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Clopidogrel Monotherapy in Patients with and without On-Treatment High Platelet Reactivity: a SMART-CHOICE sub-study

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Short title: Impact of HPR on clopidogrel monotherapy

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Abstract

Background: Although $P2Y_{12}$ inhibitor monotherapy has been emerged as a promising alternative for dual antiplatelet therapy (DAPT), there remains concern regarding safety of clopidogrel monotherapy.

Aims: We sought to investigate clinical outcomes of clopidogrel monotherapy in patients with and without on-treatment high platelet reactivity (HPR).

Methods: In the SMART-CHOICE study, 3-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy was compared with 12-month DAPT undergoing percutaneous coronary intervention. Of these, platelet function test was performed for 833 patients with clopidogrel-based therapy. The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE: a composite of all-cause death, myocardial infarction, or stroke) at 12 months.

Results: Overall, 108 (13.0%) patients had HPR on clopidogrel. Patients with HPR had a significantly higher rate of MACCE than patients without HPR (8.7% vs 1.5%, adjusted HR 3.036, 95% CI 1.060-8.693, P=0.038). Treatment effect of clopidogrel monotherapy for the 12-month MACCE was not significantly different compared with DAPT among patients with HPR (8.0% vs. 9.4%, adjusted HR 0.718, 95% CI 0.189-2.737, P=0.628) and without HPR (2.2% vs. 0.9%, adjusted HR 2.587, 95% CI 0.684-9.779, P=0.161; adjusted P for interaction=0.170).

Conclusions: Clopidogrel monotherapy showed treatment effects comparable to DAPT for MACCE in patients with or without HPR. However, HPR was significantly associated with an increased risk of MACCE in clopidogrel-treated patients regardless of maintenance of aspirin.

Clinical Trial Registration: Comparison Between $P2Y_{12}$ Antagonist Monotherapy and Dual Antiplatelet Therapy After DES (SMART-CHOICE), ClinicalTrials.gov: NCT02079194

Key Words: Adjunctive pharmacotherapy; drug-eluting stent; clinical research

Condensed Abstract

There remains a concern regarding the safety of clopidogrel monotherapy, especially in patients with HPR. In this SMART-CHOICE sub-study, 13.0% showed HPR on clopidogrel. HPR was associated with a significantly higher rate of MACCE among clopidogrel-treated patients. Our data suggests that maintaining aspirin might not be helpful in reducing ischemic risk in patients with HPR on clopidogrel.

Abbreviations

CI = confidence intervals

DAPT = dual antiplatelet therapy

MACCE = major adverse cardiovascular and cerebrovascular events

HPR = high platelet reactivity

HR = hazard ratio

PFT = platelet function test

PCI = percutaneous coronary intervention

PRU = platelet reactivity unit

Introduction

The cornerstone of treatment for patients undergoing percutaneous coronary intervention (PCI) is antiplatelet therapy.[1,2] Previous studies have consistently reported that prolonged dual antiplatelet therapy (DAPT) can reduce myocardial infarction and stent thrombosis. However, it also increases the risk of bleeding compared to DAPT for a short or standard duration followed by aspirin monotherapy.[3-5] The optimal duration of DAPT has not yet been determined, although numerous trials have been conducted on this issue. In this regard, $P2Y_{12}$ inhibitor monotherapy after a short duration of DAPT has emerged as a promising novel alternative treatment strategy.[6]

Several randomized trials have consistently reported that a short duration of DAPT followed by $P2Y_{12}$ inhibitor monotherapy and conventional DAPT have comparable protective effects against recurrent ischemic events, leading to reduced risk of bleeding in patients undergoing PCI.[7-11] The Smart Angioplasty Research Team: Comparison Between $P2Y_{12}$ Antagonist Monotherapy vs. Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) trial has demonstrated that 3-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy is noninferior to 12-month DAPT for the composite of all-cause death, myocardial infarction, and stroke in patients receiving contemporary drug-eluting stents (DES).[8]

Clopidogrel was predominantly used as a $P2Y_{12}$ inhibitor for DAPT in the SMART-CHOICE trial. However, there remain concerns on the clopidogrel monotherapy among patients with on-treatment high platelet reactivity (HPR). It has been well known that patients with HPR show an increased risk of ischemic events.[12] Although routine platelet function test (PFT) has not been recommended in contemporary practice, PFT has been assessed in part of patients enrolled

in the SMART-CHOICE trial. In this context, this study sought to investigate whether effects of clopidogrel monotherapy would be similar to clopidogrel-based DAPT for patients with or without HPR.

Methods

Study Design and Population

The study design and main results of the SMART-CHOICE trial have been reported previously.[8,13] Briefly, the SMART-CHOICE was a multicenter, randomized clinical trial that demonstrated the noninferiority of $P2Y_{12}$ inhibitor monotherapy after 3-month DAPT to 12-month DAPT for the composite of ischemic events in patients receiving current-generation DES (ClinicalTrials.gov: NCT02079194). Detailed enrollment criteria are available in the previous report.[8] The Institutional Review Board at each participating center approved the trial protocol. All participants provided written informed consent.

Randomization, Procedure, and Medical Treatment

Patients were randomized into the $P2Y_{12}$ inhibitor monotherapy group (aspirin plus a $P2Y_{12}$ inhibitor for 3 months and a $P2Y_{12}$ inhibitor alone thereafter) or the long-term DAPT group (aspirin plus a $P2Y_{12}$ inhibitor for at least 12 months) in a 1:1 ratio at the index procedure or at the follow-up visit within 3 months after the index procedure. Coronary angiography and PCI were performed according to standard guidelines.[14] The diameter and length of the stent were not restricted, and the stents were limited to second-generation stents which allowed short term DAPT.[8] Antithrombotic treatment related to PCI was also performed according to standard guidelines.[2] All patients received 300 mg of aspirin and 300-600 mg of clopidogrel loading dose orally before PCI,

unless they had previously received these antiplatelet agents. When patients presented with acute coronary syndrome, 60 mg of prasugrel, 180 mg of ticagrelor, or clopidogrel loading dose were used. After the procedure, all patients received DAPT with aspirin 100 mg once daily plus clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily for 3 months. Administration of aspirin was stopped at 3 months after the index procedure in the $P2Y_{12}$ inhibitor monotherapy group but was continued indefinitely in the DAPT group. Administration of the $P2Y_{12}$ inhibitor was continued in both groups. Other medications, including beta-blockers, renin-angiotensin system blockade, and statins, were prescribed according to guidelines if indicated.[2]

Selection of $P2Y_{12}$ Inhibitor and On-treatment Platelet Function Test

In the SMART-CHOICE trial, 3 kinds of $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, and prasugrel) were allowed. The selection of the $P2Y_{12}$ inhibitor was left to the discretion of treating physicians. PFT was performed using a VerifyNow $P2Y_{12}$ assay (Accumetrics Inc., San Diego, CA, USA) at 2-4 weeks after randomization. The decision to perform PFT was fully at the discretion of the attending physician. VerifiyNow tests were performed by an experienced laboratory at each participating center blinded to clinical data following the instructions of the device company. Regardless of results of PFT, patients were assigned to randomized arms until clinical events occurred.

For this post-hoc analysis, HPR on clopidogrel was defined as a platelet reactivity unit (PRU) level of more than 275, based on previous studies for the same regional and racial population.[15,16] The cut-off value of HPR was re-evaluated within the study population. Sensitivity analysis with different cut-off values of HPR (PRU >208) based on the latest expert consensus

document[12] was also performed. Clinical outcomes between $P2Y_{12}$ inhibitor monotherapy after 3-month DAPT and 12-month DAPT were compared among patients with or without HPR. We also compared outcomes between patients receiving clopidogrel and those receiving a potent $P2Y_{12}$ inhibitor monotherapy (**Figure 1**).

Study Endpoints and Definition

The primary endpoint was major adverse cardiovascular and cerebrovascular event (MACCE) defined as a composite of all-cause death, myocardial infarction, and stroke at 12 months. Secondary endpoints included each component of MACCE, cardiac death, stent thrombosis, and bleeding events at 12 months after the index procedure. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of myocardial infarction.[17] All deaths were considered cardiac unless an undisputed noncardiac cause was present. Periprocedural cardiac enzyme level within 48 hours after the index procedure without concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia was not counted as a clinical event. Stroke was defined as any nonconvulsive focal or global neurologic deficit of abrupt onset lasting for more than 24 hours or leading to death, which was caused by ischemia or hemorrhage within the brain. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium classification. Bleeding events were adjudicated and classified according to the Bleeding Academic Research Consortium classification.[18] Major bleeding was defined as Bleeding Academic Research Consortium type 3, 4, or 5 bleeding.

