Journal of the American Heart Association

ORIGINAL RESEARCH

Patterns of Antiplatelet Therapy During Noncardiac Surgery in Patients With Second-Generation Drug-Eluting Stents

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BACKGROUND: Continuing antiplatelet therapy (APT) has been generally recommended during noncardiac surgery, but it is uncertain if preoperative discontinuation of APT has been avoided or harmful in patients with second-generation drug-eluting coronary stents.

METHODS AND RESULTS: Patients undergoing noncardiac surgery after second-generation drug-eluting coronary stent implantation were assessed in a multicenter cohort in Korea. Net adverse clinical events within 30 days postoperatively, defined as all-cause death, major adverse cardiac events, and major bleeding, were evaluated. Of 3582 eligible patients, 49% patients discontinued APT during noncardiac surgery. The incidence of net adverse clinical events was comparable between patients with continuation versus discontinuation (4.1% versus 3.4%; *P*=0.257) of APT during noncardiac surgery. Perioperative discontinuation of APT did not impact on net adverse clinical events (adjusted hazard ratio [HR], 1.00; 95% CI, 0.69–1.44; *P*=0.995). In subgroup analysis, patients undergoing intra-abdominal surgery were exposed to less risk of major bleeding by discontinuing APT (adjusted HR, 0.26; 95% CI, 0.08–0.91; *P*=0.035). Prolonged discontinuation of APT for ≥9 days was associated with higher risk of a major adverse cardiac event compared with continuing APT (adjusted HR, 3.38; 95% CI, 1.36–8.38; *P*=0.009).

CONCLUSIONS: APT was discontinued preoperatively in almost half of patients with second-generation drug-eluting coronary stents. Our explorative analysis showed that there was no significant impact of discontinuing APT on the risk of perioperative adverse events except that discontinuing APT may be associated with decreased hemorrhagic risk in patients undergoing intra-abdominal surgery.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03908463.

Key Words: antiplatelet agent ■ stent ■ surgery

Second-generation drug-eluting stents (DESs) reflect technological improvements to provide better efficacy and safety, with a lower risk of restenosis and stent thrombosis after percutaneous coronary intervention (PCI).[1,2] Continuous antiplatelet therapy (APT) is important to prevent ischemic events following PCI[3–5]; however, platelet inhibition increases the risk of hemorrhage, especially during invasive procedures.

In patients with DESs, clinicians must decide whether to continue or discontinue APT before

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.016218

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Among patients undergoing noncardiac surgery after second-generation drug-eluting stent implantation, preoperative discontinuation of antiplatelet therapy was common and safe in terms of both ischemic and hemorrhagic risk.
- Discontinuing APT may be associated with lower risk of major bleeding in the certain types of surgery (eg, intra-abdominal) compared with continuing antiplatelet therapy in patients with second-generation drug-eluting stents.

What Are the Clinical Implications?

- Our study supports the notion that discontinuing antiplatelet therapy may be considered an acceptable option for patients undergoing coronary revascularization with second-generation drug-eluting stents before noncardiac surgery unless unduly prolonged (≥9 days).

Nonstandard Abbreviations and Acronyms

APT	antiplatelet therapy
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
HR	hazard ratio
MACE	major adverse cardiac event
MI	myocardial infarction
NACE	net adverse clinical event
NCS	noncardiac surgery
PCI	percutaneous coronary intervention
POISE-2	Perioperative Ischemic Evaluation 2

noncardiac surgery (NCS) to achieve the appropriate balance between thromboembolic and bleeding risks. In the POISE-2 (Perioperative Ischemic Evaluation 2) randomized trial, continuing aspirin did not reduce ischemic events and increased bleeding risk in patients overall,[6] but a secondary analysis demonstrated an association between aspirin use and lower ischemic risk after NCS among patients with previous PCI.[7] Conversely, a large population-based cohort study of patients with previous PCI reported no reduction of ischemic events with continuing APT perioperatively.[8] Nevertheless, continuing APT is widely regarded as optimal perioperative management in patients undergoing NCS without excessive bleeding risk, for which prompt discontinuation of all antiplatelet agents, including aspirin and P2Y12 inhibitors, may also be considered.[6,8] Evidence is especially limited regarding continuation or discontinuation of APT in patients with second-generation DESs undergoing NCS. The objectives of this study were to describe patterns of perioperative APT in this setting and to evaluate whether discontinuing APT is safe in patients with second-generation DESs.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

We used data from a prospective multicenter cohort registry (KOMATE [Korean Multicenter Angioplasty Team registry]; NCT03908463), which collects information regarding all patients undergoing PCI at major medical centers in Korea. The registry records include demographic, anatomic, and procedural characteristics, and postprocedure clinical outcomes. Nine centers participated in this study. Among 41 083 patients with a second-generation DES in 9 institutes, we identified 3791 who underwent NCS from May 2008 to October 2018. We included 3582 patients in the final analysis, after excluding those undergoing emergency surgery, which should not be delayed >3 days since initial decision (n=87), receiving anticoagulants without an antiplatelet agent (n=55), with life-threatening conditions at the time of surgery (n=33), missing critical data (n=15), and lost to follow-up (n=12), as well as those who underwent coronary artery bypass graft (n=6) or heart transplantation (n=1) before NCS (Figure 1). If patients underwent >1 NCS after second-generation DES implantation, we considered only the first operation in our analyses. Investigators at each study site collected the medical records regarding surgery-related variables and cessation of antiplatelet agents. The institutional review board at each site approved the study protocol and waived the need for informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[9]

End Points

We primarily assessed clinical outcomes within 30 days post-NCS, including death and adverse cardiac and hemorrhagic events. Net adverse clinical event (NACE) was defined as a composite of all-cause death, major adverse cardiac event (MACE), and major bleeding. MACE included cardiac death, myocardial infarction (MI), and stent thrombosis. Cardiac death was defined as death with ischemic symptoms, typical electrocardiographic ischemic

