CLINICAL RESEARCH STUDY

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Perioperative Antiplatelet Strategy in Patients Undergoing Noncardiac Surgery Within One Year After Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND: The optimal antiplatelet therapy (APT) for patients undergoing non-cardiac surgery within 1 year after percutaneous coronary intervention (PCI) is not yet established.

METHODS: Patients who underwent non-cardiac surgery within 1 year after second-generation drug-eluting stent implantation were included from a multicenter prospective registry in Korea. The primary endpoint was 30-day net adverse clinical event (NACE), including all-cause death, major adverse cardiovascular event (MACE), and major bleeding events. Covariate adjustment using propensity score was performed.

RESULTS: Among 1130 eligible patients, 708 (62.7%) continued APT during non-cardiac surgery. After propensity score adjustment, APT continuation was associated with a lower incidence of NACE (3.7% vs 5.5%; adjusted odds ratio [OR], 0.48; 95% confidence interval [CI], 0.26-0.89; $P = .019$) and MACE (1.1% vs 1.9%; adjusted OR, 0.35; 95% CI, 0.12-0.99; $P = .046$), whereas the incidence of major bleeding events was not different between the 2 APT strategies (1.7% vs 2.6%; adjusted OR, 0.61; 95% CI, 0.25-1.50; $P = .273$).

CONCLUSIONS: The APT continuation strategy was chosen in a substantial proportion of patients and was associated with the benefit of potentially reducing 30-day NACE and MACE with similar incidence of major bleeding events, compared with APT discontinuation. This study suggests a possible benefit of APT continuation in non-cardiac surgery within 1 year of second-generation drug-eluting stent implantation.

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KEYWORDS: Antiplatelet therapy; Net adverse clinical events; Non-cardiac surgery; Percutaneous coronary intervention

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INTRODUCTION

Percutaneous coronary intervention (PCI) is one of the most commonly used revascularization strategies for coronary artery disease. After the introduction of second-generation drug-eluting stent, post-PCI adverse events, such as stent thrombosis, have decreased remarkably, especially compared with first-generation drug-eluting stent.[1] However, lifelong antiplatelet therapy (APT) has still been strictly recommended after PCI due to remaining cardiovascular risk. Specifically, dual APT, including aspirin and a P2Y12 receptor inhibitor, is still emphasized as a key strategy for reducing ischemic risk during the early post-procedural phase, especially the first year. Accordingly, the current guidelines for management of coronary artery disease recommend that dual APT be mandatorily maintained for 6-12 months after drug-eluting stent implantation, according to clinical presentation.[2-4]

CLINICAL SIGNIFICANCE

- Optimal antiplatelet therapy strategy during non-cardiac surgery performed within 1 year of percutaneous coronary intervention is undefined.
- The continuation of antiplatelet therapy was associated with reduction of cardiovascular risk without an increase of bleeding risk.
- Single antiplatelet therapy had similar clinical efficacy and safety to dual antiplatelet therapy. These should be considered hypothesis-generating results, as they may be open to interpretation.

Previous studies demonstrated that non-cardiac surgery is required during the mandatory period for up to 20% of patients.[5-8] The competing effect of APT on stent-related ischemic risk and surgery-related bleeding risk complicates the decision of the proper APT strategy for each patient undergoing non-cardiac surgery. The current guidelines recommend postponing an elective non-cardiac surgery 6-12 months after PCI, according to clinical presentation for the index PCI.[9-11]

Several studies have investigated the effect of APT on patients undergoing non-cardiac surgery after PCI; however, the results of these studies are conflicting, possibly owing to the heterogeneity of the characteristics of patients, surgeries, and APT strategies.[12-15] Furthermore, a limited number of patients undergoing non-cardiac surgery within 1 year of PCI has been analyzed, including those with bare-metal stent or first-generation drug-eluting stent implantation. In this study, we investigated the effect of APT strategy on patients undergoing non-cardiac surgery within 1 year of second-generation drug-eluting stent implantation.

METHODS

Study Population and Definitions

Patients who underwent non-cardiac surgery between May 2008 and September 2021 within 1 year of second-generation drug-eluting stent implantation were included from a multicenter prospective registry (KOMATE [Korean Multicenter Angioplasty Team], NCT03908463) that enrolls patients undergoing PCI from 8 major cardiovascular centers in Korea. All surgeries requiring general anesthesia, including laparoscopic operations or open procedures, were included. The major exclusion criteria were: 1) surgeries involving the heart and its adjacent great vessels and 2) surgeries within 14 days after the index PCI. Eligible patients were stratified by the APT strategy (APT continuation or APT discontinuation) at the time of surgery. APT continuation was defined as any antiplatelet agent being used at the time of surgery, and APT discontinuation was defined as all antiplatelet agents having been interrupted at least 1 day before surgery. The procedure-related data were obtained from the registry, and perioperative data were retrospectively collected from the electronic medical records of each participating center.

Non-cardiac surgery was classified into 2 groups, according to the surgical risk based on 30-day incidence of cardiovascular death or myocardial infarction: low risk (<1%) or intermediate-to-high risk (≥1%).[10] The surgery was considered urgent if needed within 30 days for a condition with the potential to quickly deteriorate into an emergency.[16] Complex PCI was defined as a procedure 1) for left main coronary artery disease; 2) for a bifurcation lesion requiring 2 stents; 3) for chronic total occlusion lesion; 4) requiring over 2 stents; 5) with a total stent length of ≥60 mm; or 6) with a minimum stent diameter of <2.5 mm.[17,18]

The institutional review board of each participating center approved the study protocol and the need for informed consent was waived.

