# P2Y12 Inhibitor Monotherapy Versus Conventional Dual Antiplatelet Therapy or Aspirin Monotherapy in Acute Coronary Syndrome: A Pooled Analysis of the SMART-DATE and SMART-CHOICE Trials

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**Controversy remains regarding the optimal antiplatelet regimen in patients with acute coronary syndrome (ACS). This study sought to investigate the efficacy and safety of P2Y12 inhibitor monotherapy compared with conventional dual antiplatelet therapy (DAPT) and aspirin monotherapy in patients with ACS undergoing percutaneous coronary intervention. Data on 4,453 patients were pooled from SMART-DATE and SMART-CHOICE randomized trials. Antiplatelet therapy regimens were categorized as P2Y12 inhibitor monotherapy (P2Y12 inhibitor monotherapy after 3-month DAPT), conventional DAPT (12-month or longer DAPT), and aspirin monotherapy (aspirin monotherapy after 6-month DAPT). The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE, a composite of all-cause death, myocardial infarction, and stroke). Inverse-probability of treatment-weighted (IPTW) analysis was performed. At 1 year, patients in the P2Y12 inhibitor monotherapy had a comparable risk of MACCE compared with those in the conventional DAPT (IPTW-adjusted hazard ratio [HR], 0.655; 95% confidence interval [CI] 0.393 to 1.094; p = 0.106), and tended to have a lower risk of MACCE than those in the aspirin monotherapy (IPTW-adjusted HR, 0.606; 95% CI, 0.347 to 1.058; p = 0.078). The adjusted hazard for the Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding was significantly lower in P2Y12 inhibitor monotherapy than in conventional DAPT (IPTW-adjusted HR, 0.341; 95% CI, 0.190 to 0.614; p < 0.001) and in aspirin monotherapy (IPTW-adjusted HR, 0.359; 95% CI, 0.182 to 0.708; p = 0.003). In conclusion, among patients with ACS undergoing PCI, P2Y12 inhibitor monotherapy after 3-month DAPT reduced risk of bleeding compared with conventional DAPT and aspirin monotherapy after 6-month DAPT without increasing MACCE.**  **(Am J Cardiol 2021;150:47−54)**

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Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the cornerstone of treatment after percutaneous coronary intervention (PCI). The current international guidelines recommend DAPT for at least 12 months after the implantation of drug-eluting stents in patients with acute coronary syndrome (ACS).[1,2] However, conventional DAPT for 12 months or longer after ACS increases the bleeding complications that counterbalance the benefit from preventing ischemic events.[3,4] Recently, an abbreviated DAPT strategy followed by a P2Y12 inhibitor monotherapy has emerged as a potential alternative to conventional DAPT regimens, aiming to reduce an excess of bleeding risk associated with the addition of aspirin while maintaining an anti-ischemic efficacy.[5] However, the ischemic and bleeding risks of an abbreviated DAPT strategy followed by a P2Y12 inhibitor monotherapy compared with conventional or 6-month DAPT in patients with ACS remain uncertain. To address these issues, we performed an analysis of the pooled data of the Smart Angioplasty Research Team-Safety of 6-Month Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome (SMART-

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DATE)[6] and Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE)[7] trials to investigate the efficacy and safety of P2Y12 inhibitor monotherapy after 3 months of DAPT strategy after DES implantation in patients with ACS.

## Methods

The SMART-DATE was a multicenter, randomized, open-label trial to investigate whether a 6-month duration of DAPT would be non-inferior to the conventional 12-month or longer duration of DAPT in patients with ACS after coronary stenting. The SMART-CHOICE trial was a multicenter, randomized, open-label trial designed to test the non-inferiority of P2Y12 inhibitor monotherapy compared with aspirin plus a P2Y12 inhibitor after mandatory 3-month DAPT in patients undergoing PCI with current-generation drug-eluting stents. Among 5,705 patients included in the pooled data, 4,453 patients who underwent PCI for ACS were selected, comprising the population used in the present analysis. The antiplatelet therapy regimens were categorized as P2Y12 inhibitor monotherapy (P2Y12 inhibitor monotherapy after 3-month DAPT); conventional DAPT (12-month or longer DAPT); and aspirin monotherapy (aspirin monotherapy after 6-month DAPT); and we compared clinical endpoints among three antiplatelet therapy regimens. *e-Figure 1* in the *Supplementary Data* displays the network of antiplatelet regimens used in the present analysis. An independent institutional review board at each study center approved two clinical trials, and all patients provided written informed consent.