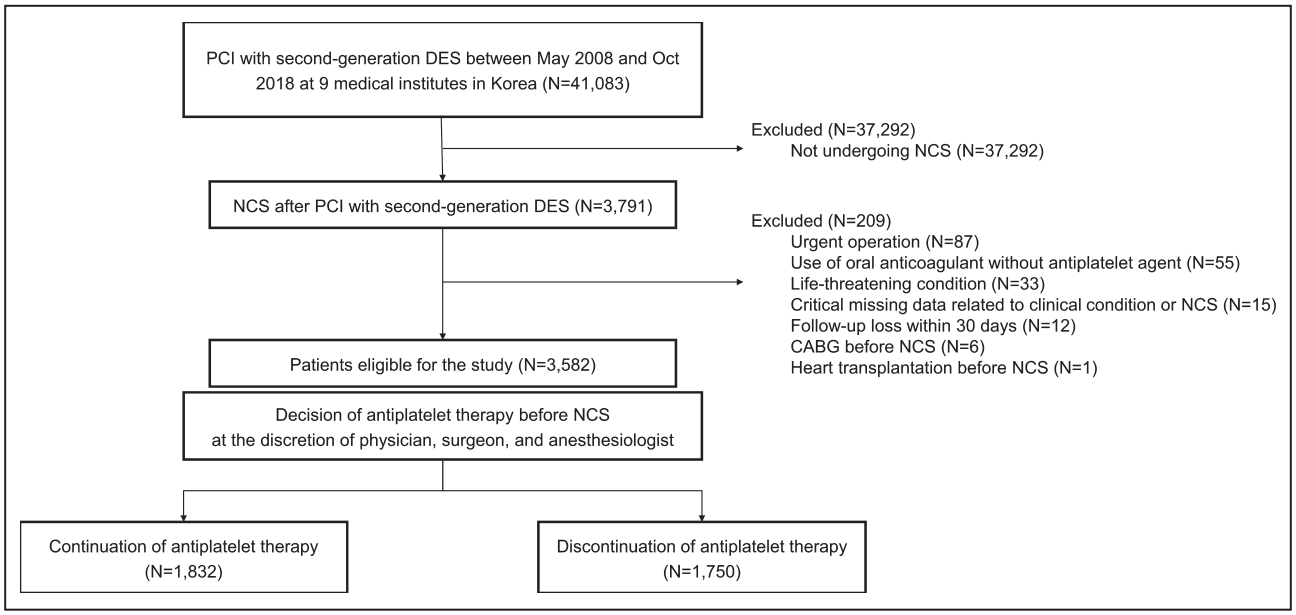

Figure 1. Flow diagram of study participants.
CABG indicates coronary artery bypass graft; DES, drug-eluting stent; NCS, noncardiac surgery; and PCI, percutaneous coronary intervention.

patterns, cardiac enzyme elevation, or fatal ventricular arrhythmia with no obvious noncardiac cause of death. MI was defined according to the Third Universal Definition as an increase in creatine kinase myocardial band fraction above the upper limit of normal or an increase in troponin-T or -I above the 99th percentile of the upper limit of normal and ≥1 of the following: symptoms, electrocardiographic changes, or imaging or angiographic findings indicative of MI.[10] Stent thrombosis was defined according to the Academic Research Consortium recommendations.[11] Major bleeding was defined according to the International Society of Thrombosis and Hemostasis (available in Data S1).[12] Each event was independently adjudicated by 2 investigators (CK, HK). In a case of disagreement, a third investigator (J-SK) reviewed it to provide final adjudication. Two independent adjudications showed 88% agreement and k=0.75 for classification of cardiac death.

Revascularization, APT, and Surgical Risk

All patients underwent PCI according to each participating site's standard protocol. Second-generation DES included durable polymer everolimus- and zotarolimus-eluting stents; biodegradable polymer everolimus-, biolimus-, and sirolimus-eluting stents; and polymer-free biolimus-eluting stents. All patients received dual APT (DAPT) with aspirin and P2Y12 inhibitor at discharge after PCI. High-risk PCI was defined as the presence of ≥1 risk factors, including left main stenting, 3 stents or long total stent length (≥60 mm), small-diameter stent (<2.5 mm), 2 stents at bifurcation, or chronic total occlusion.[13,14] All study sites share a policy of consensus decision for perioperative APT before NCS in patients with previous PCI. Cardiologists recommended whether each antiplatelet agent should be continued or discontinued for a certain period of time before NCS. Surgeons and anesthesiologists finally decided and recorded the duration of APT discontinuation before NCS. Investigators reviewed medical records to confirm the discontinuation duration for antiplatelet drugs. Patients who were guided to withdraw all antiplatelet agents for ≥1 days were classified as discontinuing APT, and prescription patterns of continuing APT were subsequently categorized into aspirin monotherapy, P2Y12 inhibitor monotherapy, and DAPT. Urgent surgery was defined as if surgery should be performed within 30 days for a condition that has the potential to deteriorate quickly and become an emergency.[15] Cardiac risk of each NCS was classified as low (<1%) or intermediate to high (≥1%), according to ≈30-day risk of cardiovascular death or MI.[4,16] Hemorrhagic risk of each NCS was categorized into 3 groups (low, intermediate, or high), according to Rossini et al.[14]