Statistical Analysis

All categorical variables are presented as numbers and relative frequencies (percent). Continuous variables are presented as means and standard deviations or medians with first and third quartiles, according to their distribution, which was checked by Kolmogorov-Smirnov test and visual inspection of Q-Q plots. Discrete or categorical variables were analyzed using the Chi-square or Fisher's exact test. Continuous variables were analyzed using the Mantel-Haenszel statistic or analysis of variance to test differences according to their distribution. Post-hoc analyses were not performed. Cumulative event rates were estimated with the Kaplan-Meier method and compared using the log-rank tests or the Breslow test. We censored patients who were lost to follow-up at the time of the last known contact. The optimal cut-off value of on-treatment PRU for predicting 12-month MACCE after the index procedure was determined if the sum of sensitivity and specificity of PRU was the highest. The derived cut-off value was validated using the maximally selected log-rank statistics as a sensitivity analysis. A Cox proportional hazard regression model was used to calculate hazard ratio (HR) and 95% confidence intervals (CI). The assumption of proportionality was assessed graphically with a log-minus-log plot and tested by Schoenfeld residuals. Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. Multivariable analysis was performed to evaluate the impact of HPR on 12-month MACCE according to clinical characteristics (***Supplementary Table 1***), and the final model was included variables of age, sex, diabetes mellitus, smoking, previous stroke, chronic kidney disease, and LVEF. Multivariable analysis for evaluating impact of treatment strategy was performed according to clinical characteristics (***Table 1***), and the final model was included variables of age and sex.

All analyses were two-tailed, and clinical significance was defined at $P<0.05$. All statistical analyses were performed using SPSS 22.0 for Windows (SPSS-PC, Chicago, IL, USA) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between March 18, 2014, and July 7, 2017, a total of 2,993 patients were enrolled. Of these, 1,495 were randomly assigned to receive $P2Y_{12}$ inhibitor monotherapy and 1498 were randomly assigned to receive 12-month DAPT **(*Figure 1*)**. Clopidogrel was used as a $P2Y_{12}$ inhibitor in 2341 (78.2%) patients and prasugrel or ticagrelor as a potent $P2Y_{12}$ inhibitor was used in 652 (21.8%) patients.

Cut-off Value for HPR Among Patients Receiving Clopidogrel

PFT was performed for 833 (35.6%) patients receiving clopidogrel at a mean of 27 days after the index procedure. The optimal cut-off value of HPR on clopidogrel for predicting 12-month MACCE was more than 275 of PRU in this population (***Supplementary Figure 1***), confirming that the cut-off value of HPR suggested previously was an appropriate determinant for predicting 12-month MACCE. Baseline characteristics of patients divided according to the derived cut-off value are summarized in ***Supplementary Table 1***.

Baseline Characteristics of the Study Population

Table 1 summarizes baseline characteristics of the study population according to the treatment strategy (short term DAPT followed by $P2Y_{12}$ inhibitor monotherapy vs. long-term DAPT) and on-treatment PRU on clopidogrel. Of 833 patients receiving clopidogrel, 108 (13.0%) patients had

HPR, including 53 patients (49.1%) in the $P2Y_{12}$ inhibitor monotherapy group and 55 (50.9%) in the long-term DAPT group. There was no significant difference in the on-treatment PRU level according to the treatment strategy (DAPT 313.4±42.2 vs. $P2Y_{12}$ inhibitor monotherapy 311.0±31.2, P=0.737) in patients with HPR. Among patients with HPR on clopidogrel, the proportion of men was higher in the clopidogrel-based monotherapy than in the DAPT group (58.5% vs. 32.7%, P=0.013). There was no significant difference in other baseline characteristics according to the treatment strategy among patients without HPR on clopidogrel.

Clinical Outcomes According to HPR on Clopidogrel and DAPT Duration

The median follow-up duration of the study population was 365 days. HPR was related to increased risk of MACCE compared to non-HPR (adjusted HR 3.036, 95% CI 1.060-8.693, P=0.038; ***Central Illustration*** **and** ***Supplementary Table 2***). The effect of clopidogrel monotherapy was not significantly different from that of clopidogrel-based long-term DAPT for MACCE among patients with HPR (8.0% vs. 9.4%, adjusted HR 0.718, 95% CI 0.189-2.737, P=0.628) or without HPR on clopidogrel (2.2% vs.0.9%, adjusted HR 2.587, 95% CI 0.684-9.779, P=0.161; ***Table 2*** **and** ***Figure 2***). In the landmark analysis for the 3-month landmark point, results also showed that the clopidogrel monotherapy was comparable to long-term DAPT (***Supplementary Figure 2***). For bleeding events (***Figure 3***), long-term DAPT showed an increased risk of events compared to clopidogrel monotherapy for patients in the non-HPR group. However, the interaction term was not significant (adjusted P for interaction=0.416). Results of subgroup analysis (***Supplementary Figure 3***) for 12-month MACCE rates between clopidogrel monotherapy and DAPT were generally consistent across multiple subgroups. Furthermore, when we defined HPR with a

different cut-off value of 208,[12] the risk of 12-month MACCE of clopidogrel monotherapy was also similar to that of DAPT regardless of HPR (***Supplementary Figure 4***).

Comparison of Outcomes with Patients Receiving Potent P2Y12 Inhibitor Monotherapy

Baseline characteristics of 330 patients receiving potent P2Y12 inhibitor monotherapy are summarized in ***Supplementary Table 3***. The rate of MACCE in patients receiving short-term DAPT followed by monotherapy using a potent P2Y12 inhibitor was 2.2%, significantly lower than that in those with HPR on clopidogrel (2.2% vs. 8.7%, HR 0.250, 95% CI 0.093-0.671, P=0.006; ***Central Illustration***). When we compared effects of potent P2Y12 inhibitor monotherapy to those with clopidogrel-based strategy, a consistently lower rate of MACCE occurred in the group receiving clopidogrel, regardless of clopidogrel monotherapy or long-term DAPT with clopidogrel (HR vs. clopidogrel monotherapy 0.281, 95% CI 0.082-0.961, P=0.043 and HR vs. clopidogrel with aspirin 0.225, 95% CI 0.071-0.708, P=0.011; ***Supplementary Figure 5***).

Discussion

The present study evaluated clinical outcomes of patients receiving clopidogrel-based antiplatelet therapy with or without HPR using data from the SMART-CHOICE trial. Overall, approximately 13% of patients with clopidogrel had HPR. They had a higher risk of 12-month MACCE than those with non-HPR on clopidogrel (***Central Illustration***). Compared with 12-month DAPT, clopidogrel monotherapy had comparable MACCE regardless of HPR on clopidogrel. Meanwhile, potent P2Y12 inhibitor monotherapy was found to be associated with a reduced risk of MACCE compared with clopidogrel-based antiplatelet therapy among patients with HPR on clopidogrel.

Clopidogrel is a prodrug that requires metabolism to inhibit the $P2Y_{12}$ receptor.[19] Response to clopidogrel is variable. In a substantial portion of patients, the response to clopidogrel is inadequate.[12,20] As a result, concerns about clopidogrel monotherapy have been raised, especially in patients with HPR on clopidogrel. The use of potent $P2Y_{12}$ inhibitors may be an alternative for these patients. However, ticagrelor and prasugrel are indicated only in patients with acute coronary syndrome and clopidogrel is the most widely used $P2Y_{12}$ inhibitor in real-world practice.[21] Therefore, to investigate the effect of clopidogrel monotherapy according to on-treatment HPR is of great clinical importance. Although 1-month DAPT followed by clopidogrel monotherapy reduced a composite of cardiovascular and bleeding events in the Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent (STOPDAPT)-2 trial,[10] no data on the safety of clopidogrel monotherapy in patients with HPR on clopidogrel are available. Therefore, we performed a post-hoc study of the SMART-CHOICE trial to compare clopidogrel monotherapy with clopidogrel plus aspirin among patients with or without HPR on clopidogrel.

In this study, patients with HPR on clopidogrel had a significantly higher risk of MACCE than those without HPR on clopidogrel. This result is in line with previous studies showing that HPR on clopidogrel is independently associated with stent thrombosis and MI.[22] However, continuation of aspirin was not associated with favorable outcomes in patients with HPR on clopidogrel or in those with non-HPR on clopidogrel. There are several explanations for these results. First, besides PRU level, patients with HPR on clopidogrel have a higher risk profile than those with non-HPR on clopidogrel. Therefore, maintenance of aspirin might not adequately improve clinical outcomes of patients with HPR on clopidogrel. In these patients, the use of potent $P2Y_{12}$ inhibitors instead of clopidogrel might be more rational than extending the duration of

aspirin treatment. In the present analysis, patients receiving potent $P2Y_{12}$ inhibitor monotherapy had comparable outcomes to those with non-HPR on clopidogrel. They showed better outcomes than those with HPR on clopidogrel regardless of the maintenance of aspirin. Recently, the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial demonstrated that among high-risk patients who underwent PCI and completed 3-month DAPT, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, without showing a higher risk of death, MI, or stroke.[9] Second, in the SMART-CHOICE trial, patients exclusively received second-generation DES, which reduced stent thrombosis and MI significantly compared to the first-generation DES. After 3 months of PCI with second-generation DES, uncovered struts were rare in optical coherence tomography study.[23] In the SMART-CHOICE trial, 3-month DAPT before clopidogrel monotherapy might have resulted in consistent $P2Y_{12}$ inhibitor monotherapy effects on MACCE regardless of the on-treatment platelet reactivity on clopidogrel.

The proportion of patients with HPR on clopidogrel seemed to be low in this study compared to that in previous studies.[15,16] It is difficult to know the exact causes, the timing of PRU measurements might explain such results. While on-treatment PFT was evaluated at approximately 4 weeks after the index procedure in the present analysis, previous studies reported PRU levels immediately or shortly after the index procedure.[24-27] Response to clopidogrel varied significantly over time, being higher at baseline than that at 1 month after PCI.[28] Although the optimal timing of PRU assessment remains controversial, in our opinion, it is rational to allow sufficient time before measuring on-treatment platelet reactivity.