In the SMART-DATE trial, all patients received 300 mg of aspirin and a 300 or 600 mg clopidogrel loading dose orally at least 12 hours before PCI unless they had previously received these antiplatelet medications. After December 2014, prasugrel and ticagrelor became available in Korea. Since then, prasugrel or ticagrelor could be used instead of clopidogrel during the course of the SMART-DATE trial. After the procedure, aspirin (100 mg orally once daily) was used indefinitely and clopidogrel (75 mg orally once daily) was maintained according to the randomization scheme (6 months vs 12 months or longer). In the SMART-CHOICE trial, 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 in both groups after the procedure. The administration of aspirin was stopped at 3 months after the index procedure in the P2Y12 inhibitor monotherapy group but was continued indefinitely in the DAPT group. A P2Y12 inhibitor was prescribed continuously in both groups. It was recommended that all patients receive optimal pharmacologic therapy, including statins, $\beta$-blockers, or renin-angiotensin system blockade, if indicated, following clinical guidelines.[1,2] At follow-up, data from patients, including clinical status, all interventions, endpoint events, and adverse events, were recorded. In particular, information on the use of aspirin and a P2Y12 inhibitor was assessed at each follow-up. Patients who discontinued antiplatelet therapy as a result of clinically significant active bleeding or for other procedures were monitored carefully for cardiac events, and, once they were stabilized, their allocated antiplatelet therapy was restarted as soon as possible. An independent clinical event adjudication committee, whose members were masked to the study group assignments, assessed all clinical endpoints.

In this pooled analysis, the primary endpoint is major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause death, myocardial infarction (MI), and stroke at 12 months after the index procedure; secondary endpoints were individual components of the MACCE and the Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding at 12 months after the index procedure. In both trials, all clinical outcomes are commonly defined according to the Academic Research Consortium.[8] The BARC bleeding was defined as reported previously.[9]

The primary analysis was done according to an intention-to-treat principle. Because the follow-up duration of the SMART-CHOICE trial was 1 year, patients enrolled in the SMART-DATE trial were censored at 12 months in the current study. The cumulative rate of clinical events was evaluated by Kaplan-Meier analyses and the significance level was assessed with the Log-rank test. To compare the clinical endpoints, the hazard ratios (HRs) of three antiplatelet regimens were calculated by a Cox proportional hazards model. An extended description of the statistical analysis is presented in the *Methods of Supplementary Data*. Categorical variables are presented as numbers of events and percentages and were compared using the chi−square test or Fisher's exact test. Continuous variables are presented as mean ± standard deviation or median (interquartile range, in the case of a non-normal distribution), and were compared using the *t* test or Mann Whitney test. All probability values were 2-sided and p values $< 0.05$ were considered statistically significant. For all analyses, we used SPSS software version 20.0 (SPSS Inc, Chicago, IL) and R software (version 3.3; "MatchIt" and "survival" packages; R Foundation for Statistical Computing, Vienna, Austria) for Windows for the statistical analyses.

## Results

Out of a total population of 4,453 ACS patients, 870 (19.5%) patients were treated P2Y12 inhibitor monotherapy, 2,226 (50.0%) with conventional DAPT, and 1,357 (30.5%) with aspirin monotherapy. Baseline characteristics according to the different treatment regimens are shown in Table 1 and Table 2. Compared to patients in the conventional DAPT group and the aspirin monotherapy group, patients in the P2Y12 inhibitor monotherapy group were older, had a higher prevalence of diabetes, hypertension, dyslipidemia, chronic renal failure, and previous coronary revascularization. Beta-blocker was less frequently prescribed at discharge in the P2Y12 inhibitor monotherapy group than in the conventional DAPT group and the aspirin monotherapy group. After adjustment with the use of inverse probability of treatment weighted (IPTW), clinical characteristics were well balanced except age, left ventricular ejection fraction, ST-segment elevation MI as a