Statistical Analysis

Continuous variables were reported as median and quartiles and compared using Mann–Whitney *U* test. Categorical variables were reported as number and percentage and compared using chi-square or Fisher's exact tests. A multivariate logistic regression model was used to identify independent factors associated with discontinuing APT by backward

elimination, which first included significant covariates identified by univariate analysis, and the final model including significant covariates was diagnosed by McFadden's R^2 statistics. Fit of the model was confirmed by using the likelihood-ratio test comparing with reduced model deleting each single covariate.[17] Kaplan–Meier estimate and the log-rank test were used to depict cumulative incidences of adverse events,[18] and the Cox proportional hazards model was used to compare the hazard of each adverse event between APT strategies, adjusting for potential confounders, which included explanatory variables finally chosen in a parsimonious multivariate model by backward stepdown deletion of covariates with the least significant variables and comparison of Akaike information criterion (Tables S1 through S3, Figure S1). Covariates associated with NACE, MACE, and major bleeding were applied to control for confounding in each subgroup model. Diabetes mellitus, chronic heart failure, chronic kidney disease, anemia, high-risk PCI, preoperative DAPT and β-blocker, urgent surgery, and surgery risk for cardiac and hemorrhagic event were adjusted for multivariate models for NACE. Chronic heart failure, anemia, use of β-blocker, high-risk PCI, duration between PCI and surgery, urgent surgery, and cardiac risk of surgery adjusted for multivariate models for MACE. Body mass index, anemia, urgent surgery, and hemorrhagic risk of surgery were applied for adjustment of multivariate models for major bleeding. Subgroup analyses were performed according to variable conditions associated with patient, procedure, surgery-related risk factors, and each type of surgery. For the analysis, particular types of surgery including ophthalmologic, spinal, head and neck, intrathoracic, gynecologic, breast, and transplantation surgeries were combined because adverse events occurred in fewer than 10 patients undergoing each surgery. A generalized additive model was applied to describe the nonparametric association between NACE and duration of APT discontinuation by using the "mgcv" package in R statistical software.[19] After duration of APT discontinuation for the least risk for NACE was determined by the nonparametric smoothing plot, different durations of discontinuation were categorized and compared with continuing APT and continuing aspirin monotherapy in regard to clinical outcomes. The multiple imputation by chained equation approach was used to impute missing values. We generated 5 complete data sets and pooled the coefficients of subsequent analyses.[20] Two-sided tests were performed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using R statistical software (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patterns of Perioperative APT

Of the 3582 eligible patients, 1832 (51%) continued APT and 1750 (49%) discontinued APT before NCS (Figure 1). The baseline characteristics of the 2 groups are shown in Table 1. Incidence of discontinuing APT widely differs across types of surgery. More patients discontinued APT before certain type of surgeries including gynecology (79%), breast (70%), head and neck (63%), and intra-abdominal (62%) surgeries; however, only some of the candidates for vascular (15%) or ophthalmologic (27%) surgeries discontinued APT. In women, preoperative use of aspirin monotherapy, β-blocker, or renin-angiotensin system inhibitor and surgery with higher cardiac or hemorrhage risk were independently associated with discontinuing APT. Chronic kidney disease, stable angina, high-risk PCI, and urgent surgery were related to discontinuing APT (Table 1, Table S4). Seventy-five percent of patients undergoing NCS within 6 months after PCI preoperatively continued APT, while 44% of patients undergoing NCS 12 months after PCI continued APT. Compared with other patterns of perioperative APT, continuing DAPT was associated with higher incidence of risk factors, including diabetes mellitus, chronic heart failure, chronic kidney disease, anemia, MI, and high-risk PCI (Table S5). Median time interval between PCI and NCS in patients continuing DAPT (7 months) was much shorter than the other groups (23–27 months; Table S5). Median duration of DAPT was 10.3 months in patients with stable angina and 11.2 months in patients with acute coronary syndrome.

Incidence and Risk of Perioperative Adverse Events

Perioperative NACE, MACE, and major bleeding occurred in 135 (3.8%), 40 (1.1%), and 97 (2.7%) patients, respectively. There were no significant differences in the incidence of NACE (4.1% versus 3.4%; $P=0.257$), MACE (1.4% versus 0.8%; $P=0.109$), and major bleeding (2.6% versus 2.9%; $P=0.664$) between continuation versus discontinuation of APT, respectively (Figure 2, Table S6). Adjusted hazard ratio (HR) of discontinuing APT was 1.00 (95% CI, 0.69–1.44; $P=0.995$) for NACE and 1.22 (95% CI, 0.80–1.87; $P=0.349$) for major bleeding (Table 2). Discontinuing APT tended to lead to a lower incidence of MACE compared with continuing APT (0.8% versus 1.4%; unadjusted HR, 0.56; 95% CI, 0.29–1.07; $P=0.081$). However, discontinuing APT did not have an independent effect on MACE in adjusted analysis (HR, 1.13; 95% CI, 0.57–2.24; $P=0.721$). Anemia, urgency, and surgical risk had independent influences on

Table 1. Baseline Patient and Surgical Characteristics

Covariates	Continuation (N=1832)	Discontinuation (N=1750)	*P* Value
Age, y	69 (61–75)	69 (61–75)	0.06
Male	1282 (70)	1120 (64)	<0.001
BMI, kg/m^2*	24.4 (22.5–26.6)	24.4 (22.2–26.4)	0.07
Comorbidity			
Hypertension	1384 (76)	1304 (75)	0.50
Diabetes mellitus	871 (48)	768 (44)	0.03
Chronic heart failure	192 (10)	145 (8)	0.03
Chronic kidney disease	365 (20)	182 (10)	<0.001
Prior cerebrovascular attack	218 (12)	184 (11)	0.21
Anemia*	317 (22)	290 (18)	0.001
Preoperative medication			
Antiplatelet therapy			<0.001
Monotherapy			
Aspirin	627 (34)	610 (35)	
Clopidogrel	215 (12)	336 (19)	
Ticagrelor	6 (0)	2 (0)	
Prasugrel	0 (0.0)	1 (0)	
Others	0 (0.0)	5 (0)	
Dual therapy	984 (54)	796 (45)	
Duration of discontinuation before surgery, d	···	5 (4–7)	···
Oral anticoagulant	6 (0)	12 (1)	0.20
β-Blocker	802 (44)	853 (49)	0.003
Calcium channel blocker	565 (31)	576 (33)	0.20
RAS inhibitor	843 (46)	926 (53)	<0.001
Percutaneous coronary intervention			
Diagnosis at revascularization			<0.001
Stable angina	893 (49)	708 (40)	
Unstable angina	443 (24)	547 (31)	
Myocardial infarction	496 (27)	495 (28)	
Stented vessel			
Left main	133 (7)	75 (4)	<0.001
Left anterior descending artery	1107 (60)	1095 (63)	0.20
Left circumflex artery	462 (25)	466 (27)	0.36
Right coronary artery	641 (35)	621 (35)	0.78
Type of DES			
Durable polymer	1210 (66)	1353 (77)	<0.001
Bioresorbable polymer	618 (34)	409 (23)	<0.001
Polymer-free	70 (4)	18 (1)	<0.001
Number of stents			0.001
1	1087 (59)	1036 (59)	
2	453 (25)	501 (29)	
≥3	292 (16)	213 (12)	
Maximum stent diameter, mm*	3.0 (3.0–3.5)	3.0 (3.0–3.5)	0.05
Total stent length, mm*	30 (18–51)	30 (18–48)	0.83
High-risk PCI	484 (26)	393 (22)	0.007
Noncardiac surgery			
Duration from PCI, mo	16 (5–37)	23 (12–41)	<0.001

