, the CHADS-P2A2RC score has not been prospectively validated. Because the risk model does not provide absolute risk estimates, model calibration in the SMART-CHOICE trial could not be performed. In addition, the prevalence of several categories (e.g., peripheral artery disease, congestive heart failure) appeared very low compared with previous reports. It would lead to the analysis being further underpowered to detect differences in ischemic events. Third, clopidogrel was the most prescribed P2Y12 inhibitor for the DAPT regimen, and potent P2Y12 inhibitors, such as ticagrelor or prasugrel, are not frequently prescribed. Although the proportion of potent P2Y12 inhibitor use did not significantly differ between the 2 antiplatelet regimens, the type of P2Y12 inhibitor used might have affected the results as a selection bias. Fourth, all the endpoints in the 3-year analysis are exploratory because the completion rate of the 3-year follow-up was only 92.5%. Last, adjustments could not be made for temporal changes of all individual variables associated with background therapies and treatment targets.

In conclusion, compared with prolonged DAPT, the effect of P2Y12 inhibitor monotherapy after 3 months of DAPT in reducing the risk of clinically relevant bleeding without any increase in all-cause mortality, MI, and stroke was consistent across ischemic categories of the CHADS-P2A2RC risk score. These findings could support the use of a P2Y12 inhibitor monotherapy after a short course of DAPT in patients at high ischemic risk who underwent PCI. Yet, Further studies are warranted to establish the optimal antithrombotic monotherapy after stopping DAPT in patients with high ischemic risk.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Inclusion and exclusion criteria

Supplementary Table 2
The distribution of the components of the CHADS-P2A2RC score

Supplementary Table 3
Baseline characteristics based on the CHADS-P2A2RC risk categories

Supplementary Table 4
Clinical outcomes between the 2 antiplatelet strategies

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Supplementary Table 5
Discrimination and calibration values of the CHADS-P2A2RC risk score on clinical outcomes in the overall population

Supplementary Table 6
Discrimination and calibration values of the CHADS-P2A2RC risk score on clinical outcomes in patients treated with P2Y12 inhibitor monotherapy

Supplementary Table 7
Discrimination and calibration values of the CHADS-P2A2RC risk score on clinical outcomes in patients treated with prolonged dual antiplatelet therapy

Supplementary Figure 1
Study flow diagram.

Supplementary Figure 2
Receiver operating characteristic curves for the (A) MACCE, (B) all-cause death, (C) MI, (D) stroke, (E) BARC types 2, 3, or 5, and (F) BARC types 3 or 5. MACCE was defined as a composite of all-cause death, MI, and stroke.

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