Table 1
Demographic and baseline characteristics of patients

| Variable | Unadjusted data | | | | Adjusted date with the use of IPTW | | | |
|---|---|---|---|---|---|---|---|---|
| | P2Y12 inhibitor monotherapy (n = 870) | Conventional DAPT (n = 2,226) | Aspirin monotherapy (n = 1,357) | p value | P2Y12 inhibitor monotherapy | Conventional DAPT | Aspirin monotherapy | p value |
| Age (year) | 64.4 ± 11.3 | 63.0 ± 11.6 | 62.0 ± 11.5 | <0.001 | 64.2 ± 10.0 | 63.1 ± 11.5 | 62.9 ± 11.4 | 0.028 |
| Gender | 629 (72.3%) | 1677 (75.3%) | 1016 (74.9%) | 0.210 | 73.1% | 74.5% | 73.7% | 0.816 |
| Body Mass Index (Kg/m$^2$) | 24.4 ± 3.3 | 24.5 ± 3.1 | 24.3 ± 3.2 | 0.299 | 24.3 ± 2.9 | 24.4 ± 3.2 | 24.5 ± 3.2 | 0.331 |
| STEMI as Presentation | 164 (18.9%) | 664 (29.8%) | 509 (37.5%) | <0.001 | 22.3% | 29.4% | 30.3% | 0.019 |
| Diabetes | 318 (36.6%) | 698 (31.4%) | 365 (26.9%) | <0.001 | 31.1% | 31.4% | 30.7% | 0.926 |
| Hypertension | 530 (60.9%) | 1175 (52.8%) | 669 (49.3%) | <0.001 | 56.2% | 53.7% | 51.7% | 0.227 |
| Dyslipidemia | 420 (48.3%) | 755 (33.9%) | 322 (23.7%) | <0.001 | 37.7% | 34.1% | 32.7% | 0.126 |
| Current smoker | 306 (35.2%) | 783 (35.2%) | 506 (37.3%) | 0.400 | 33.1% | 35.7% | 35.3% | 0.549 |
| History of CVA | 52 (6.0%) | 105 (4.7%) | 52 (3.8%) | 0.065 | 3.9% | 4.9% | 4.2% | 0.472 |
| History of CRF | 25 (2.9%) | 32 (1.4%) | 13 (1.0%) | 0.001 | 1.6% | 1.7% | 1.4% | 0.770 |
| History of previous MI | 34 (3.9%) | 60 (2.7%) | 30 (2.2%) | 0.056 | 2.4% | 2.7% | 2.2% | 0.616 |
| Previous revascularization | 79 (9.1%) | 147 (6.6%) | 65 (4.8%) | <0.001 | 6.4% | 6.5% | 5.7% | 0.628 |
| LVEF (%) | 58.2 ± 11.2 | 56.7 ± 10.5 | 55.7 ± 10.6 | <0.001 | 57.9 ± 9.9 | 56.7 ± 10.7 | 56.5 ± 10.6 | 0.028 |

Plus−minus values are means ± SD.

CRF = chronic renal failure; CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; IPTW = inverse probability treatment weighting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

presentation, trans-radial approach for PCI, and potent P2Y12 inhibitor prescription at discharge.

At 12 months, the primary endpoint of the MACCE occurred in 25 (2.9%) patients in the P2Y12 inhibitor monotherapy group, 72 (3.2%) patients in the conventional DAPT group, and 49 (3.6%) in the aspirin monotherapy group (Figure 1). After adjusting for potential confounders using IPTW, there was no significant difference between the P2Y12 inhibitor monotherapy and conventional DAPT with respect to the MACCE (Table 3). The rate of MACCEs tended to be lower in the P2Y12 inhibitor monotherapy group than in the aspirin monotherapy group. Regarding MI, there was no significant difference between the P2Y12 inhibitor monotherapy and conventional DAPT. When