(*Continued*)

Table 1. Continued

Covariates	Continuation (N=1832)	Discontinuation (N=1750)	*P* Value
<6	491 (27)	181 (10)	<0.001
6 to <12	290 (16)	252 (14)	
≥12	1051 (57)	1317 (75)	
Urgent surgery	281 (15)	88 (5)	<0.001
Risk of cardiac event			<0.001
Low (<1%)	1082 (59)	892 (51)	
Intermediate to high (≥1%)	750 (41)	858 (49)	
Risk of hemorrhage			<0.001
Low	1268 (69)	896 (51)	
Intermediate to high	425 (23)	654 (37)	
High	139 (8)	200 (11)	
Type			<0.001
Orthopedic	276 (15)	358 (20)	
Superficial	324 (18)	301 (17)	
Ophthalmologic	403 (22)	147 (8)	
Intra-abdominal	198 (11)	317 (18)	
Urologic	183 (10)	207 (12)	
Vascular	210 (11)	37 (2)	
Spinal	82 (4)	129 (7)	
Head and neck	51 (3)	87 (5)	
Intrathoracic	26 (1)	37 (2)	
Gynecologic	12 (1)	46 (3)	
Intracranial	49 (3)	65 (4)	
Breast	6 (0)	14 (1)	
Transplantation	12 (1)	5 (0)	

Data are median (interquartile range) or number (percentage). BMI indicates body mass index; DES, drug-eluting stent; PCI, percutaneous coronary intervention; and RAS, renin-angiotensin system.

*These comparisons were performed among patients without missing values (values were missing for hemoglobin in 517 patients, BMI in 77 patients, stent diameter in 4 patients, and total stent length in 3 patients).

NACE, MACE, and major bleeding. Chronic heart failure, nonuse of β-blocker, and high-risk PCI were independent predictors for NACE and MACE (Table 2). Shorter duration between PCI and NCS was associated with increased risk of MACE in univariate analysis. NCS <6 months after PCI also tended to increase ischemic risk after adjustment (HR, 1.99; 95% CI, 0.98–4.01; *P*=0.056). However, the risk of major bleeding was not significantly affected by the post-PCI duration (Table 2). Risk of discontinuing APT was not significant for NACE, MACE, and major bleeding in subgroups (Figure 3, Figures S2 and S3) However, the effect of discontinuing APT widely differed across different types of surgeries. In patients undergoing intra-abdominal surgery, discontinuing APT tended to be beneficial in terms of NACE (adjusted HR, 0.40; 95% CI, 0.15–1.08; *P*=0.070), which was mainly driven by a reduction in major bleeding (adjusted HR, 0.26; 95% CI, 0.08–0.91; *P*=0.035). When continuing APT categorized into aspirin, P2Y12 inhibitor monotherapy, and DAPT, incidence of NACE was not significantly different among the 3 groups and patients who discontinued APT. However, patients continued DAPT had the highest incidence of all-cause death (3.8% versus 1.1–1.4%; *P*<0.001) and MACE (2.8% versus 0.8%; *P*=0.008) than other groups (Table S7).

Duration of Antiplatelet Therapy Discontinuation and Perioperative Adverse Events

Because a nonparametric smoothing plot indicated that discontinuing APT for 6 days was associated with the lowest risk of NACE in patients undergoing NCS, an interval of 4 to 8 days for discontinuing APT would be optimal for the least risk for NACE (Figure S4). In univariate analysis, discontinuing APT for 4 to 8 days was associated with the lowest risk for NACE (unadjusted HR, 0.59; 95% CI, 0.39–0.92; *P*=0.019) and MACE (unadjusted HR, 0.12; 95% CI, 0.03–0.52; *P*=0.004) compared with continuing APT (Figure 4). After adjustment,

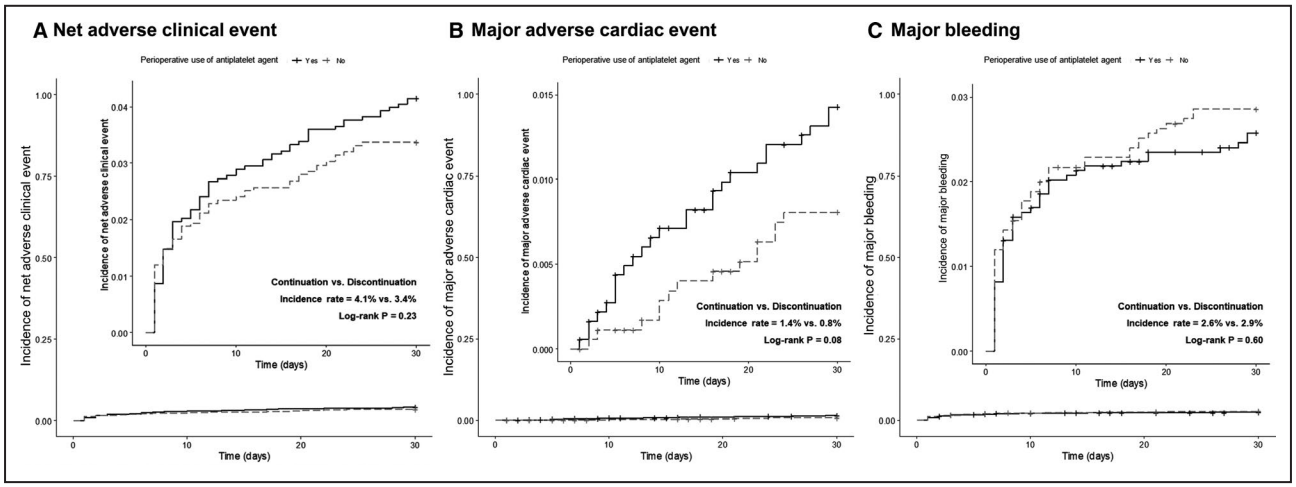

Figure 2. Cumulative incidence of perioperative adverse events comparing continuation vs discontinuation of antiplatelet therapy.
Net adverse clinical event (**A**), major adverse cardiac event (**B**), and major bleeding (**C**).