Limitations

This study has several limitations. First, the number of patients with HPR on clopidogrel and their rates of adverse events at 12 months were relatively small to have adequate power to confirm our findings. Second, PFTs were not available at all centers and performed based on clinicians' discretion. As a result, not all patients underwent PFT, and 35.6% of patients receiving clopidogrel were assessed with PFT. There is no doubt there might be a selection bias. Patients at high-risk who might benefit from conventional DAPT might have been excluded. Additionally, the study protocol did not define the exact time for blood collection according to the last clopidogrel administration. Furthermore, although CYP2C19 genotyping might be used as an optional tool for guiding antiplatelet therapy,[12,29] it was not available for this study. Third, the attending physicians selected the type of $P2Y_{12}$ inhibitors. Ticagrelor or prasugrel might have been prescribed instead of clopidogrel in patients whose clopidogrel monotherapy might be inadequate to prevent adverse events. Although the selection of $P2Y_{12}$ inhibitors was done at the timing of randomization and before measuring on-treatment PRU on clopidogrel, there might be a potential of selection bias in this analysis. Fourth, although the SMART-CHOICE trial was a randomized study, this was a post-hoc study. Randomization was not stratified by on-treatment platelet reactivity on clopidogrel. Although baseline characteristics were mostly well balanced between the groups, unmeasured factors might have affected study outcomes. Fifth, cut-off value of HPR remains controversial and the previous expert consensus document has recommended PRU >208.[12,25,26] However, it should be noted that this cut-off value was based on a Western population study.[30] For East-Asians, previous studies have reported that the cut-off value was to be higher than Westerns. Additionally, when we analyzed patients with cut-off for HPR more than 208, results consistently showed no significant difference in the treatment effect of

clopidogrel monotherapy regardless of HPR. Sixth, information on the use of aspirin or a $P2Y_{12}$ inhibitor was assessed at each follow-up. In the SMART-CHOICE trial, the overall adherence to the study protocol was 79.3% in the $P2Y_{12}$ inhibitor monotherapy group and 95.2% in the DAPT group. In the main paper, intention-to-treat and per-protocol analyses showed similar conclusions, suggesting that potential biases caused by differential adherence and treatment crossover are likely to be small. However, in the present study, it was hard to analyze exact drug adherences. Thus, these results were not liberal from non-adherence issues.

Conclusion

Although $P2Y_{12}$ inhibitor monotherapy after short DAPT has emerged as a novel promising antiplatelet strategy after PCI, HPR on clopidogrel is one of major concerns with clopidogrel monotherapy. Our results indicated that clopidogrel monotherapy and clopidogrel plus aspirin showed comparable treatment effects for MACCE among patients with or without HPR. However, HPR on clopidogrel was significantly associated with an increased risk of MACCE in clopidogrel-treated patients regardless of maintenance of aspirin. A potent $P2Y_{12}$ inhibitor rather than prolonged clopidogrel-based DAPT can be considered for patients with HPR on clopidogrel. To validate this escalating strategy of $P2Y_{12}$ inhibitors according to the on-treatment PRU, large-scaled and long-term clinical trials are needed.

Impact on daily practice

This sub-study of SMART-CHOICE tested the clinical impact of high platelet reactivity (HPR) on clopidogrel of those who were treated with clopidogrel-based antiplatelet therapy after PCI. Clopidogrel monotherapy and clopidogrel plus aspirin showed comparable treatment effects on major adverse cardiovascular and cerebrovascular events (MACCEs) among patients with or without HPR. However, HPR was significantly associated with an increased risk of ischemic events. Dual antiplatelet therapy (DAPT) had no additional benefit in reducing ischemic events. Potent P2Y12 inhibitor monotherapy rather than prolonged clopidogrel-based DAPT might be a rational antiplatelet strategy in patients with HPR on clopidogrel. However, this strategy requires confirmation with a large clinical trial.

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Conflict of Interest Disclosures

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Figure Legends

Central illustration. Comparison of 12-Month MACCE Rate According to On-treatment PRU Level and Type of $P2Y_{12}$ inhibitor.

The cumulative incidence of MACCE at 12 months was compared according to HPR among patients receiving clopidogrel. It was also compared to those who received potent $P2Y_{12}$ inhibitor monotherapy. The incidence of 12-month MACCE was significantly higher in patients with HPR than in other groups.

Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events; other abbreviations as in Figure 1.

Figure 1. Study Flow.

Abbreviations: DAPT, dual antiplatelet therapy; HPR, high platelet reactivity; PRU, platelet reactivity unit.

Figure 2. Comparison of 12-Month MACCE Rate According to HPR on Clopidogrel.

The cumulative incidence of MACCE at 12 months was compared between long-term DAPT and monotherapy groups for those **(A)** with HPR (>275) or **(B)** without HPR (≤275) among patients on clopidogrel.

* Multivariable analysis after adjusting for age and sex.

Abbreviations: CI, confidence interval; HR, hazard ratio; other abbreviations as in Figure 1.

Figure 3. Comparison of 12-Month BARC 2-5 Bleeding Rate According to HPR on Clopidogrel.

The cumulative incidence of BARC 2-5 Bleeding at 12 months was compared between long-term DAPT and monotherapy groups for those **(A)** with HPR (>275) or **(B)** without HPR (≤275) among patients on clopidogrel.

* Multivariable analysis after adjusting for age and sex.

Abbreviations: BARC, Bleeding Academic Research Consortium; other abbreviations as in Figures 1 and 3.

Table 1. Baseline Characteristics of Study Population

	Non-HPR (≤275) n=725			HPR (>275) n=108		
	Long-term DAPT	**$P2Y_{12}$ inhibitor monotherapy**	**P value**	**Long-term DAPT**	**$P2Y_{12}$ inhibitor monotherapy**	**P value**
	356/725 (49.1%)	**369/725 (50.9%)**		**55/108 (50.9%)**	**53/108 (49.1%)**	
Test for PRU						
PCI-to-test, days	26.7 ± 24.1	28.7 ± 24.9	0.278	20.4 ± 18.9	25.0 ± 30.7	0.382
PRU value	172.0 ± 63.2	177.2 ± 62.1	0.266	313.4 ± 42.2	311.0 ± 31.2	0.737
General characteristics						
Age, years	63.6 ± 10.1	65.0 ± 9.9	0.068	69.5 ± 8.7	70.5 ± 7.6	0.525
Men	271 (76.1)	270 (73.2)	0.408	18 (32.7)	31 (58.5)	0.013
Body mass index, kg/m^2	24.5 ± 2.8	24.3 ± 2.9	0.624	24.2 ± 3.1	24.4 ± 3.1	0.724
Comorbidities						
Hypertension	220 (61.8)	218 (59.1)	0.501	37 (67.3)	34 (64.2)	0.889
Diabetes mellitus	125 (35.1)	136 (36.9)	0.681	28 (50.9)	23 (43.4)	0.556
Dyslipidemia	149 (41.9)	158 (42.8)	0.851	23 (41.8)	20 (37.7)	0.813
Current smoking	57 (16.0)	68 (18.4)	0.445	4 (7.3)	7 (13.2)	0.483
Previous revascularization	49 (13.8)	55 (14.9)	0.740	10 (18.2)	4 (7.5)	0.174
Previous stroke	26 (7.3)	23 (6.2)	0.670	7 (12.7)	6 (11.3)	1.000
Previous myocardial infarction	21 (5.9)	19 (5.1)	0.780	1 (1.8)	2 (3.8)	0.974
Chronic kidney disease	8 (2.2)	10 (2.7)	0.872	6 (10.9)	2 (3.8)	0.295
LVEF, %	61.4 ± 9.9	62.5 ± 9.2	0.147	60.9 ± 9.8	57.4 ± 12.1	0.113
Clinical presentation			**0.971**			**0.683**

Stable ischemic heart disease	205 (57.6)	214 (58.0)		26 (47.3)	22 (41.5)	
Acute coronary syndrome	151 (42.4)	155 (42.0)		29 (52.7)	31 (58.5)	
Location of lesions						
Left main	5 (1.4)	13 (3.5)	0.093	2 (3.6)	1 (1.9)	1.000
Left anterior descending artery	229 (64.3)	236 (64)	0.979	37 (67.3)	32 (60.4)	0.585
Left circumflex	94 (26.4)	95 (25.7)	0.906	13 (23.6)	12 (22.6)	1.000
Right coronary artery	135 (37.9)	122 (33.1)	0.197	17 (30.9)	17 (32.1)	1.000
Lesion complexity						
Calcified	58 (16.3)	63 (17.1)	0.842	15 (27.3)	16 (30.2)	0.903
Bifurcation	51 (14.3)	60 (16.3)	0.525	5 (9.1)	4 (7.5)	1.000
Thrombotic	14 (3.9)	18 (4.9)	0.655	2 (3.6)	5 (9.4)	0.405
Use of intravascular ultrasound	81 (22.8)	78 (21.2)	0.677	18 (32.7)	14 (26.4)	0.612
Multivessel intervention	101 (28.4)	98 (26.6)	0.643	14 (25.5)	8 (15.1)	0.272
Multilesion intervention	123 (34.6)	110 (29.8)	0.198	16 (29.1)	11 (20.8)	0.437
Total stent number	1.5 ± 0.8	1.5 ± 0.8	0.587	1.5 ± 0.8	1.3 ± 0.7	0.189
Total stent length, mm	39.3 ± 22.5	38.2 ± 22.5	0.530	41.0 ± 27.8	34.8 ± 19.2	0.177

Values expressed as mean ± SD or number (%).