Table 2
Angiographic and procedural characteristics of patients

| Variable | Unadjusted data | | | | Adjusted date with the use of IPTW | | | |
|---|---|---|---|---|---|---|---|---|
| | P2Y12 inhibitor monotherapy (n = 870) | Conventional DAPT (n = 2,226) | Aspirin monotherapy (n = 1,357) | p value | P2Y12 inhibitor monotherapy | Conventional DAPT | Aspirin monotherapy | p value |
| Multi-vessel disease | 435 (50.0%) | 1069 (48.0%) | 591 (43.6%) | 0.005 | 47.0% | 47.4% | 45.9% | 0.788 |
| Trans-radial access | 569 (65.4%) | 1203 (54.0%) | 637 (46.9%) | <0.001 | 63.1% | 54.0% | 53.3% | 0.001 |
| Use of IVUS | 217 (24.9%) | 582 (26.1%) | 311 (22.9%) | 0.096 | 23.6% | 24.9% | 24.3% | 0.856 |
| PCI for calcified lesion | 110 (12.6%) | 291 (13.1%) | 165 (12.2%) | 0.727 | 11.6% | 12.5% | 12.8% | 0.730 |
| PCI for thrombotic lesion | 100 (11.5%) | 434 (19.5%) | 325 (23.9%) | <0.001 | 13.5% | 19.3% | 19.7% | 0.062 |
| Bifurcation PCI | 110 (12.6%) | 227 (10.2%) | 124 (9.1%) | 0.028 | 9.3% | 10.3% | 10.5% | 0.659 |
| Treated vessel | | | | | | | | |
| *LM* | 11 (1.3%) | 37 (1.7%) | 29 (2.1%) | 0.287 | 0.9% | 1.6% | 1.7% | 0.235 |
| *LAD* | 507 (58.3%) | 1370 (61.5%) | 767 (56.5%) | 0.009 | 62.5% | 59.7% | 59.5% | 0.424 |
| *LCx* | 249 (28.6%) | 561 (25.2%) | 331 (24.4%) | 0.068 | 24.6% | 25.7% | 24.5% | 0.810 |
| *RCA* | 311 (35.7%) | 817 (36.7%) | 504 (37.1%) | 0.799 | 33.0% | 36.6% | 38.1% | 0.111 |
| Multi-vessel PCI | 199 (22.9%) | 506 (22.7%) | 263 (19.4%) | 0.041 | 20.4% | 21.7% | 22.4% | 0.657 |
| Degradable polymer DES | 282 (32.4%) | 697 (31.3%) | 391 (28.8%) | 0.146 | 30.8% | 31.4% | 30.1% | 0.821 |
| Total Stent Length (mm) | 37.6 ± 21.6 | 35.1 ± 21.4 | 32.3 ± 18.1 | <0.001 | 34.8±18.1 | 34.5±20.4 | 34.5 ± 20.4 | 0.923 |
| No. of stent implanted | 1.46 ± 0.72 | 1.46 ± 0.77 | 1.39 ± 0.75 | 0.004 | 1.37±0.63 | 1.44±0.74 | 1.46 ± 0.81 | 0.051 |
| Discharge medications | | | | | | | | |
| *Statin* | 840 (96.6%) | 2064 (92.7%) | 1212 (89.3%) | <0.001 | 94.3% | 92.6% | 92.1% | 0.535 |
| *Beta-blocker* | 531 (61.0%) | 1509 (67.8%) | 961 (70.8%) | <0.001 | 66.1% | 67.9% | 68.1% | 0.642 |
| *RAAS blocker* | 538 (61.8%) | 1430 (64.2%) | 929 (68.5%) | 0.003 | 66.4% | 64.54% | 65.7% | 0.730 |
| *Potent P2Y12 Inhibitor* | 305 (35.1%) | 541 (24.3%) | 275 (20.3%) | <0.001 | 29.8% | 25.1% | 23.7% | 0.028 |

Plus−minus values are means ± SD

DAPT = dual antiplatelet therapy; DES = drug-eluting stent; IPTW = inverse probability treatment weighting; IVUS =intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; PCI = percutaneous coronary intervention; RAAS = renin-angiotensin-aldosterone system; RCA= right coronary artery.