Definition of Study Endpoints

The primary endpoint was the 30-day net adverse clinical event (NACE), defined as a composite of all-cause death, major adverse cardiovascular event (MACE), and major bleeding events. All-cause death included both cardiac and non-cardiac death. Cardiac death was defined as death with ischemic symptoms, typical ischemic patterns of electrocardiography, cardiac enzyme elevation, or fatal ventricular arrhythmia with no obvious non-cardiac cause of death. MACE was defined as a composite of cardiac death, myocardial infarction, and stent thrombosis. Myocardial infarction was defined according to the third universal definition as an increase in creatine kinase myocardial fraction above the upper normal limit, an increase in troponin-T or troponin-I of >99th percentile of the upper normal limit, and ≥1 of these symptoms: electrocardiographic changes or imaging or angiographic findings indicative of myocardial infarction.[19] Stent thrombosis was defined according to the recommendations of the Academic Research Consortium.[20] Major bleeding was defined according to the criteria of the International Society of Thrombosis and Hemostasis.[21]

Table 1 Baseline Characteristics Stratified by Treatment Strategy*

	All (N = 1130)	APT Continuation (n = 708)	APT Discontinuation (n = 422)	*P* Value
Age, years	69 (60-76)	69 (60-76)	69 (60-75)	.485
Female sex	345 (30.5)	202 (28.5)	143 (33.9)	.068
Body mass index, kg/m^2	24.1 (22.0-26.3)	24.0 (22.0-26.1)	24.2 (22.1-26.9)	.062
Hypertension	862 (76.3)	538 (76.0)	324 (76.8)	.819
Diabetes mellitus	557 (49.3)	358 (50.6)	199 (47.2)	.295
Dyslipidemia	633 (56.0)	421 (59.5)	212 (50.2)	.003
Chronic heart failure	71 (6.3)	46 (6.5)	25 (5.9)	.797
Chronic kidney disease	254 (22.5)	179 (25.3)	75 (17.8)	.004
Prior cerebrovascular accident	148 (13.1)	99 (14.0)	49 (11.6)	.293
Anemia	379/966 (39.2)	229/562 (40.7)	150/404 (37.1)	.285
Clinical diagnosis at index PCI				.003
Stable angina	507 (44.9)	342 (48.3)	165 (39.1)	
Acute coronary syndrome	623 (55.1)	366 (51.7)	257 (60.9)	
Complex PCI	254 (22.5)	168 (23.7)	86 (20.4)	.218
PCI-surgery interval, days	174 (84-260)	147 (73-247)	210 (109-285)	<.001
15-90	314 (27.8)	227 (32.1)	87 (20.6)	<.001
91-180	268 (23.7)	186 (26.3)	82 (19.4)	
181-365	548 (48.5)	295 (41.7)	253 (60.0)	
Surgical risk				<.001
Low	612 (54.2)	430 (60.7)	182 (43.1)	
Intermediate-to-high	518 (45.8)	278 (39.3)	240 (56.9)	
Urgent or emergent surgery	121 (10.7)	99 (14.0)	22 (5.2)	<.001
Medication before surgery				
Renin-angiotensin-system inhibitors	534 (47.3)	300 (42.4)	234 (55.5)	<.001
Beta blockers	517 (45.8)	301 (42.5)	216 (51.2)	.006
Calcium channel blockers	342 (30.3)	193 (27.3)	149 (35.3)	.005
Anticoagulant agents	5 (0.4)	3 (0.4)	2 (0.5)	>.999
Antiplatelet agents				
Aspirin	1050 (92.9)	678 (95.8)	372 (88.2)	<.001
P2Y12 receptor inhibitors	969 (85.8)	608 (85.9)	361 (85.5)	.947
Clopidogrel	892/969 (92.1)	553/608 (91.0)	339/361 (93.9)	
Ticagrelor	66/969 (6.8)	47/608 (7.7)	19/361 (5.3)	
Prasugrel	11/969 (1.1)	8/608 (1.3)	3/361 (0.8)	
Preoperative pattern of APT				<.001
Dual APT	919 (81.3)	578 (81.6)	341 (80.8)	
Single APT	181 (16.0)	130 (18.4)	51 (12.1)	
No APT	30 (2.7)	0 (0)	30 (7.1)	
APT at surgery				
Dual APT	—	450 (63.6)	—	
Aspirin monotherapy	—	213 (30.1)	—	
P2Y12 receptor inhibitor monotherapy	—	45 (6.4)	—	
APT discontinuation period				
Aspirin†	—	5 (1-6)	4 (1-5)	
P2Y12 receptor inhibitors†	—	5 (1-5)	3 (1-5)	

APT = antiplatelet therapy; PCI = percutaneous coronary intervention.

*Data are presented as median (interquartile range), n (%), or n/N (%).

†Aspirin and P2Y12 receptor inhibitors were discontinued in 15 and 113 patients among patients with APT continuation and 372 and 361 patients among patients with APT discontinuation, respectively.

An independent adjudication was performed for each event until an acceptable agreement was obtained among adjudicators.