Abbreviations: HPR, high platelet reactivity; PRU, platelet reactivity unit; LVEF, left ventricular ejection fraction.

Table 2. Comparison of 12-Month Clinical Outcome According to the Treatment Strategy (Clopidogrel-Based Monotherapy vs. Long-term DAPT) within Clopidogrel Strata and HPR

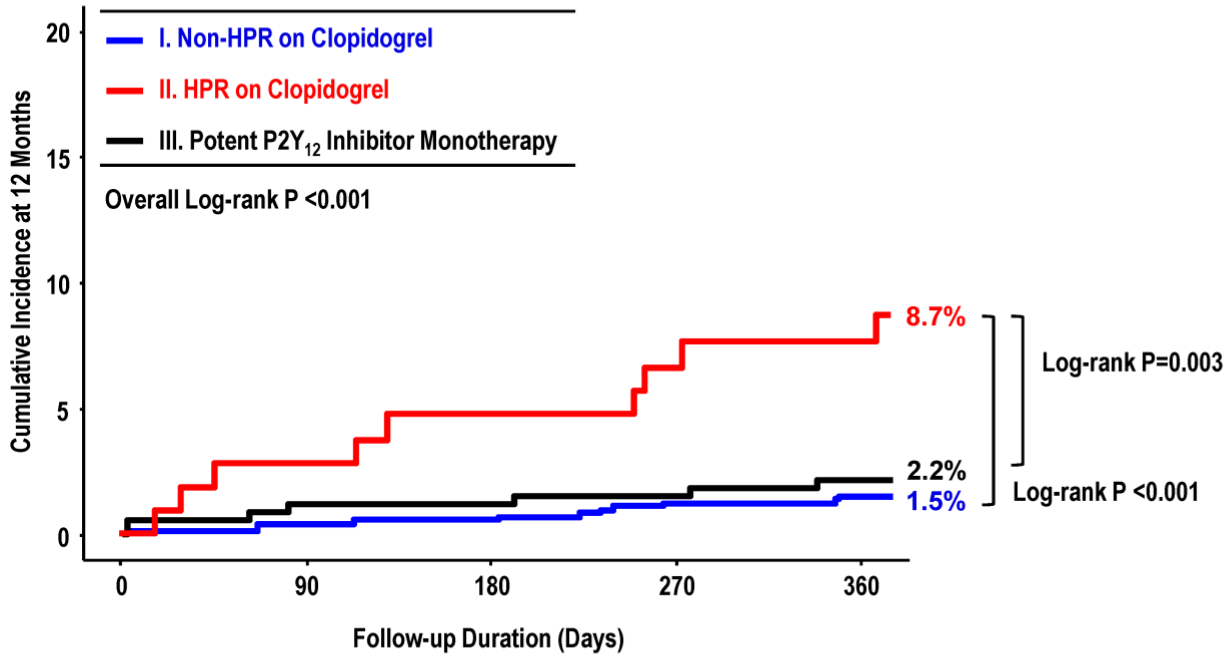
	HPR on Clopidogrel						Non-HPR on Clopidogrel						Adjusted P value for interaction
	Long-term DAPT	$P2Y_{12}$ inhibitor monotherapy	Crude HR (95% CI)	P value	Adjusted* HR (95% CI)	P value	Long-term DAPT	$P2Y_{12}$ inhibitor monotherapy	Crude HR (95% CI)	P value	Adjusted* HR (95% CI)	P value	
	n=55	**n=53**					**n=356**	**n=369**					
MACCE†	9.4% (5)	8.0% (4)	0.806 (0.217-3.003)	0.748	0.718 (0.189-2.737)	0.628	0.9% (3)	2.2% (8)	2.587 (0.686-9.752)	0.160	2.587 (0.684-9.779)	0.161	0.170
All-cause death	5.7% (3)	3.8% (2)	0.666 (0.111-3.988)	0.657	0.706 (0.115-4.342)	0.707	0.6% (2)	0.3% (1)	0.483 (0.044-5.323)	0.552	0.456 (0.041-5.044)	0.522	0.807
Cardiac death	5.7% (3)	3.8% (2)	0.666 (0.111-3.988)	0.657	0.706 (0.115-4.342)	0.707	0.6% (2)	0.3% (1)	0.483 (0.044-5.323)	0.552	0.456 (0.041-5.044)	0.522	0.807
Myocardial infarction	3.8% (2)	0% (0)	0 (0-inf)	0.999	0 (0-inf)	0.999	0.3% (1)	1.1% (4)	3.854 (0.431-34.480)	0.228	3.667 (0.408-32.912)	0.246	0.998
Stroke	3.9% (2)	4.2% (2)	0.513 (0.046-5.653)	0.585	0.983 (0.124-7.791)	0.987	0% (0)	0.8% (3)	0 (0-inf)	0.999	0 (0-inf)	0.999	0.998
Stent thrombosis	1.8% (1)	0% (0)	0 (0-inf)	0.999	0 (0-inf)	1.000	0% (0)	0% (0)	-	-	-	-	-
BARC 2-5 bleeding	5.8% (3)	3.8% (2)	0.664 (0.111-3.973)	0.654	0.936 (0.143-6.111)	0.945	5.1% (18)	1.9% (7)	0.370 (0.155-0.887)	0.026	0.368 (0.153-0.882)	0.025	0.416
Major bleeding‡	0% (0)	3.8% (2)	0 (0-inf)	0.999	0 (0-inf)	0.999	1.4% (5)	0.5% (2)	0.384 (0.074-1.978)	0.252	0.366 (0.071-1.888)	0.230	0.997

The cumulative incidence of clinical outcomes is presented as Kaplan-Meier estimates during a median follow-up of 365.0 days. The number of patients with specific events is also presented in parentheses.

* Multivariable analysis after adjusting for age and sex.
† MACCE includes all-cause death, any myocardial infarction, and stroke.
‡ BARC type 3 to 5 bleeding.

Abbreviations: HPR, high platelet reactivity; PRU, platelet reactivity unit; MACCE, major adverse cardiac and cerebrovascular events; BARC, Bleeding Academic Research Consortium.

Central Illustration. Comparison of 12-Month MACCE Rate According to On-treatment PRU Level and Type of $P2Y_{12}$ inhibitor.



Number at risk

Group I	725	721	718	714	589
Group II	108	101	99	97	85
Group III	330	319	314	309	263

Figure 1. Study Flow

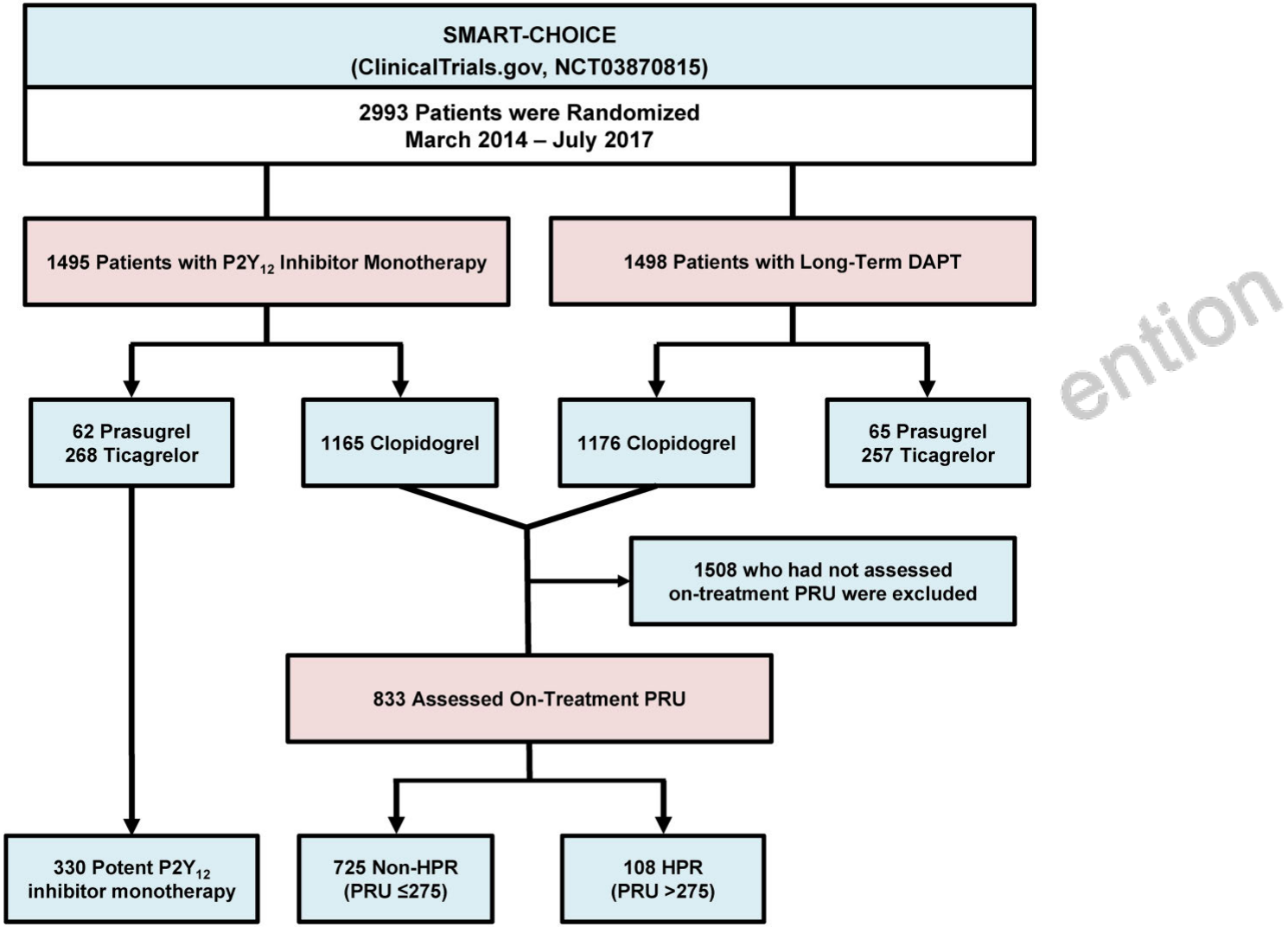


Figure 2. Comparison of 12-Month MACCE Rate According to HPR on Clopidogrel.