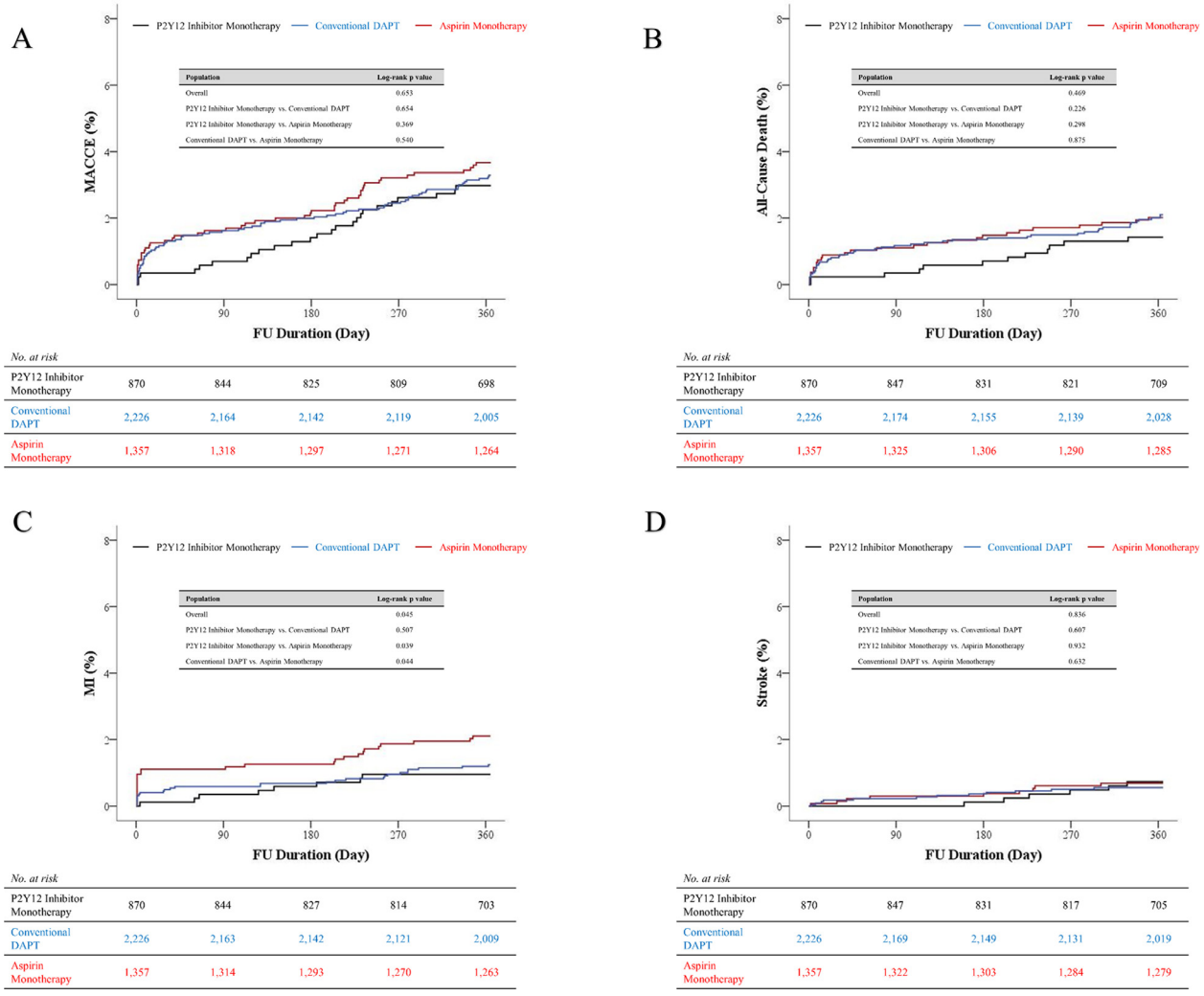



Figure 1. Time-to-Event Curves for Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) (A), All-Cause Death (B), Myocardial Infarction (MI) (C), and Stroke (D). DAPT: dual antiplatelet therapy, FU: follow-up.

compared with aspirin monotherapy, however, P2Y12 inhibitor monotherapy was associated with a significantly lower risk of MI (Table 3). A total of 118 BARC type 2−5 bleeding events (2.6%) occurred at 12 months after the index PCI. Pairwise comparisons between groups are presented in Figure 2. The adjusted HR for bleeding endpoint was significantly lower for P2Y12 inhibitor monotherapy regimen compared with the conventional DAPT and aspirin monotherapy regimens (Table 3). In addition, patients treated with P2Y12 inhibitor monotherapy had a lower IPTW-adjusted all-cause death rate than those treated with conventional DAPT. The rate of all-cause death was also lower in the P2Y12 inhibitor monotherapy group than in the aspirin monotherapy group. Results from the per-protocol analysis were similar to those from the intention-to-treat analysis (*e-Table 2* in the *Supplementary Data*). Details of results in patients with per-protocol treatment are presented in the *Results* in the *Supplementary Data.*

The treatment effects of the P2Y12 inhibitor monotherapy compared with conventional DAPT or aspirin monotherapy were consistent across various subgroups for the MI, including in subgroups analyzed according to the presence versus absence of ST-segment elevation and type of P2Y12 inhibitors (*e-Figure 2* in the *Supplementary Data*). In subgroup analyses for the risk of BARC type 2-5 bleeding, the results were also consistent across various subgroups (*e-Figure 3* in the *Supplementary Data*).