Statistical Analyses

Continuous variables were reported as median with quartiles and compared using the Mann-Whitney U test when not normally distributed, and those were reported as mean with standard deviation and compared using the Student t-test when normally distributed. Categorical variables were reported as numbers with proportion in percentage and compared using the χ^2 or Fisher exact test. To overcome bias, adjustment using propensity score was used. The propensity score indicating the probability of each patient being allocated to APT continuation was calculated by a

logistic regression model with the following variables: age (<65 years vs ≥65 years), sex, dyslipidemia, chronic kidney disease, clinical diagnosis at index PCI (stable angina vs acute coronary syndrome), complex PCI, PCI-surgery interval (15-90 days vs 91-180 days vs 181-365 days), surgical risk, urgent or emergent surgery, and preoperative dual APT usage. To compare the odds ratio (OR) of each adverse event between 2 APT strategies, logistic regression models using propensity score as a covariate were generated. Sensitivity analysis was performed to assess whether therapy effects (APT continuation vs APT discontinuation) differed according to other confounding factors by formal interaction tests. All statistical analyses were performed using R statistical software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The study flow is shown in Supplementary Figure 1 (available online). Baseline characteristics of the eligible patients are shown in Table 1. Of the total 1130 eligible patients, 708 (62.7%) continued APT during non-cardiac surgery. APT continuation was associated with a higher proportion of dyslipidemia (59.5% vs 50.2%), chronic kidney disease (25.3% vs 17.8%), and urgent or emergent surgery (14.0% vs 5.2%), compared with APT discontinuation. The PCI-surgery interval was shorter in the APT continuation group (147 days vs 210 days). The proportion of acute coronary syndrome at index PCI was lower in the APT continuation group (51.7% vs 60.9%) than in the APT discontinuation group and so was that of intermediate-to-high risk surgery (39.3% vs 56.9%).

Among patients who continued APT, 450 (63.6%) continued dual APT. The perioperative APT pattern is shown in Figure 1. Among 919 (81.3%) patients who received dual APT before non-cardiac surgery, 341 (37.1%) discontinued all the antiplatelet agents. The proportion of patients whose dual APT were discontinued was 74/269 (27.5%), 69/215 (32.1%), and 198/435 (45.5%) for non-cardiac surgery performed within 90, 180, and after 180 days, respectively.

Clinical Outcomes

The incidence of the study endpoints stratified by PCI-surgery interval is presented in Table 2 and Figure 2. After propensity score adjustment, APT continuation was associated with a lower incidence of both NACE (3.7% vs 5.5%; adjusted OR, 0.48; 95% confidence interval [CI], 0.26-0.89; P = .019) and MACE (1.1% vs 1.9%; adjusted OR, 0.35; 95% CI, 0.12-0.99; P = .046), whereas the incidence of major bleeding events did not differ between the 2 APT strategies (1.7% vs 2.6%; adjusted OR, 0.61; 95% CI, 0.25-1.50; P = .273). Among patients who underwent surgery within 6 months, the incidence of NACE (3.9% vs 5.9%; adjusted OR, 0.44; 95% CI, 0.19-1.05; P = .056) and major bleeding events (1.9% vs 2.4%; adjusted OR, 0.75; 95% CI, 0.22-2.93; P = .650) did not differ between the 2 APT strategies, whereas the incidence of MACE was lower in the APT continuation group (1.0% vs 3.0%; adjusted OR, 0.21; 95% CI, 0.05-0.84; P = .026) than in the APT discontinuation group. Among patients who underwent surgery within 3 months, there was no difference between the 2 APT strategies in terms of NACE, MACE, or major bleeding events. There was no significant interaction between APT strategy and other confounding factors (Figure 3).

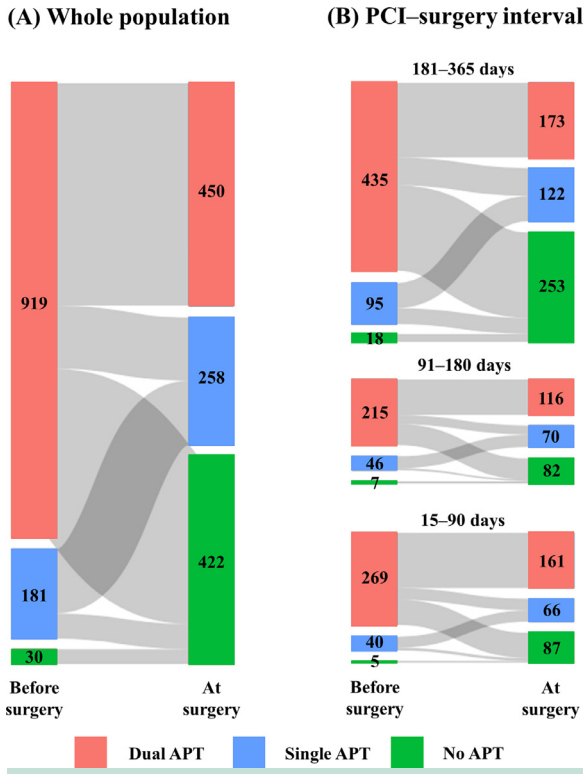

Figure 1 The pattern of APT before and at non-cardiac surgery, stratified by PCI-surgery interval. The columns on the left of each pair represent the APT pattern before surgery, and the numbers inside indicate the number of patients under the APT strategies. The columns on the right and the numbers inside represent those at surgery. (**A**) The APT pattern in the whole study population. (**B**) The APT pattern according to the PCI-surgery interval. APT = antiplatelet therapy; PCI = percutaneous coronary intervention.

The comparison of dual and single APT among the APT continuation group is shown in Table 3. There was no difference in the incidences of the study endpoints between patients with dual and single APT, regardless of the stratified PCI-surgery interval. The comparison of aspirin and P2Y12 receptor inhibitors among patients receiving single APT is shown in Supplementary Table 1 (available online).