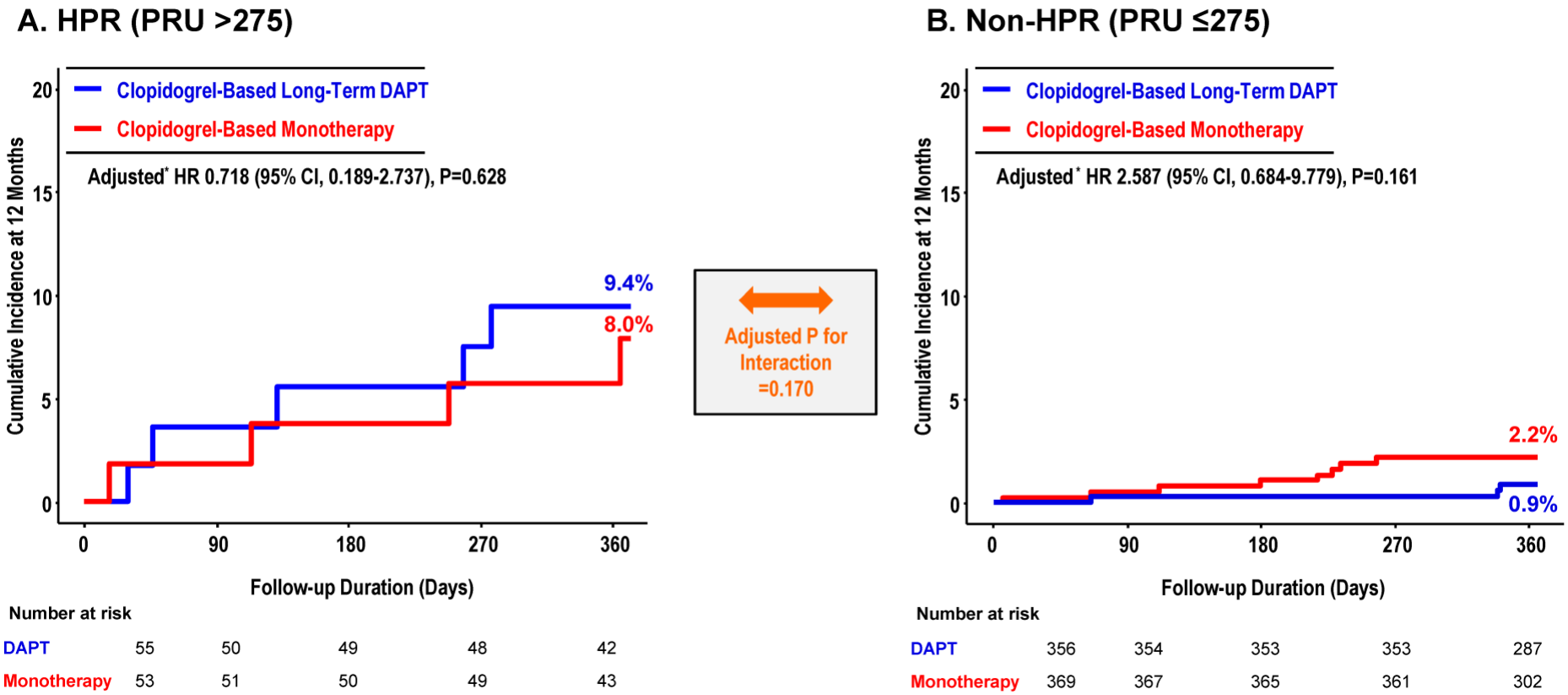
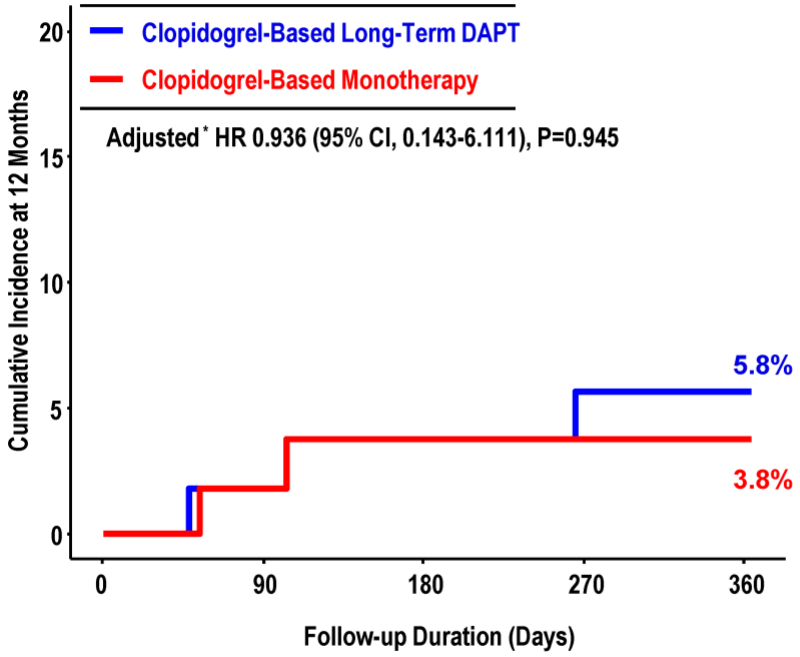


Figure 3. Comparison of 12-Month BARC 2-5 Bleeding Rate According to HPR on Clopidogrel.

A. HPR (PRU >275)

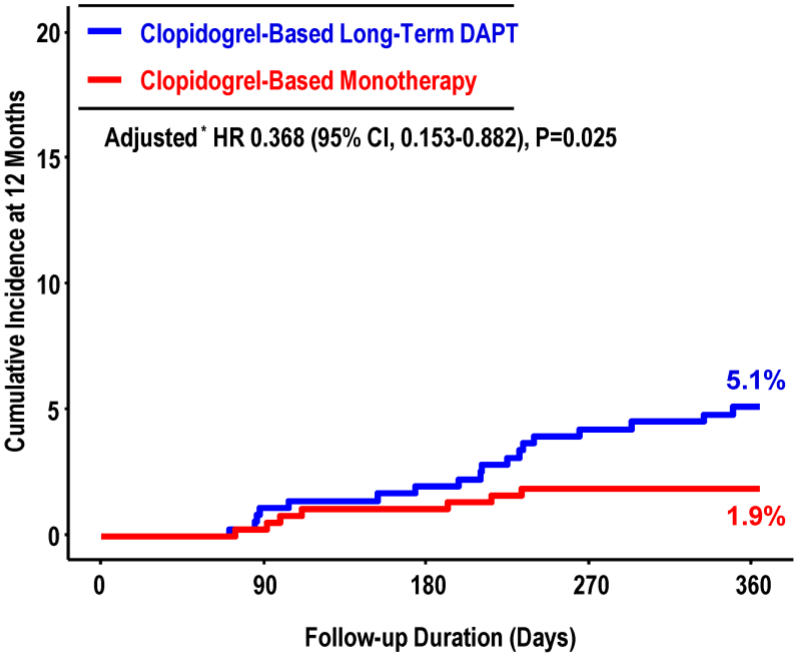


Number at risk

DAPT	55	50	48	47	41
Monotherapy	53	51	49	48	42

Adjusted P for Interaction =0.416

B. Non-HPR (PRU ≤275)



Number at risk

DAPT	356	351	348	340	272
Monotherapy	369	368	364	361	302

Supplementary Appendix

Clopidogrel Monotherapy in Patients with and without On-Treatment High Platelet Reactivity : a SMART-CHOICE sub-study

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(1) Supplementary Tables

(2) Supplementary Figure and Figure Legend

(1) Supplementary Tables

Supplementary Table 1. Baseline Characteristics According to HPR on Clopidogrel

	Total Population	Non-HPR (≤275)	HPR (>275)	P value
	n=833	**725/833 (87.0%)**	**108/833 (13.0%)**	
Test for PRU				
PCI-to-test, days	27.1 ± 24.6	27.8 ± 24.5	22.7 ± 25.3	0.057
PRU value	192.5 ± 75.7	174.7 ± 62.7	312.2 ± 37.1	<0.001
General characteristics				
Age, years	65.1 ± 10.0	64.3 ± 10.0	70.0 ± 8.1	<0.001
Men	590 (70.8)	541 (74.6)	49 (45.4)	<0.001
Body mass index, kg/m^2	24.4 ± 2.9	24.4 ± 2.8	24.3 ± 3.1	0.640
Comorbidities				
Hypertension	509 (61.1)	438 (60.4)	71 (65.7)	0.340
Diabetes mellitus	312 (37.5)	261 (36.0)	51 (47.2)	0.032
Dyslipidemia	350 (42.0)	307 (42.3)	43 (39.8)	0.695
Current smoking	136 (16.3)	125 (17.2)	11 (10.2)	0.087
Previous revascularization	118 (14.2)	104 (14.3)	14 (13.0)	0.813
Previous stroke	62 (7.4)	49 (6.8)	13 (12.0)	0.080
Previous myocardial infarction	43 (5.2)	40 (5.5)	3 (2.8)	0.348
Chronic kidney disease	26 (3.1)	18 (2.5)	8 (7.4)	0.014