## Discussion

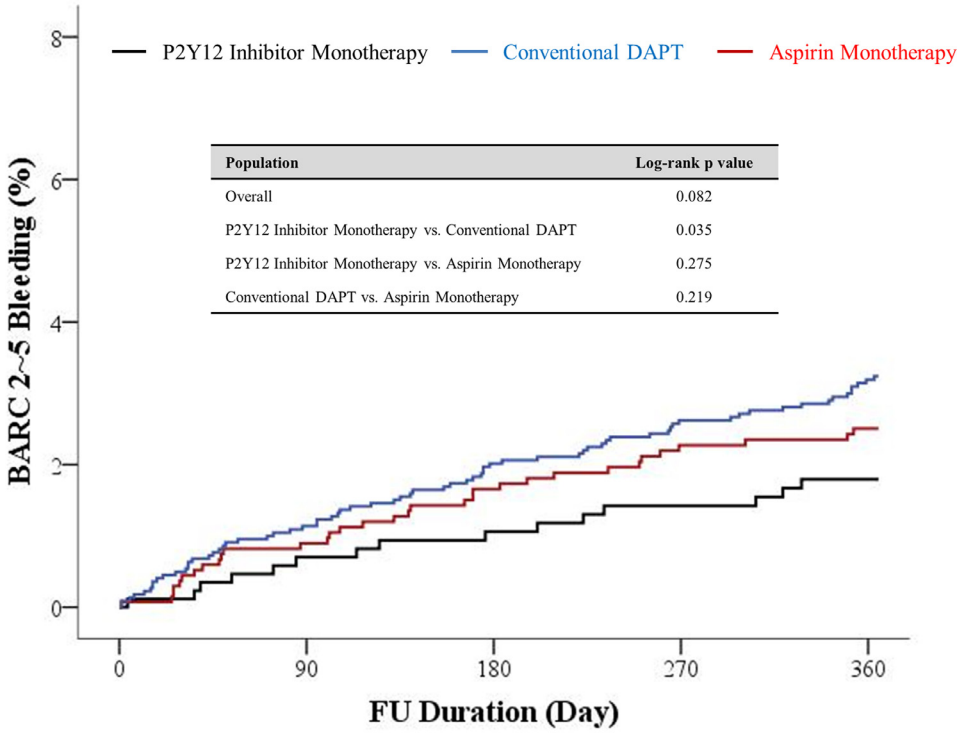
Our analysis demonstrates that there were no significant differences between P2Y12 inhibitor monotherapy after 3-month DAPT and conventional DAPT for the primary endpoint of MACCE at 12 months after the index procedure. Compared with conventional DAPT, P2Y12 inhibitor monotherapy was associated with a significant reduction in BARC type 2 to 5 bleeding. Compared to aspirin monotherapy, P2Y12 inhibitor monotherapy significantly reduced the risk for MI. The results were consistent in per-protocol analyses and exploratory subgroup analysis.

Practice guidelines recommend DAPT for 12 months or longer in patients with ACS.[1,2] Recently, with the improved safety and efficacy of DES, a couple of studies challenged these guidelines and tested the safety of aspirin

Table 3
Crude, adjusted, and IPTW-adjusted hazard ratios for antiplatelet therapy regimens in ITT analysis

| Variable | Overall (n = 4,453) | P2Y12 inhibitor monotherapy (n = 870) | vsConventional DAPT (n = 2,226) | vsAspirin monotherapy (n = 1,357) | p-Value |
|---|---|---|---|---|---|
| *MACCE* | | | | | |
| Number of events | 146 (3.3%) | 25 (2.9%) | 72 (3.2%) | 49 (3.6%) | |
| Unadjusted HR (95% CI) | | *Reference* | 0.901 (0.571−1.420) p = 0.652 | 0.804 (0.496−1.300) p = 0.374 | 0.654 |
| Adjusted HR (95% CI) | | *Reference* | 0.806 (0.510−1.274) p = 0.356 | 0.705 (0.434−1.147) p = 0.160 | 0.371 |
| IPTW-Adjusted | | *Reference* | 0.655 (0.393−1.094) p = 0.106 | 0.606 (0.347−1.058) p = 0.078 | 0.186 |
| *All-Cause Death* | | | | | |
| Number of events | 85 (1.9%) | 12 (1.4%) | 46 (2.1%) | 27 (2.0%) | |
| Unadjusted HR (95% CI) | | *Reference* | 0.676 (0.358−1.276) p = 0.227 | 0.702 (0.356−1.385) p = 0.307 | 0.474 |
| Adjusted HR (95% CI) | | *Reference* | 0.566 (0.296−1.083) p = 0.086 | 0.541 (0.272−1.076) p = 0.080 | 0.178 |
| IPTW-Adjusted | | *Reference* | 0.386 (0.197−0.756) p = 0.005 | 0.428 (0.202−0.908) p = 0.027 | 0.020 |
| *Myocardial Infarction* | | | | | |
| Number of events | 63 (1.4%) | 8 (0.9%) | 27 (1.2%) | 28 (2.1%) | |
| Unadjusted HR (95% CI) | | *Reference* | 0.766 (0.348−1.686) p = 0.507 | 0.448 (0.204−1.018) p = 0.045 | 0.050 |
| Adjusted HR (95% CI) | | *Reference* | 0.707 (0.320−1.558) p = 0.389 | 0.398 (0.180−0.876) p = 0.022 | 0.026 |
| IPTW-Adjusted | | *Reference* | 0.655 (0.267−1.610) p = 0.357 | 0.353 (0.141−0.883) p = 0.026 | 0.033 |
| *Stroke* | | | | | |
| Number of events | 27 (0.6%) | 6 (0.7%) | 12 (0.5%) | 9 (0.7%) | |
| Unadjusted HR (95% CI) | | *Reference* | 1.292 (0.484−3.436) p = 0.609 | 1.045 (0.372−2.933) p = 0.934 | 0.836 |
| Adjusted HR (95% CI) | | *Reference* | 1.183 (0.443−3.155) p = 0.737 | 0.927 (0.329−2.611) p = 0.885 | 0.850 |
| IPTW-Adjusted | | *Reference* | 1.211 (0.432−3.390) p = 0.717 | 0.664 (0.209−2.105) p = 0.487 | 0.476 |
| *BARC type 2−5 Bleeding* | | | | | |
| Number of events | 118 (2.6%) | 15 (1.7%) | 70 (3.1%) | 33 (2.4%) | |
| Unadjusted HR (95% CI) | | *Reference* | 0.553 (0.317−0.965) p = 0.037 | 0.7158 (0.389-1.318) p = 0.283 | 0.086 |
| Adjusted HR (95% CI) | | *Reference* | 0.499 (0.285−0.874) p = 0.015 | 0.605 (0.327−1.120) p = 0.109 | 0.049 |
| IPTW-Adjusted | | *Reference* | 0.341 (0.190−0.614) p < 0.001 | 0.359 (0.182−0.708) p = 0.003 | 0.001 |