DISCUSSION

The Perioperative Ischemic Evaluation (POISE)-2 trial demonstrated that aspirin does not reduce the ischemic risk

Table 2 Regression Models of Antiplatelet Therapy Strategy for Incidence of Study Endpoints

	Event Rate, n (%)		Unadjusted		PS-Adjusted	
	APT Continuation	APT Discontinuation	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PCI-surgery interval ≤12 months						
	n = 708	n = 422				
NACE	26 (3.7)	23 (5.5)	0.66 (0.37-1.18)	.158	0.48 (0.26-0.89)	.019
MACE	8 (1.1)	8 (1.9)	0.59 (0.22-1.62)	.297	0.35 (0.12-0.99)	.046
Cardiac death	6 (0.8)	6 (1.4)	—	—	—	—
Myocardial infarction	2 (0.3)	3 (0.7)	—	—	—	—
Stent thrombosis	0 (0)	1 (0.2)	—	—	—	—
Major bleeding event	12 (1.7)	11 (2.6)	0.64 (0.28-1.50)	.297	0.61 (0.25-1.50)	.273
PCI-surgery interval ≤6 months						
	n = 413	n = 169				
NACE	16 (3.9)	10 (5.9)	0.64 (0.29-1.49)	.282	0.44 (0.19-1.05)	.056
MACE	4 (1.0)	5 (3.0)	0.32 (0.08-1.23)	.093	0.21 (0.05-0.84)	.026
Cardiac death	4 (1.0)	4 (2.4)	—	—	—	—
Myocardial infarction	0 (0)	2 (1.2)	—	—	—	—
Stent thrombosis	0 (0)	1 (0.6)	—	—	—	—
Major bleeding event	8 (1.9)	4 (2.4)	0.81 (0.25-3.09)	.741	0.75 (0.22-2.93)	.650
PCI-surgery interval ≤3 months						
	n = 227	n = 87				
NACE	9 (4.0)	4 (4.6)	0.86 (0.27-3.23)	.801	0.64 (0.19-2.45)	.472
MACE	3 (1.3)	1 (1.1)	1.15 (0.15-23.5)	.903	0.68 (0.08-1.44)	.751
Cardiac death	3 (1.3)	1 (1.1)	—	—	—	—
Myocardial infarction	0 (0)	0 (0)	—	—	—	—
Stent thrombosis	0 (0)	0 (0)	—	—	—	—
Major bleeding event	4 (1.8)	3 (3.4)	0.50 (0.11-2.59)	.374	0.50 (0.10-2.69)	.387

Event rate of study endpoints are presented as n (%) with OR and 95% CI. *P* value derived from unadjusted and PS-based adjusted regression model indicate the comparison between APT strategies (APT continuation vs APT discontinuation). APT = antiplatelet therapy; CI = confidence interval; MACE = major adverse cardiovascular event; NACE = net adverse clinical event; OR = odds ratio; PCI = percutaneous coronary intervention; PS = propensity score.

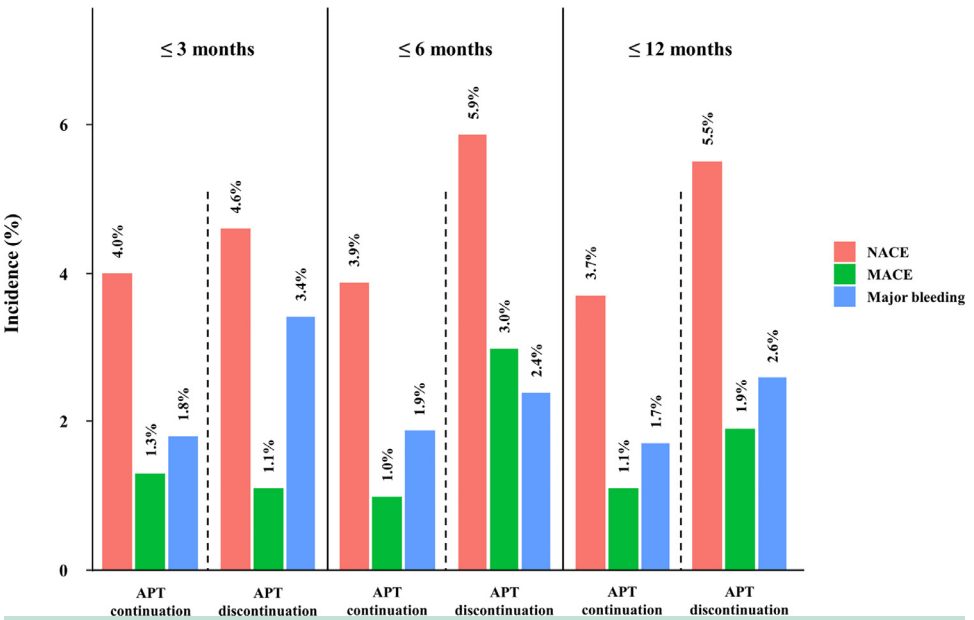

Figure 2 Incidence of study endpoints stratified by APT strategies and PCI-surgery interval. Bar plots for the incidences of study endpoints, stratified by APT strategies (APT discontinuation vs APT continuation) and PCI-surgery interval (≤3 months vs ≤6 months vs ≤12 months). APT = antiplatelet therapy; MACE = major adverse cardiovascular event; NACE = net adverse clinical event; PCI = percutaneous coronary intervention.