prolonged discontinuation of APT for ≥9 days led to higher risk of MACE compared with continuing APT (adjusted HR, 3.38; 95% CI, 1.36–8.38; *P*=0.009) or aspirin monotherapy (adjusted HR, 4.57; 95% CI, 1.44–14.5; *P*=0.010), however, discontinuation for ≤8 days was similar to continuing APT or continuing aspirin monotherapy in terms of the risk of NACE, MACE, and major bleeding (Figure S5).

DISCUSSION

Our study demonstrated that discontinuation of APT was presented in almost half of patients with second-generation DESs before NCS. Discontinuing APT was more frequent as surgical risk for cardiac or hemorrhagic risk increased. It was not of importance for the risk of NACE, MACE, and major bleeding in overall patients; however, it led to less major bleeding in intra-abdominal surgery. Prolonged discontinuation of APT for ≥9 days seemed to be associated with increased risk of MACE than continuing APT or aspirin monotherapy.

Current guidelines have stressed continuing APT during NCS. According to 2014 European Society of Cardiology/European Society of Anaesthesiology guidelines regarding NCS, continuing aspirin or a P2Y12 inhibitor may be recommended for surgery within 3 to 12 months of DES implantation, although discontinuing aspirin is another option if difficult hemostasis is anticipated.[4] The 2014 American College of Cardiology/American Heart Association guidelines regarding NCS also recommended that patients with coronary stents continue aspirin during NCS, if possible.[3] However, no firm evidence supports maintaining antiplatelet therapy; thus, both guidelines contain a proviso that the decision to continue or discontinue APT should be based on weighing the risks of bleeding and stent thrombosis in each individual.

Multidisciplinary approaches regarding perioperative APT during NCS have suggested classifying thrombotic and hemorrhagic risks for each type of surgery, type of coronary stent, and clinical and angiographic characteristics. While this is reasonable in usual situations, it remains unclear whether continuing aspirin is preferred for patients with a second-generation DES.[14] Indeed, predicting bleeding or ischemic events or comparing risk levels is difficult because high cardiac risk is frequently linked to an increased bleeding risk, and many instances of perioperative bleeding, stent thrombosis, and MI occur unpredictably. The reduced risk of ischemic events following PCI with second-generation DES is also relevant: These stents are associated with a lower risk of MI and stent thrombosis than first-generation DES[2] and bare-metal stents.[1] Accordingly, continuing APT may be less necessary with second-generation DESs in those with previous stents. Although a cardiologist may recommend continuing APT to minimize ischemic events, a surgeon may recommend discontinuation, especially in the presence of clinical or surgical factors increasing hemorrhagic risk, which would commonly increase cardiac risk as well. Thus, decisions should be individualized while considering various clinical factors. Practical methods of risk stratification or comprehensive discussion should be explored to optimize perioperative APT to minimize both ischemic and bleeding risks.

Discontinuing APT was more common in intermediate or high-cardiac-risk surgery, which was contrary to our expectations and previous recommendations for continuing APT based on the cardiac risk of surgery. Cardiac risk factors including chronic kidney disease,

Table 2. Predictors of Net Adverse Clinical Event, Major Adverse Cardiac Event, and Major Bleeding After Noncardiac Surgery

Predictors	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Net adverse clinical events				
Discontinuing antiplatelet therapy	0.81 (0.58–1.14)	0.228	1.00 (0.69–1.44)	0.995
Age, per 1-y increase	1.03 (1.01–1.04)	0.006	···	···
BMI, per 1-kg/m^2 increase	0.94 (0.89–0.99)	0.014	···	···
Diabetes mellitus	1.58 (1.13–2.23)	0.008	1.36 (0.95–1.95)	0.094
Chronic heart failure	2.10 (1.35–3.26)	0.001	1.63 (1.03–2.57)	0.038
Chronic kidney disease	2.04 (1.40–2.99)	<0.001	1.53 (0.99–2.37)	0.058
Anemia	2.71 (1.92–3.83)	<0.001	1.89 (1.28–2.79)	0.001
High-risk PCI	1.67 (1.17–2.38)	0.005	1.54 (1.08–2.21)	0.017
Preoperative medication				
DAPT	1.77 (1.18–2.64)	<0.001	1.42 (0.94–2.14)	0.096
β-Blocker	0.73 (0.51–1.03)	0.073	0.68 (0.48–0.96)	0.030
Duration between PCI and surgery, mo				
<6	1.68 (1.13–2.50)	0.010	···	···
6 to <12	1.33 (0.83–2.11)	0.235	···	···
≥12	(Reference)			
Urgent surgery	6.81 (4.84–9.58)	<0.001	5.37 (3.74–7.69)	<0.001
Surgery with intermediate to high cardiac risk	3.73 (2.53–5.51)	<0.001	1.81 (1.16–2.81)	0.008
Surgery with hemorrhagic risk				
Intermediate	2.17 (1.44–3.28)	<0.001	2.10 (1.36–3.24)	0.001
High	6.80 (4.48–10.3)	<0.001	4.38 (2.69–7.14)	<0.001
Major adverse cardiac events				
Discontinuing antiplatelet therapy	0.56 (0.29–1.07)	0.081	1.13 (0.57–2.24)	0.721
Age, per 1-y increase	1.03 (1.00–1.06)	0.087	···	···
Diabetes mellitus	1.79 (0.95–3.37)	0.072	···	···
Chronic heart failure	5.28 (2.76–10.1)	<0.001	3.06 (1.53–6.13)	0.002
Chronic kidney disease	2.42 (1.23–4.75)	0.011	···	···
Anemia	4.17 (2.24–7.74)	<0.001	2.65 (1.36–5.14)	0.004
Use of β-blocker	0.44 (0.22–0.88)	0.020	0.40 (0.20–0.80)	0.010
High-risk PCI	2.55 (1.37–4.75)	0.003	2.28 (1.21–4.28)	0.011
Duration between PCI and surgery, mo				
<6	3.17 (1.61–6.21)	0.001	1.99 (0.98–4.01)	0.056
6 to <12	1.47 (0.58–3.69)	0.417	1.36 (0.54–3.43)	0.517
≥12	(Reference)		(Reference)	
Urgent surgery	12.6 (6.74–23.6)	<0.001	10.2 (5.35–19.5)	<0.001
Surgery with intermediate to high cardiac risk	4.30 (2.05–9.03)	<0.001	3.81 (1.79–8.13)	0.001
Major bleeding				
Discontinuing antiplatelet therapy	1.11 (0.75–1.66)	0.597	1.22 (0.80–1.87)	0.349
Age, per 1-y increase	1.02 (1.00–1.04)	0.033	···	···
BMI, per 1-kg/m^2 increase	0.92 (0.86–0.98)	0.008	0.94 (0.88–1.00)	0.054
Anemia	2.58 (1.71–3.88)	<0.001	2.33 (1.54–3.54)	<0.001
Prior cerebrovascular attack	1.69 (1.00–2.86)	0.049	···	···
DAPT before surgery	1.77 (1.18–2.64)	0.006	···	···
Urgent surgery	5.43 (3.59–8.19)	<0.001	4.21 (2.72–6.51)	<0.001