BARC = Bleeding Academic Research Consortium, CI = confidence interval, DAPT = dual antiplatelet therapy, HR = hazard ratio, IPTW = inverse probability treatment weighting, ITT = intention-to-treat, MACCE = major adverse cardiac and cerebrovascular events (a composite of all-cause death, myocardial infarction, and stroke).




| Population | Log-rank p value |
|---|---|
| Overall | 0.082 |
| P2Y12 Inhibitor Monotherapy vs. Conventional DAPT | 0.035 |
| P2Y12 Inhibitor Monotherapy vs. Aspirin Monotherapy | 0.275 |
| Conventional DAPT vs. Aspirin Monotherapy | 0.219 |

| *No. at risk* | | | | | |
|---|---|---|---|---|---|
| P2Y12 Inhibitor Monotherapy | 870 | 841 | 823 | 809 | 699 |
| Conventional DAPT | 2,226 | 2,151 | 2,116 | 2,088 | 1,973 |
| Aspirin Monotherapy | 1,357 | 1,314 | 1,286 | 1,263 | 1,257 |

Figure 2. Time-to-Event Curves for BARC type 2-5 Bleeding. BARC: Bleeding Academic Research Consortium, DAPT: dual antiplatelet therapy.

monotherapy after shortened DAPT compared with conventional DAPT in patients with ACS.[10,11] However, in the SMART-DATE trial, the risk of recurrent MI significantly increased with 6-month DAPT than with 12-month or longer DAPT in patients with ACS undergoing PCI in contemporary practice.[6] Therefore, the conventional DAPT regimen remains the standard of care in patients with ACS without excessive risk of bleeding. However, conventional DAPT increases bleeding and counteracts the benefit of reducing ischemic events. Therefore, the abbreviated duration of DAPT followed by P2Y12 inhibitor monotherapy has recently emerged as a promising alternative strategy.[12] Several randomized trials have demonstrated that P2Y12 inhibitor monotherapy is non-inferior to conventional DAPT regimen in the broad spectrum of patients.[7,13,14] However, data in patients with ACS are limited and, moreover, there have been no comparisons between 6-month DAPT followed by aspirin monotherapy and 3-month DAPT followed by P2Y12 inhibitor monotherapy. Therefore, in this pooled analysis of 2 randomized trials, we investigated the efficacy and safety of P2Y12 inhibitor monotherapy compared with conventional DAPT or aspirin monotherapy in patients with ACS after coronary stenting.