	APT continuation	APT discontinuation	PS-adjusted odds ratio (95% CI)	P-value for interaction
	no. of events/total no.(event rate, %)			
Overall	***26/708 (3.7)***	***23/422 (5.5)***	***0.48 (0.26–0.89)***	
Clinical diagnosis at index PCI				0.200
Stable angina	14/342 (4.1)	7/165 (4.2)	0.74 (0.29–2.05)	
Acute coronary syndrome	12/366 (3.3)	16/257 (6.2)	0.34 (0.14–0.78)	
Complex PCI				0.481
No	15/540 (2.8)	16/336 (4.8)	0.42 (0.19–0.92)	
Yes	11/168 (6.5)	7/86 (8.1)	0.63 (0.23–1.83)	
PCI–surgery interval				0.731
15–90 days	9/227 (4.0)	4/87 (4.6)	0.64 (0.19–2.45)	
91–180 days	7/186 (3.8)	6/82 (7.3)	0.30 (0.09–1.01)	
181–365 days	10/295 (3.4)	13/253 (5.1)	0.55 (0.22–1.34)	
Surgical risk				0.448
Low	8/430 (1.9)	3/182 (1.6)	0.67 (0.18–3.23)	
Intermediate-to-high	18/278 (6.5)	20/240 (8.3)	0.44 (0.21–0.89)	
Urgent/emergent surgery				0.971
No	10/609 (1.6)	16/400 (4.0)	0.47 (0.20–1.08)	
Yes	16/99 (16.2)	7/22 (31.8)	0.34 (0.11–1.07)	
Age				0.190
<65 years	11/252 (4.4)	6/161 (3.7)	0.97 (0.33–3.05)	
≥65 years	15/456 (3.3)	17/261 (6.5)	0.34 (0.16–0.72)	
Sex				0.374
Male	20/506 (4.0)	19/279 (6.8)	0.38 (0.19–0.76)	
Female	6/202 (3.0)	4/143 (2.8)	1.14 (0.30–4.84)	
Hypertension				0.316
No	7/170 (4.1)	3/98 (3.1)	0.66 (0.16–3.40)	
Yes	19/538 (3.5)	20/324 (6.2)	0.44 (0.22–0.88)	
Diabetes mellitus				0.846
No	10/350 (2.9)	10/223 (4.5)	0.52 (0.20–1.37)	
Yes	16/358 (4.5)	13/199 (6.5)	0.46 (0.21–1.04)	
Dyslipidemia				0.636
No	9/287 (3.1)	11/210 (5.2)	0.38 (0.14–1.00)	
Yes	17/421 (4.0)	12/212 (5.7)	0.56 (0.25–1.27)	
Chronic heart failure				0.648
No	21/662 (3.2)	20/397 (5.0)	0.48 (0.25–0.95)	
Yes	5/46 (10.9)	3/25 (12.0)	0.40 (0.07–2.45)	
Chronic kidney disease				0.884
No	17/529 (3.2)	17/347 (4.9)	0.51 (0.24–1.07)	
Yes	9/179 (5.0)	6/75 (8.0)	0.46 (0.15–1.45)	
Prior cerebrovascular accident				0.685
No	23/609 (3.8)	20/373 (5.4)	0.47 (0.24–0.90)	
Yes	3/99 (3.0)	3/49 (6.1)	0.56 (0.09–3.49)	
Dual APT before surgery				0.175
No	3/130 (2.3)	6/81 (7.4)	0.13 (0.02–0.58)	
Yes	23/578 (4.0)	17/341 (5.0)	0.63 (0.32–1.25)	

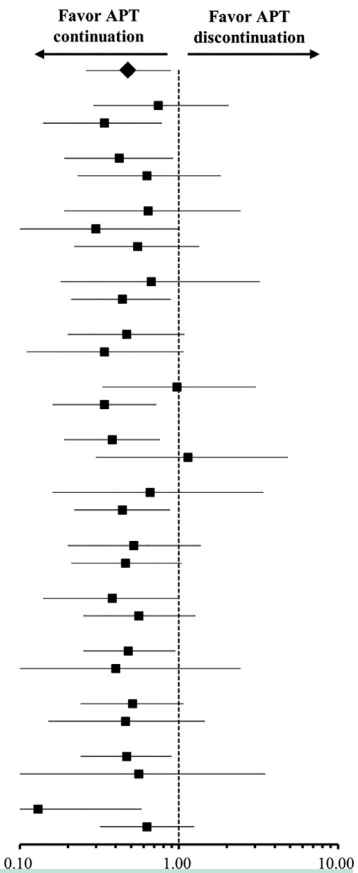

Figure 3 Forest plot of APT strategies for NACE. The effect of APT continuation compared with APT discontinuation on NACE are presented in terms of event rates, PS-adjusted odds ratios, and interaction terms. *P* value for interaction indicates the *P* value for the association between APT strategy and each confounding factor. APT = antiplatelet therapy; CI = confidence interval; NACE = net adverse clinical event; PCI = percutaneous coronary intervention; PS = propensity score.

for patients undergoing non-cardiac surgery, but rather increases the bleeding risk. However, for the POISE-2 subpopulation, which included patients with previous PCI, aspirin significantly reduced ischemic events without increasing bleeding events, when compared with a placebo.[22,23] Accordingly, it is still strongly recommended that aspirin be maintained during non-cardiac surgery for patients who previously received PCI, even in the case of urgent surgery, if bleeding risk allows.[9,11]

The current multicenter registry study demonstrated that about two-thirds of the patients continued APT during non-cardiac surgery performed within 1 year after second-generation drug-eluting stent implantation. APT was continued more frequently in patients with comorbidities, such as dyslipidemia and chronic kidney disease, and in surgeries performed during a relatively early period (before 6 months) after PCI and in emergent settings.