LVEF, %	61.6 ± 9.8	62.0 ± 9.6	59.2 ± 11.1	0.020
Clinical presentation				**0.012**
Stable ischemic heart disease	467 (56.1)	419 (57.8)	48 (44.4)	
Acute coronary syndrome	366 (43.9)	306 (42.2)	60 (55.6)	
Location of lesions				
Left main	21 (2.5)	18 (2.5)	3 (2.8)	0.746
Left anterior descending artery	534 (64.1)	465 (64.1)	69 (63.9)	1.000
Left circumflex artery	214 (25.7)	189 (26.1)	25 (23.1)	0.596
Right coronary artery	291 (34.9)	257 (35.4)	34 (31.5)	0.485
Lesion complexity				
Calcified	152 (18.3)	121 (16.7)	31 (28.7)	0.004
Bifurcation	120 (14.4)	111 (15.3)	9 (8.3)	0.074
Thrombotic	39 (4.7)	32 (4.4)	7 (6.5)	0.483
Use of intravascular ultrasound	191 (23.0)	159 (22.0)	32 (29.6)	0.100
Multivessel intervention	221 (26.5)	199 (27.4)	22 (20.4)	0.151
Multilesion intervention	260 (31.2)	233 (32.1)	27 (25.0)	0.167
Total stent number	1.5 ± 0.8	1.5 ± 0.8	1.4 ± 0.7	0.317
Total stent length, mm	38.6 ± 22.7	38.7 ± 22.5	37.9 ± 24.1	0.730

Values expressed as mean ± SD or number (%).

Abbreviations: HPR, high platelet reactivity; PRU, platelet reactivity unit; LVEF, left ventricular ejection fraction.

Supplementary Table 2. Clinical Outcomes According to HPR on Clopidogrel and Potent $P2Y_{12}$ Inhibitor Monotherapy

	Non-HPR on Clopidogrel n=725	HPR on Clopidogrel n=108	Potent $P2Y_{12}$ Inhibitor Monotherapy n=330	P Value
MACCE†	1.5% (11)	8.7% (9)	2.2% (7)	<0.001
All-cause death	0.4% (3)	4.8% (5)	1.2% (4)	<0.001
Cardiac death	0.4% (3)	4.8% (5)	0.6% (2)	<0.001
Myocardial infarction	0.7% (5)	1.9% (2)	0.6% (2)	0.385
Repeat revascularization	2.7% (19)	2.1% (2)	1.0% (3)	0.223
Stroke	0.4% (3)	4.0% (4)	0.3% (1)	0.007
Stent thrombosis	0% (0)	0.9% (1)	0% (0)	0.008
BARC 2-5 bleeding	3.5% (25)	4.8% (5)	1.3% (4)	0.079
Major bleeding‡	1.0% (7)	1.9% (2)	0.6% (2)	0.488

The cumulative incidence of clinical outcomes is presented as Kaplan-Meier estimates during a median follow-up of 365.0 days. The number of patients with specific events is also presented in parentheses. The P values were log-rank or Breslow P value in survival analysis.

† MACCE includes all-cause death, any myocardial infarction, and stroke.
‡ BARC type 3 to 5 bleeding.

Abbreviations: HPR, high platelet reactivity; PRU, platelet reactivity unit; MACCE, major adverse cardiac and cerebrovascular events; BARC, Bleeding Academic Research Consortium

Supplementary Table 3. Baseline Characteristics According to Treatment Strategy for the Patients with HPR on Clopidogrel and Potent $P2Y_{12}$ Inhibitor Monotherapy

	HPR on Clopidogrel		Potent $P2Y_{12}$ Inhibitor Monotherapy n=330	P value
	Long Term DAPT n=55	Monotherapy n=53		
General characteristics				
Age, years	69.5 ± 8.7	70.5 ± 7.6	60.4 ± 10.4	<0.001
Men	18 (32.7)	31 (58.5)	278 (84.2)	0.001
Body mass index, kg/m^2	24.2 ± 3.1	24.4 ± 3.1	24.7 ± 3.5	0.537
Comorbidities				
Hypertension	37 (67.3)	34 (64.2)	186 (56.4)	0.217
Diabetes mellitus	28 (50.9)	23 (43.4)	115 (34.8)	0.051
Dyslipidemia	23 (41.8)	20 (37.7)	162 (49.1)	0.224
Current smoking	4 (7.3)	7 (13.2)	157 (47.7)	0.001
Previous revascularization	10 (18.2)	4 (7.5)	13 (3.9)	0.001
Previous stroke	7 (12.7)	6 (11.3)	12 (3.6)	0.005
Previous myocardial infarction	1 (1.8)	2 (3.8)	8 (2.4)	0.793
Previous bleeding	3 (5.5)	4 (7.5)	8 (2.4)	0.110
Chronic kidney disease	6 (10.9)	2 (3.8)	6 (1.8)	0.002
LVEF, %	60.9 ± 9.8	57.4 ± 12.1	58.3 ± 11.4	0.237
Clinical presentation				**<0.001**
Stable ischemic heart disease	26 (47.3)	22 (41.5)	25 (7.6)	
Acute coronary syndrome	29 (52.7)	31 (58.5)	305 (92.4)	

Location of lesions				
Left main	2 (3.6)	1 (1.9)	5 (1.5)	0.553
Left anterior descending artery	37 (67.3)	32 (60.4)	195 (59.1)	0.517
Left circumflex artery	13 (23.6)	12 (22.6)	91 (27.6)	0.659
Right coronary artery	17 (30.9)	17 (32.1)	120 (36.4)	0.648
Lesion complexity				
Calcified	15 (27.3)	16 (30.2)	44 (13.4)	0.001
Bifurcation	5 (9.1)	4 (7.5)	57 (17.3)	0.075
Thrombotic	2 (3.6)	5 (9.4)	48 (14.6)	0.058
Use of intravascular ultrasound	18 (32.7)	14 (26.4)	110 (33.5)	0.590
Multivessel intervention	14 (25.5)	8 (15.1)	79 (23.9)	0.330
Multilesion intervention	16 (29.1)	11 (20.8)	99 (30.0)	0.385
Total stent number	1.5 ± 0.8	1.3 ± 0.7	1.5 ± 0.8	0.351
Total stent length, mm	41.0 ± 27.8	34.8 ± 19.2	39.2 ± 23.1	0.339

Values expressed as mean ± SD or number (%).

Abbreviations: HPR, high platelet reactivity; PRU, platelet reactivity unit; LVEF, left ventricular ejection fraction.

(2) Supplementary Figure and Figure Legend

Supplementary Figure 1. Determination of Cut-off Value of PRU for Predicting 12-Month MACCE.

The optimal cut-off value of on-treatment PRU for the occurrence of MACCE was 275. The PRU showed good diagnostic accuracy for MACCE at 12 months.

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; NPV, negative predictive value; PPV, positive predictive value; PRU, platelet reactivity unit.

Supplementary Figure 2. Landmark Analysis for the 3-Month Landmark Point for MACCE.

The landmark analysis showed consistent results that long-term DAPT showed no additional clinical benefit within and after 3 months in the patients with HPR or without HPR.

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; HPR, high platelet reactivity; DAPT, dual antiplatelet therapy; PRU, platelet reactivity unit.

Supplementary Figure 3. Subgroup Analysis of the Primary Composite Outcomes at 12 months.

The primary endpoint was the MACCE, composite of all-cause death, myocardial infarction, or stroke. Event rates were based on Kaplan-Meier estimates; the rate is not the same as the ratio of the numerator and denominator. There were no significant differences between the treatment effects of clopidogrel monotherapy and DAPT across all subgroups.

Abbreviations: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; HPR, high platelet reactivity; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiovascular and cerebrovascular events; No., number; PCI, percutaneous coronary intervention; PRU, platelet reactivity unit; SIHD, stable ischemic heart disease.

Supplementary Figure 4. Comparison of 12-Month MACCE Rate According to Different Cut-off Value of HPR on Clopidogrel.

The cumulative incidence of MACCE at 12 months was compared between long-term DAPT and monotherapy groups for those **(A)** with HPR (>208) or **(B)** without HPR (≤208) among patients on clopidogrel.

* Multivariable analysis after adjusting for age and sex.