In the present study, 3-month DAPT followed by P2Y12 inhibitor monotherapy was comparable to conventional DAPT with regards to the prevention of recurrent ischemic events, such as MI and stroke. Compared with 6-month DAPT followed by aspirin monotherapy, 3-month DAPT followed by P2Y12 inhibitor monotherapy was associated with a lower risk of MI. Although there are no randomized comparisons between P2Y12 inhibitor monotherapy and aspirin monotherapy after the current DES implantation, our results are in line with previous studies. In recent systematic review and meta-analysis, $P2Y_{12}$ inhibitor monotherapy is associated with a risk reduction for MI compared with aspirin monotherapy.[15] There is also supportive pharmacodynamic evidence. P2Y12 receptor activation is important to platelet thromboxane A2 production, and the inhibition of P2Y12 can result in a substantial degree of thromboxane A2 inhibition.[16,17]

Another important finding is that, compared with conventional DAPT, a significant reduction in BARC type 2 to

5 bleeding was prominent with P2Y12 inhibitor monotherapy. Even when compared to 6-month DAPT followed by aspirin monotherapy, the risk of bleeding was lower in the 3-month DAPT followed by P2Y12 inhibitor monotherapy. Three-month vs 6-month DAPT and the less adverse effect of clopidogrel on the gastrointestinal system when compared with aspirin might explain our results.[18,19]

Thereby, the rate of all-cause death was significantly lower in the P2Y12 inhibitor monotherapy group than in the conventional DAPT and aspirin monotherapy groups. In addition, the 3-month DAPT followed by P2Y12 inhibitor monotherapy tended to be better to aspirin monotherapy following 6-month DAPT with respect to the prevention of MACCE. Taken together, an abbreviated duration of DAPT followed by P2Y12 inhibitor monotherapy might be a promising strategy in patients with ACS after coronary stenting with a similar risk of ischemic events and reduction in bleeding complications compared with conventional DAPT, and with a lower risk of ischemic events compared with aspirin monotherapy.

This study has several limitations. First, a substantial proportion of patients in the P2Y12 inhibitor monotherapy group or in the aspirin monotherapy group received DAPT after 3 months or after 6 months, respectively. Therefore, the possibility of biases from low adherence in the P2Y12 inhibitor monotherapy group or in the aspirin monotherapy group could not be excluded. However, we also did a per-protocol analysis, which showed results consistent with the intention-to-treat analysis, suggesting that any potential biases caused by differential adherence and treatment crossover are likely to be small. Second, this was a post hoc exploratory analysis of 2 randomized trials; our report can identify correlations but does not prove causality. Third, the choice of the antiplatelet therapy regimen was randomly assigned in each trial, but significant differences were found in several variables between three antiplatelet regimen groups in the present analysis. Although we rigorously adjusted for these differences using multivariable Cox models and IPTW, unmeasured confounders may have affected our results. Fourth, event rates were low, so the present analysis may not be able to detect between-group differences in clinical endpoints. In terms of interaction tests, subgroup analyses reduced the sample size even more, therefore most are underpowered. Consequently, all the presented findings must be interpreted strictly as hypothesis-generating, which requires further prospective randomized validation.

In conclusion, 3-month DAPT followed by P2Y12 inhibitor monotherapy was comparable to conventional DAPT with regard to the prevention of ischemic events at 1 year after index PCI for ACS. Compared with conventional DAPT, P2Y12 inhibitor monotherapy was associated with a lower risk of BARC type 2 to 5 bleeding. In addition, P2Y12 inhibitor monotherapy after 3-month DAPT seems to more effectively prevent ischemic events than aspirin monotherapy after 6-month DAPT. These findings indicate that 3-month DAPT followed by P2Y12 inhibitor monotherapy could be a reasonable strategy in patients with ACS after implantation of current-generation DES. However, these findings should be interpreted as exploratory and hypothesis-generating and should be tested in dedicated randomized trials.

## Author Contributions

Pil Sang Song: Conceptualization, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization; Yong Hwan Park: Conceptualization, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization; Ju-Hyeon Oh: Methodology, Software, Resources, Data Curation, Supervision, Project administration, Funding acquisition; Young Bin Song: Conceptualization, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision; Seung-Hyuk Choi: Conceptualization, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision; Hyeon-Cheol Gwon: Methodology, Software, Resources, Data Curation, Writing - Review & Editing, Supervision, Project administration, Funding acquisition; Deok-Kyu Cho: Methodology, Software, Resources, Data Curation, Supervision, Project administration, Funding acquisition; Seung-Woon Rha: Methodology, Software, Resources, Data Curation, Supervision, Project administration, Project administration, Funding acquisition; Jang-Whan Bae: Methodology, Software, Resources, Data Curation, Supervision, Project administration, Project administration, Funding acquisition; Jin-Ok Jeong: Conceptualization, Methodology, Software, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Project administration, Funding acquisition; Joo-Yong Hahn: Conceptualization, Methodology, Software, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Project administration, Funding acquisition.

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## Supplementary materials

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