In this study, the incidence of NACE was lower than that reported in previous studies (4-7% incidence of MACE and 5-7% incidence of bleeding events).[14,24-26] The difference may be because we only included second-generation drug-eluting stent, which is thought to have lower thromboembolic risk than bare-metal or first-generation drug-eluting stents. This study demonstrated that the incidence of NACE and MACE was lower in the APT continuation group than in the APT discontinuation group with similar incidence of major bleeding events. This result suggests that although the contemporary coronary stent proves less thrombogenic, prevention of ischemic events during the perioperative period, rather than bleeding, needs to be considered as a top priority, especially for surgeries within 1 year.

Although the current guidelines for management of coronary artery disease and revascularization recommend mandatory dual APT after PCI, dual APT is often required to be interrupted to prevent excessive bleeding risk during surgeries. As unplanned discontinuation of dual APT may increase the patients' ischemic risk, APT strategy during non-cardiac surgery for patients receiving dual APT should also be determined with careful consideration of minimizing the ischemic risk from coronary stent and preventing bleeding risk from surgery.[9,10] The recent guideline for non-cardiac surgery strongly recommended that dual APT

Table 3 Regression Models of Dual Antiplatelet Therapy vs Single Antiplatelet Therapy for Incidence of Study Endpoints

	Event Rate, n (%)		Unadjusted	PS-Adjusted
	Dual APT	Single APT	OR (95% CI)	OR (95% CI)
PCI-surgery interval ≤12 months				
	n = 450	n = 258		
NACE	16 (3.6)	10 (3.9)	0.91 (0.41-2.12)	0.74 (0.33-1.73)
MACE	7 (1.6)	1 (0.4)	4.06 (0.72-76.1)	3.28 (0.57-61.9)
Cardiac death	6 (1.3)	0 (0)	-	-
Myocardial infarction	1 (0.2)	1 (0.4)	-	-
Stent thrombosis	0 (0)	0 (0)	-	-
Major bleeding event	6 (1.3)	6 (2.3)	0.57 (0.18-1.83)	0.51 (0.15-1.68)
PCI-surgery interval ≤6 months				
	n = 277	n = 136		
NACE	10 (3.6)	6 (4.4)	0.81 (0.29-2.43)	0.67 (0.24-2.06)
MACE	4 (1.4)	0 (0)	-	-
Cardiac death	4 (1.4)	0 (0)	-	-
Myocardial infarction	0 (0)	0 (0)	-	-
Stent thrombosis	0 (0)	0 (0)	-	-
Major bleeding event	4 (1.4)	4 (2.9)	0.48 (0.11-2.07)	0.43 (0.10-1.87)
PCI-surgery interval ≤3 months				
	n = 161	n = 66		
NACE	5 (3.1)	4 (6.1)	0.50 (0.13-2.06)	0.37 (0.09-1.62)
MACE	3 (1.9)	0 (0)	-	-
Cardiac death	3 (1.9)	0 (0)	-	-
Myocardial infarction	0 (0)	0 (0)	-	-
Stent thrombosis	0 (0)	0 (0)	-	-
Major bleeding event	2 (1.2)	2 (3.0)	0.40 (0.05-3.41)	0.36 (0.04-3.12)

Event rate of study endpoints are presented as n (%) with OR and 95% CI. APT = antiplatelet therapy; CI = confidence interval; MACE = major adverse cardiovascular event; NACE = net adverse clinical event; OR = odds ratio; PCI = percutaneous coronary intervention; PS = propensity score.

be maintained for patients undergoing non-cardiac surgery unless high bleeding risk is expected.[11]

In this study, single APT was associated with comparable net clinical outcome compared with dual APT. Notably, myocardial infarction or stent thrombosis was substantially low, and cardiac death was the most common MACE that occurred in patients receiving dual APT (6/7) and 5 of these patients died after emergent surgery. Thus, APT could not be discontinued in a timely manner in these cases. The patient who experienced myocardial infarction during dual APT continuation was at extremely high ischemic risk, underwent PCI on vein graft for coronary artery bypass graft, and suffered from end-stage renal disease under hemodialysis. The myocardial infarction event for the patient occurred due to compromised left internal mammary artery flow resulting from left subclavian artery stenosis. Although definite conclusions comparing dual and single APT cannot be drawn from this study due to the limited number of patients and events, the substantially low incidence of myocardial infarction and stent thrombosis among patients receiving single APT suggests that de-escalation from dual APT to single APT could be an alternative strategy for patients undergoing non-cardiac surgery. A retrospective study revealed that a between-physician consensus in APT strategy for each patient could improve the net clinical outcome. It emphasized the importance of careful individual assessment of the ischemic and bleeding risks.[27] In a similar context, an individually tailored APT strategy should be considered, and in order to optimize the balance between ischemic and bleeding risk of each patient, intravenous antiplatelet agents, such as cangrelor are considered useful.[28,29] Cangrelor reversibly binds to the P2Y12 receptor of platelets to block their activation and aggregation. This agent can be administered intravenously, as it has a short half-life and a rapid plasma clearance rate. As the net clinical outcome could be sensitively affected by the timing of APT discontinuation, a bridging therapy using intravenous agents could be a reasonable option for optimizing ischemia-bleeding balance during non-cardiac surgery.