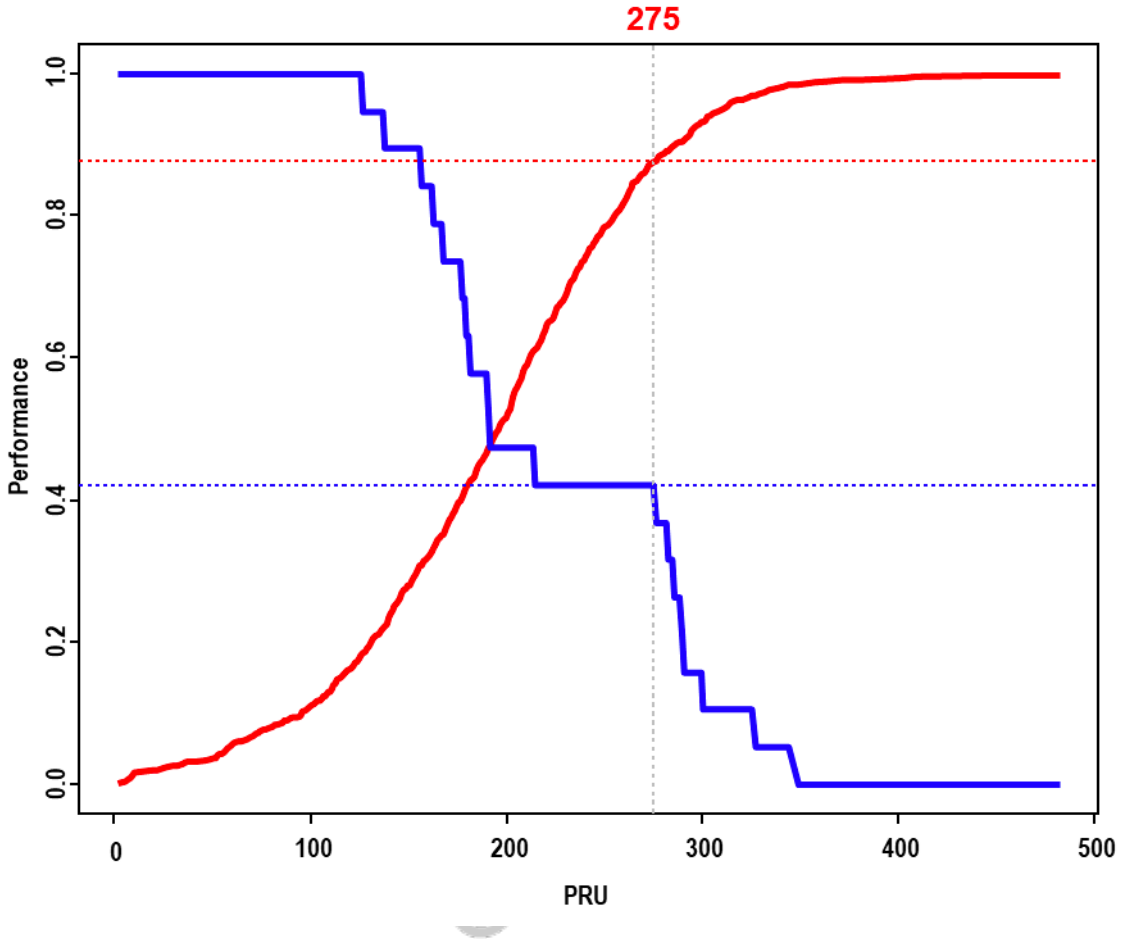
Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; HPR, high platelet reactivity; HR, hazard ratio; PRU, platelet reactivity unit.

Supplementary Figure 5. Prognostic Impact of Potent $P2Y_{12}$ Inhibitor Monotherapy Compared with the Patients with HPR on Clopidogrel.

The potent $P2Y_{12}$ inhibitor monotherapy was associated with a lower risk of MACCE at 12 months, regardless of treatment strategy (monotherapy or long-term DAPT) in the patients with HPR on clopidogrel.

Abbreviations: HPR, high platelet reactivity; dual antiplatelet therapy.

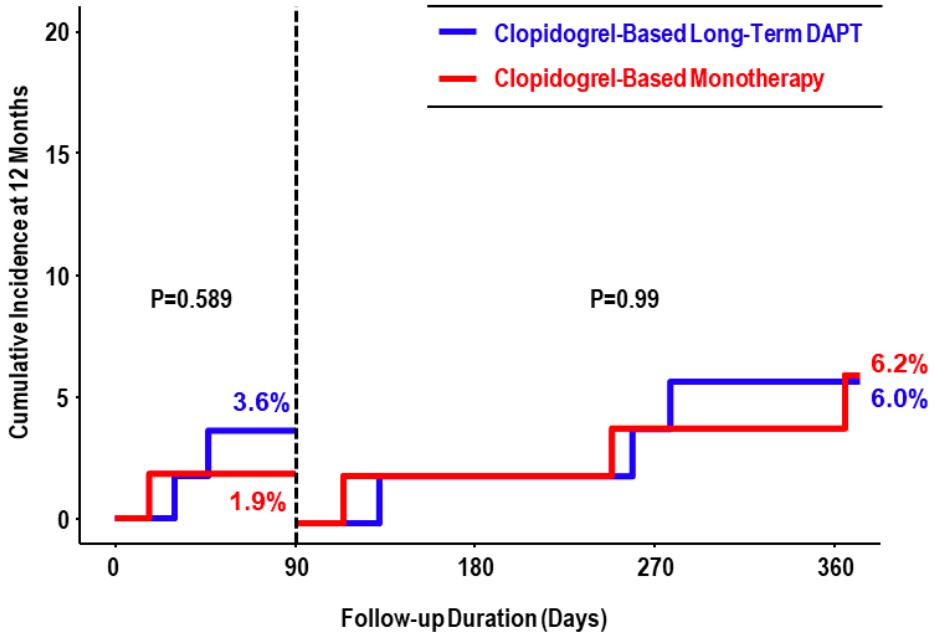
Supplementary Figure 1. Determination of Cut-off Value of PRU for Predicting 12-Month MACCE.



Event (+) vs. Event (-)	
Cut-off	275
Sensitivity	42.1%
Specificity	87.7%
PPV	7.4%
NPV	98.5%
Accuracy	86.7%

Supplementary Figure 2. Landmark Analysis at the 3-Month Landmark Point for MACCE

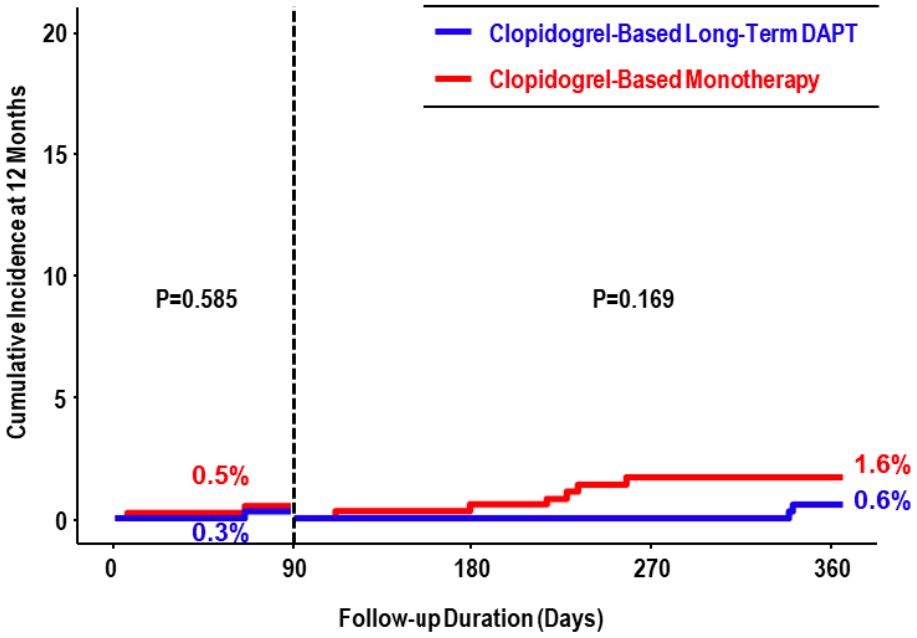
A. HPR (PRU >275)