(*Continued*)

Table 2. Continued

Predictors	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Surgery with hemorrhagic risk				
Intermediate	2.71 (1.59–4.59)	<0.001	2.68 (1.57–4.58)	<0.001
High	11.5 (6.94–19.0)	<0.001	9.21 (5.49–15.5)	<0.001

BMI indicates body mass index; DAPT, dual antiplatelet therapy; and PCI, percutaneous coronary intervention.

PCI characteristics, or time interval since PCI would concern the decision of continuing APT. However, patients receiving potent APT with P2Y12 inhibitors, which may be required for more powerful prevention against ischemic events, were discouraged from continuing APT during NCS. The discrepancy between the scopes of

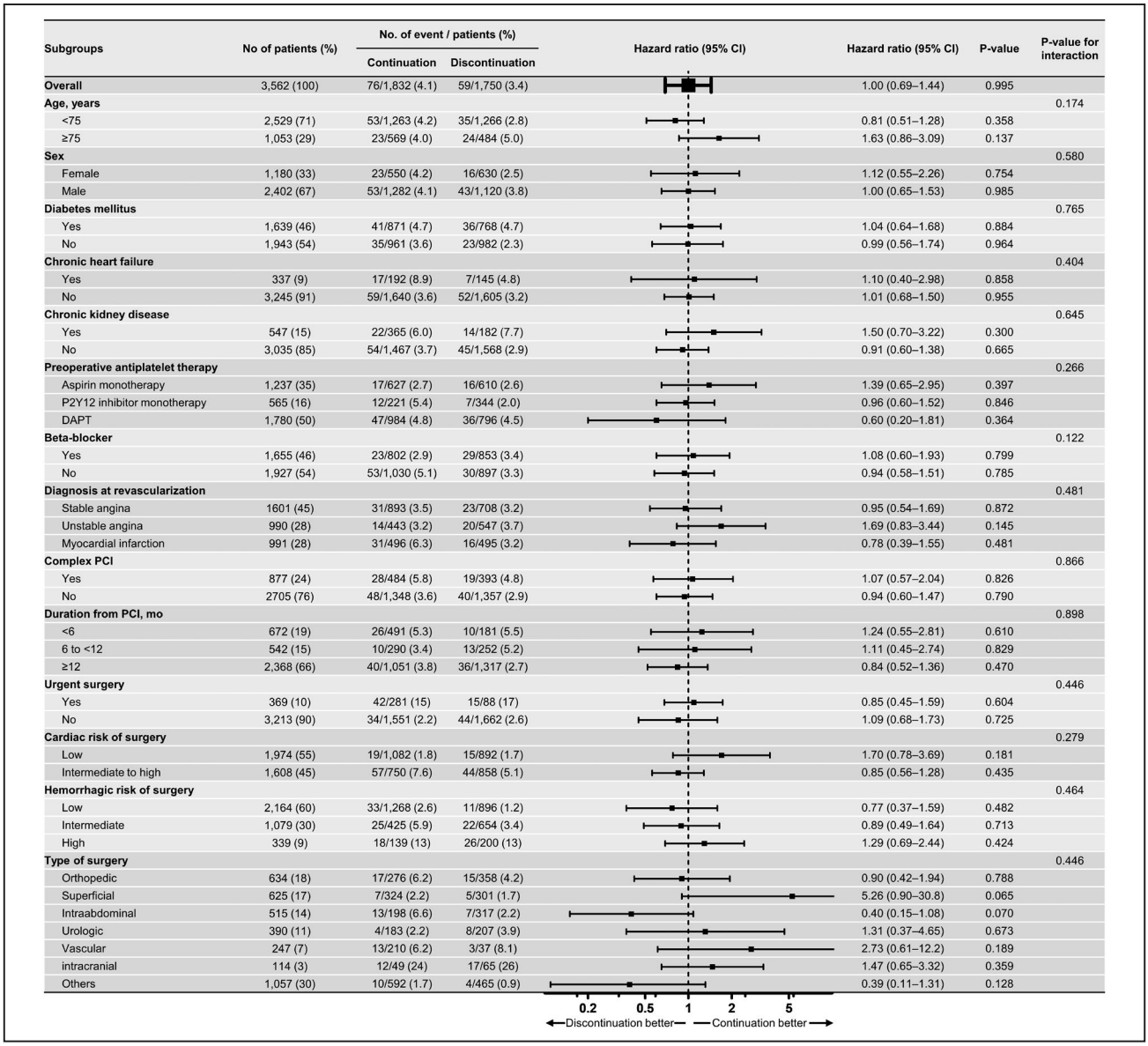

Figure 3. Forest plot of adjusted hazard ratio of discontinuing antiplatelet therapy for net adverse clinical event in subgroup analysis.