This study contrasts with most studies regarding optimal APT strategy for non-cardiac surgery for the following reasons: 1) this study focused on surgeries within 1 year of PCI; 2) only PCI with second-generation drug-eluting stent implantation was included; and 3) this study demonstrated a net clinical benefit, including both ischemic and bleeding events.[12-15] Because the heterogeneity of patients, PCI, and surgeries may affect the interpretation, such specific criteria could support our results.

Study Limitations

This study has some limitations. First, because choice of APT strategy was not randomized, residual confounding factors such as perioperative frailty might have affected the

results despite the propensity score adjustment. Subsequently, this study should be interpreted as purely exploratory and hypothesis-generating. Second, the statistical power of this study might have been too limited to demonstrate between-group differences because of the small sample size and number of events. Therefore, this study cannot provide a meaningful conclusion regarding comparison between aspirin and P2Y12 receptor inhibitors. However, our results do indicate that further studies with a large sample size are warranted.

Future Directions

The heterogeneity of patients' clinical characteristics, surgeries, and PCI procedures are key hurdles for evaluating the independent effect of each APT strategy. As procedure techniques and devices improve, the incidence of ischemic events decreases, requiring large sample sizes for hypothesis testing. Accordingly, a randomized controlled trial with multinational participating centers or meta-analysis including a large number of patients is warranted.

CONCLUSIONS

The APT continuation strategy was chosen in a substantial proportion of patients and was associated with the benefit of potentially reducing 30-day NACE and MACE with similar incidence of major bleeding events, compared to APT discontinuation. This study suggests a possible benefit of APT continuation in non-cardiac surgery within 1 year of second-generation drug-eluting stent implantation.

References

1. Philip F, Agarwal S, Bunte MC, et al. Stent thrombosis with second-generation drug-eluting stents compared with bare-metal stents: network meta-analysis of primary percutaneous coronary intervention trials in ST-segment−elevation myocardial infarction. *Circ Cardiovasc Interv* 2014;7(1):49–61.
2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41(3):407–77.
3. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42(14):1289–367.
4. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145(3):e18–e114.
5. To AC, Armstrong G, Zeng I, Webster MW. Noncardiac surgery and bleeding after percutaneous coronary intervention. *Circ Cardiovasc Interv* 2009;2(3):213–21.
6. Gandhi NK, Abdel-Karim AR, Banerjee S, Brilakis ES. Frequency and risk of noncardiac surgery after drug-eluting stent implantation. *Catheter Cardiovasc Interv* 2011;77(7):972–6.
7. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA* 2013;310(14):1462–72.
8. Egholm G, Kristensen SD, Thim T, et al. Risk associated with surgery within 12 months after coronary drug-eluting stent implantation. *J Am Coll Cardiol* 2016;68(24):2622–32.
9. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130(24):2215–45.
10. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on Non-cardiac Surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;35(35):2383–431.
11. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing noncardiac surgery. *Eur Heart J* 2022;43(39):3826–924.
12. Rossini R, Musumeci G, Capodanno D, et al. Perioperative management of oral antiplatelet therapy and clinical outcomes in coronary stent patients undergoing surgery. Results of a multicentre registry. *Thromb Haemost* 2015;113(2):272–82.
13. Egholm G, Thim T, Olesen KK, et al. Dual anti-platelet therapy after coronary drug-eluting stent implantation and surgery-associated major adverse events. *Thromb Haemost* 2016;116(1):172–80.
14. Park SK, Jung DE, SA Jung, Kim WH, Bahk JH. Risk of non-cardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Sci Rep* 2017;7(1):16393.
15. Cao D, Levin MA, Sartori S, et al. Perioperative risk and antiplatelet management in patients undergoing non-cardiac surgery within 1 year of PCI. *J Thromb Thrombolysis* 2022;53(2):380–9.
16. Russell C, Roberts M, Williamson TG, McKercher J, Jolly SE, McNeil J. Clinical categorization for elective surgery in Victoria. *ANZ J Surg* 2003;73(10):839–42.
17. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol* 2016;68(17):1851–64.
18. Rossini R, Tarantini G, Musumeci G, et al. A multidisciplinary approach on the perioperative antithrombotic management of patients with coronary stents undergoing surgery: Surgery After Stenting 2. *JACC Cardiovasc Interv* 2018;11(5):417–34.
19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60(16):1581–98.
20. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115(17):2344–51.
21. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 2010;8(1):202–4.
22. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014;370(16):1494–503.
23. Graham MM, Sessler DI, Parlow JL, et al. Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. *Ann Intern Med* 2018;168(4):237–44.
24. Wijeysundera DN, Wijeysundera HC, Yun L, et al. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation* 2012;126(11):1355–62.
25. Saia F, Belotti LM, Guastaroba P, et al. Risk of adverse cardiac and bleeding events following cardiac and noncardiac surgery in patients with coronary stent: how important is the interplay between stent type and time from stenting to surgery? *Circ Cardiovasc Qual Outcomes* 2016;9(1):39–47.
26. Cao D, Chandiramani R, Capodanno D, et al. Non-cardiac surgery in patients with coronary artery disease: risk evaluation and periprocedural management. *Nat Rev Cardiol* 2021;18(1):37–57.
27. Kim C, Kim JS, Kim H, et al. Consensus decision-making for the management of antiplatelet therapy before non-cardiac surgery in patients who underwent percutaneous coronary intervention with second-generation drug-eluting stents: a cohort study. *J Am Heart Assoc* 2021;10(8):e020079.