Number at risk

DAPT	55	50	49	48	42
Monotherapy	53	51	50	49	43

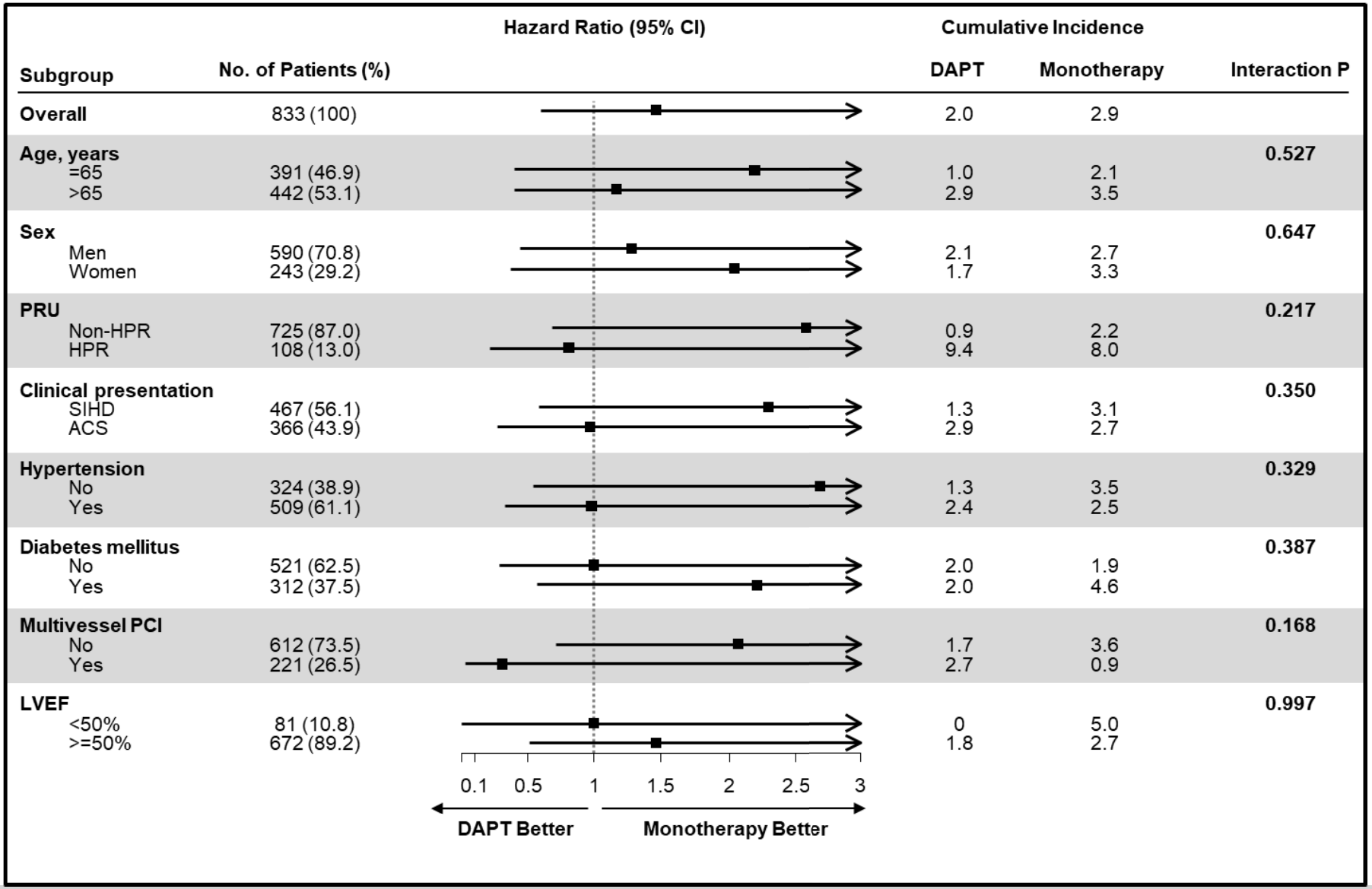
B. Non-HPR (PRU ≤275)



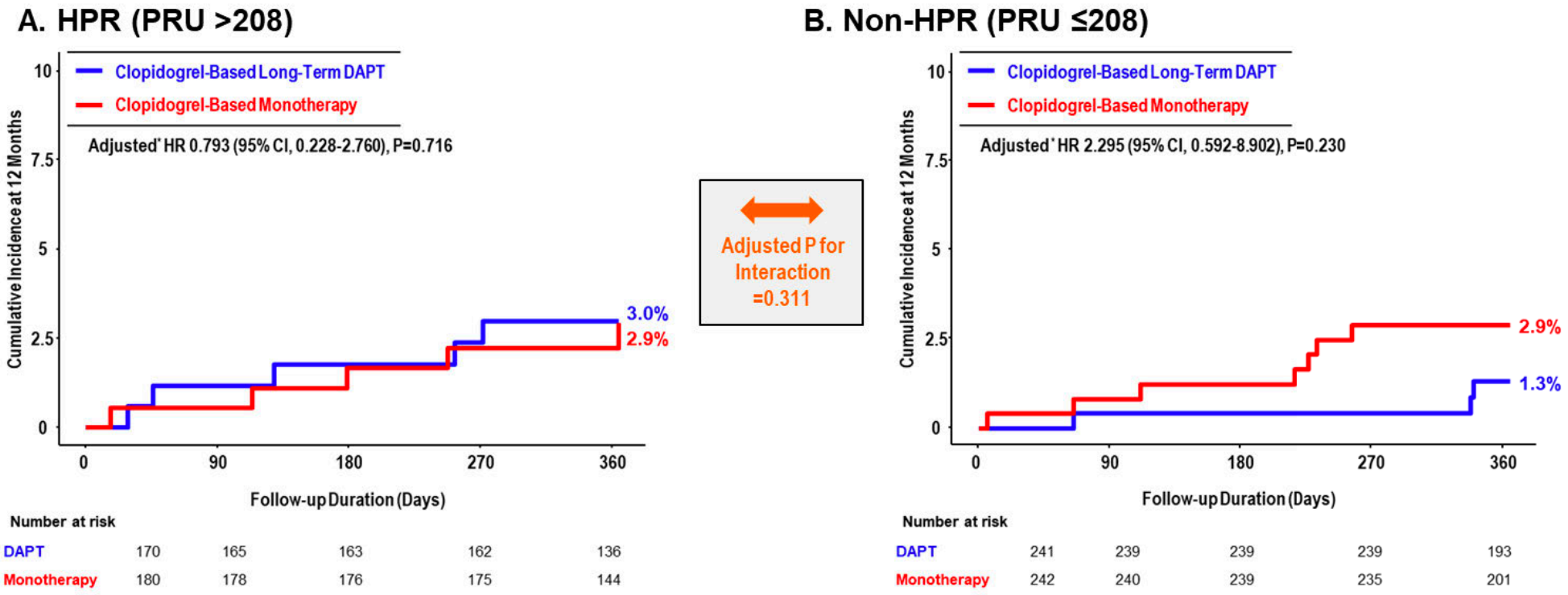
Number at risk

DAPT	356	354	353	353	287
Monotherapy	369	367	365	361	302

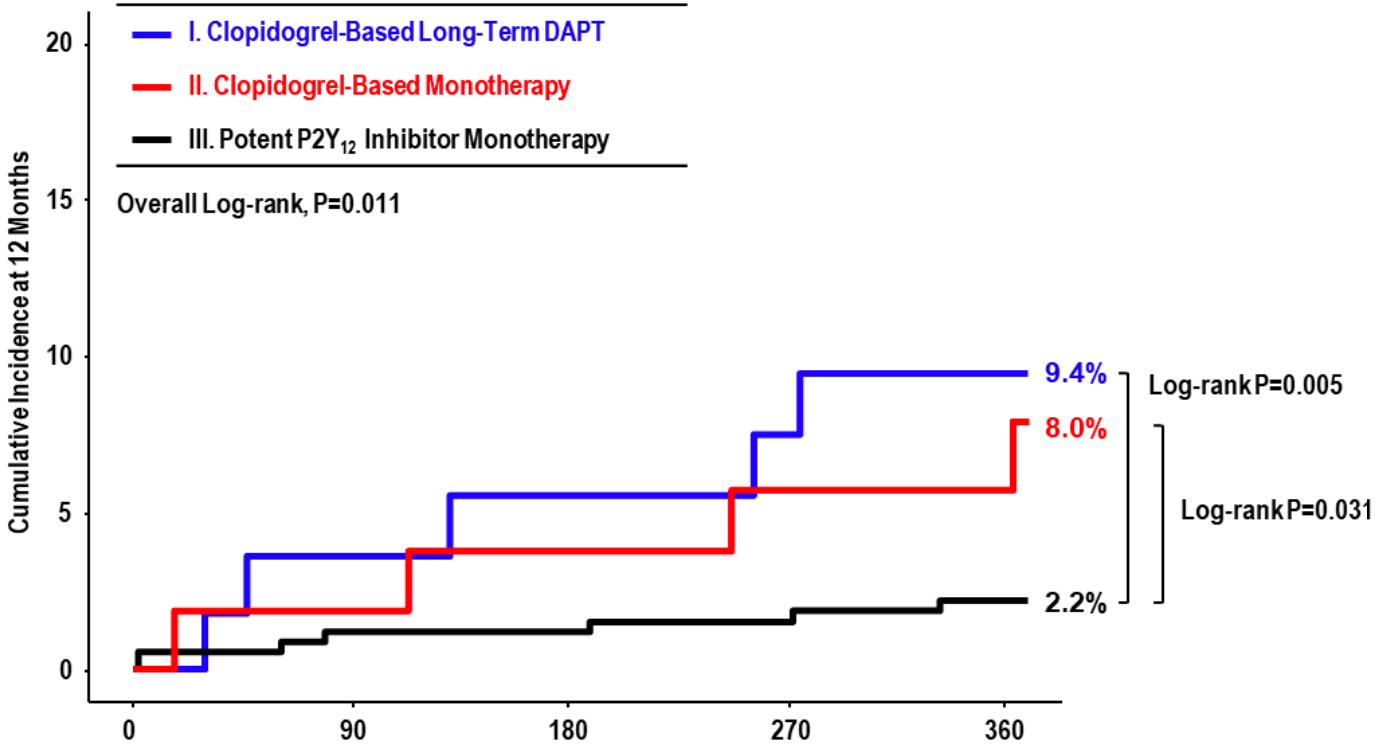
Supplementary Figure 3. Subgroup Analysis of the 12-Month MACCE.



Supplementary Figure 4. Comparison of 12-Month MACCE Rate According to Different Cut-off Value of HPR on Clopidogrel.



Supplementary Figure 5. Prognostic Impact of Potent $P2Y_{12}$ Inhibitor Monotherapy Compared with the Patients with HPR on Clopidogrel.



Number at risk					
Group I	55	50	49	48	42
Group II	53	51	50	49	43
Group III	330	319	314	309	263