Cox proportional hazards model for net adverse clinical event was adjusted with diabetes mellitus, chronic heart failure, chronic kidney disease, anemia, high-risk PCI, preoperative use of antiplatelet therapy and β-blocker, urgent surgery, and surgical risk for cardiac and hemorrhagic risk. Center dots and whiskers indicate hazard ratios and 95% CIs, respectively. DAPT indicates dual antiplatelet therapy; and PCI, percutaneous coronary intervention.

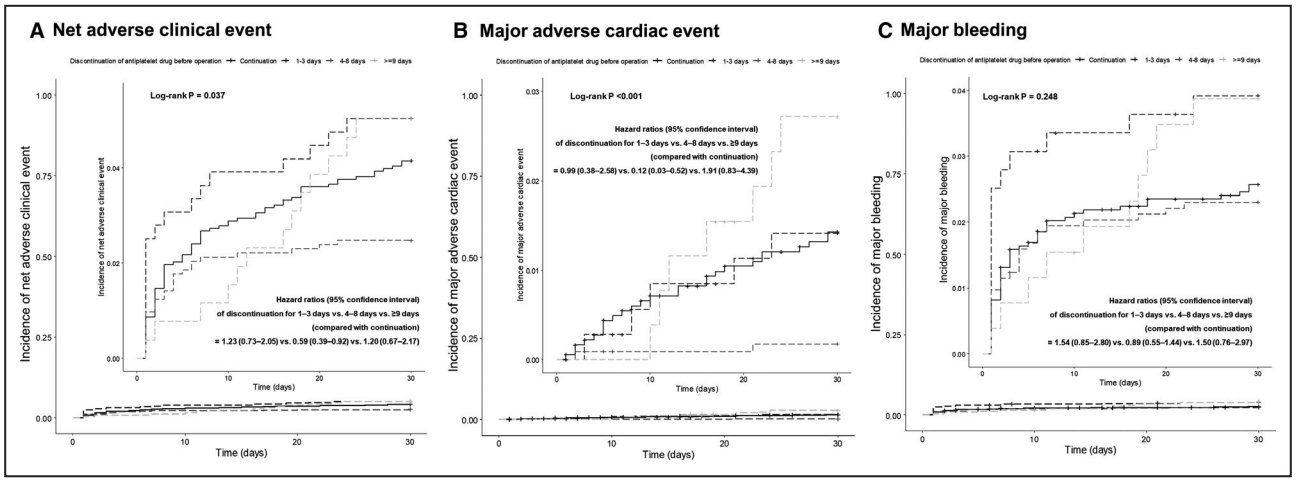

Figure 4. Cumulative incidence of perioperative adverse events comparing continuation of antiplatelet therapy vs different durations of antiplatelet therapy discontinuation.
Duration of 4 to 8 days was determined to be associated with the lowest risk for net adverse clinical event by generalized additive model. Discontinuation for 1 to 3, 4 to 8, and ≥9 days was compared with continuing antiplatelet therapy in regard to net adverse clinical event (**A**), major adverse cardiac event (**B**), and major bleeding (**C**).

APT during the post-PCI period and during the perioperative period should be carefully taken on board.

Our 49% incidence of discontinuing APT during NCS is higher than previously reported rates. In a recent observation study with 847 patients receiving coronary stents,[21] only 96 (11%) received no antiplatelet therapy during NCS. However, the study included patients with all stent types, including bare-metal stents and first-generation DES. It also claimed harmfulness of DAPT, which led to a higher likelihood of bleeding (odds ratio, 4.00; *P*=0.031) without reduction in ischemic events (odds ratio, 1.83; *P*=0.32). The incidence of MACEs was similar between antiplatelet (mostly aspirin) monotherapy (3.0%), and no antiplatelet therapy (3.1%), as was the risk of bleeding.[21]

Our incidences of MACEs (40 events, 1.1%) and MI (13 events, 0.4%) were lower than those previously reported. POISE-2 reported 30-day MI after NCS in 6.1% of patients without PCI and 8.1% of patients with PCI,[6,7] and observational studies reported in-hospital or 30-day MACEs in 3.8% to 5.4% of patients after NCS.[8,21–23] However, most previous studies enrolled small numbers of patients with PCI[8] and included patients with primarily previous generation DES. Our low percentage of ischemic events may be at least partially attributed to the use of second-generation DES. It may also relate to our lack of routinely measuring cardiac enzyme levels, which are associated with 30-day mortality and elevated ≈10% after NCS.[24] However, participating sites in our study usually recommend routine measurement of postoperative cardiac enzyme and ECG after surgery with cardiac risk, and clinically relevant myocardial infarction requiring any further attention or further management by physician were included in our study.

It is uncertain how effectively short-term discontinuation of APT would withdraw platelet inhibition in patients undergoing NCS. Interestingly, we found that continuation of APT was very similar to short-term discontinuation of APT (for 1–3 days) regarding both ischemic and hemorrhagic risk during the perioperative period. Instead, prolonged discontinuation (≥9 days), which would reflect almost complete withdrawal of platelet inhibition, was independently associated with MACE. The finding may suggest the hypothesis that sustained and complete withdrawal of platelet inhibition would be still harmful during NCS. Further investigation is warranted.