28. Khan AA, Murtaza G, Khalid M, Finniss M, Helton T. Efficacy of cangrelor as bridging therapy post PCI. *Cardiovasc Hematol Disord Drug Targets* 2020;20(3):227–31.
29. Valenti R, Muraca I, Marcucci R, et al. Tailored" antiplatelet bridging therapy with cangrelor: moving toward personalized medicine. *Platelets* 2022;33(5):687–91.

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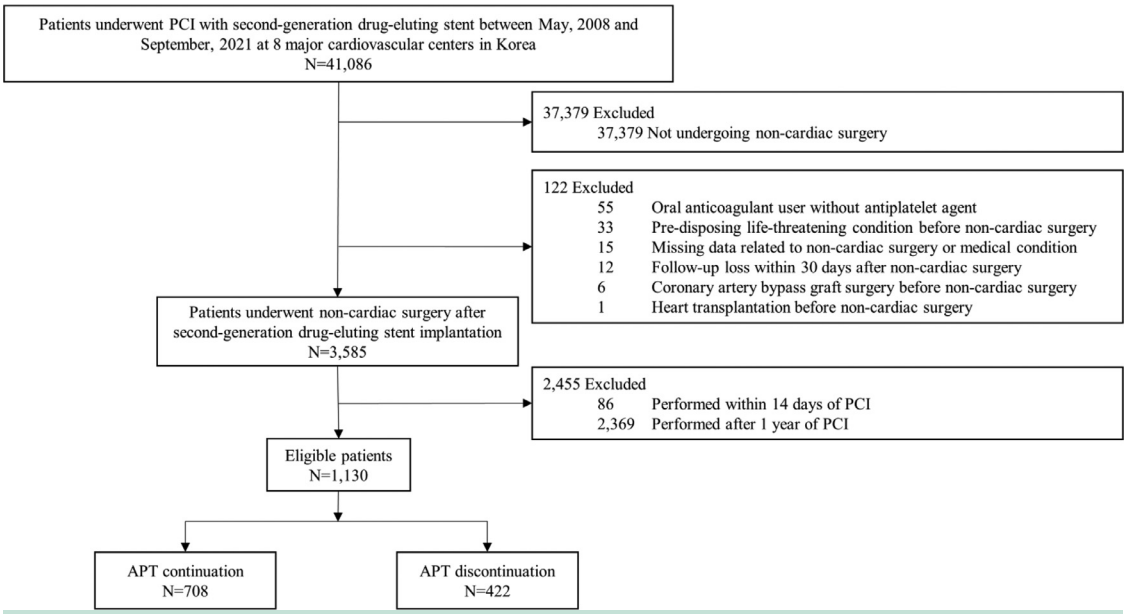
SUPPLEMENTARY DATA

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjmed.2023.06.003.



Supplemental Figure 1 The study flow chart.
Patients who underwent non-cardiac surgery within 1 year of PCI with second-generation drug-eluting stent were included. Among 1,130 eligible patients, 708 patients continued APT and 422 patients discontinued APT during the perioperative period. APT = antiplatelet therapy; PCI = percutaneous coronary intervention.

Supplemental Table 1 Regression models of aspirin versus P2Y12 receptor inhibitor for incidence of study endpoints

	Event rate, n (%)		Unadjusted	PS-adjusted
	Aspirin	P2Y12 receptor inhibitor	OR (95% CI)	OR (95% CI)
PCI-surgery interval ≤ 12 months				
	n=213	n=45		
NACE	7 (3.3)	3 (6.7)	0.48 (0.13−2.28)	0.52 (0.13−2.51)
MACE	1 (0.5)	0 (0)	-	-
Cardiac death	0 (0)	0 (0)	-	-
Myocardial infarction	1 (0.5)	0 (0)	-	-
Stent thrombosis	0 (0)	0 (0)	-	-
Major bleeding event	4 (1.9)	2 (4.4)	0.41 (0.08−3.04)	0.42 (0.08−3.18)
PCI-surgery interval ≤ 6 months				
	n=108	n=28		
NACE	4 (3.7)	2 (7.1)	0.50 (0.09−3.75)	0.64 (0.11−4.99)
MACE	0 (0)	0 (0)	-	-
Cardiac death	0 (0)	0 (0)	-	-
Myocardial infarction	0 (0)	0 (0)	-	-
Stent thrombosis	0 (0)	0 (0)	-	-
Major bleeding event	3 (2.8)	1 (3.6)	0.77 (0.09−15.9)	0.85 (0.10−17.9)
PCI-surgery interval ≤ 3 months				
	n=54	n=12		
NACE	3 (5.6)	1 (8.3)	0.65 (0.07−13.8)	0.75 (0.08−1.66)
MACE	0 (0)	0 (0)	-	-
Cardiac death	0 (0)	0 (0)	-	-
Myocardial infarction	0 (0)	0 (0)	-	-
Stent thrombosis	0 (0)	0 (0)	-	-
Major bleeding event	2 (3.7)	0 (0)	-	-

Event rate of study endpoints are presented as n (%) with OR and 95% CI. APT = antiplatelet therapy; CI = confidence interval; MACE = major adverse cardiovascular event; NACE = net adverse clinical event; OR = odds ratio; PCI = percutaneous coronary intervention; PS = propensity score.