Limitations

Because of the observational manner, bias may have existed regarding the decision to discontinue APT. Although differences in covariates were adjusted for when comparing patterns of perioperative APT, undetected confounders may have affected our results. One-way decision or randomized assignment of APT was not appropriate because our population included a wide spectrum of clinical, surgical, and PCI-related factors. Another limitation was the lower incidence of MACEs than in previous studies, the potential reasons for which are discussed above. Furthermore, although our study included the largest number of patients with second-generation DES, the number was insufficient to allow comparisons of individual outcomes. As this study was conducted in Korea, the results may not be generalizable to other clinical settings. This study is thereby considered hypothesis generating, and further investigations are necessary to determine whether discontinuing APT

during NCS is appropriate for patients with second-generation DES. There would be the possibility of inflated type 1 errors since adjustments of multiplicity under a predefined protocol were not applied. However, the adjustment would not be necessary because of the exploratory nature of the study.

CONCLUSIONS

APT was discontinued preoperatively in almost half of patients undergoing PCI with second-generation DES by consensus decision before NCS. Our explorative analysis found that discontinuing APT may not be associated with increased risk of NACE, MACE, and major bleeding unless it is extended beyond 8 days. Discontinuing APT may be better in terms of NACE or MACE in selected patients awaiting certain types of surgery such as intra-abdominal surgery in which it would be more impactful for limiting hemorrhagic risk. Our findings may not imply causality and should be carefully interpreted considering the retrospective manner.

ARTICLE INFORMATION

Received February 13, 2020; accepted April 23, 2020.

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Sources of Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (No: HI15C1277), a grant from the National Research Foundation of Korea (NRF) grant, funded by the Korean Government (MSIT) (No. 2017R1A2B2003191), the Ministry of Science & ICT (2017M3A9E9073585) and the Cardiovascular Research Center (Seoul, Korea).

Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S7
Figures S1–S5

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Definition of major bleeding according to ISTH criteria

Any one of the followings:

1. Fatal bleeding, and/or
2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or
3. Extrasurgical site bleeding causing a fall in hemoglobin level of ≥2.0 g/dL, or leading to transfusion of ≥2 units of whole blood or red cells, with temporal association within 24 to 48 h to the bleeding
4. Surgical site bleeding that requires a second intervention or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection
5. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least ≥2.0 g/dL, or transfusion, indicated by the bleeding, of ≥2 units of whole blood or red cells, with temporal association within 24 h to the bleeding.

6. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).

Table S1. Comparison of the Akaike Information Criterion (AIC) of the Cox proportional hazard model for net adverse clinical event.

Models	Degrees of freedom	AIC Values
(Continuing APT) + (age) + (BMI) + (DM) + (CHF) + (CKD) + (anemia) + (preoperative APT) + (preoperative beta blocker) + (high risk PCI) + (duration between PCI and surgery) + (urgent surgery) + (surgical risk for cardiac event) + (surgical risk for hemorrhagic event)	17	2017.70
(Continuing APT) + (age) + (BMI) + (DM) + (CHF) + (CKD) + (anemia) + (preoperative APT) + (preoperative beta blocker) + (high risk PCI) + (urgent surgery) + (surgical risk for cardiac event) + (surgical risk for hemorrhagic event)	15	2014.32
(Continuing APT) + (age) + (DM) + (CHF) + (CKD) + (anemia) + (preoperative APT) + (preoperative beta blocker) + (high risk PCI) + (urgent surgery) + (surgical risk for cardiac event) + (surgical risk for hemorrhagic event)	14	2013.52
(Continuing APT) + (DM) + (CHF) + (CKD) + (anemia) + (preoperative APT) + (preoperative beta blocker) + (high risk PCI) + (urgent surgery) + (surgical risk for cardiac event) + (surgical risk for hemorrhagic event)	13	2013.26

APT = antiplatelet therapy, BMI = body mass index, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, PCI = percutaneous coronary intervention

Table S2. Comparison of the Akaike Information Criterion (AIC) of the Cox proportional hazard model for major adverse cardiac event.

Models	Degrees of freedom	AIC Values
(Continuing APT) + (age) + (DM) + (CHF) + (CKD) + (anemia) + (preoperative beta blocker) + (high risk PCI) + (duration between PCI and surgery) + (urgent surgery) + (surgical risk for cardiac event)	12	567.90
(Continuing APT) + (age) + (DM) + (CHF) + (anemia) + (preoperative beta blocker) + (high risk PCI) + (duration between PCI and surgery) + (urgent surgery) + (surgical risk for cardiac event)	11	566.55
(Continuing APT) + (DM) + (CHF) + (anemia) + (preoperative beta blocker) + (high risk PCI) + (duration between PCI and surgery) + (urgent surgery) + (surgical risk for cardiac event)	10	565.54
(Continuing APT) + (CHF) + (anemia) + (preoperative beta blocker) + (high risk PCI) + (duration between PCI and surgery) + (urgent surgery) + (surgical risk for cardiac event)	9	565.46

APT = antiplatelet therapy, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, PCI = percutaneous coronary intervention

Table S3. Comparison of the Akaike Information Criterion (AIC) of the Cox proportional hazard model for major bleeding.

Models	Degrees of freedom	AIC Values
(Continuing APT) + (age) + (BMI) + (anemia) + (CVA) + (preoperative APT) + (urgent surgery) + (surgical risk for hemorrhagic event)	10	1452.60
(Continuing APT) + (BMI) + (anemia) + (CVA) + (preoperative APT) + (urgent surgery) + (surgical risk for hemorrhagic event)	9	1450.87
(Continuing APT) + (BMI) + (anemia) + (preoperative APT) + (urgent surgery) + (surgical risk for hemorrhagic event)	8	1449.46
(Continuing APT) + (BMI) + (anemia) + (urgent surgery) + (surgical risk for hemorrhagic event)	6	1448.13

APT = antiplatelet therapy, BMI = body mass index, CVA = cerebrovascular attack.

Table S4. Independent factors for discontinuing antiplatelet therapy before non–cardiac surgery determined by multivariate logistic regression model.

Covariates	Odds ratio	95% confidence interval	*P*–value
Female	1.28	1.10–1.49	0.002
Chronic kidney disease	0.52	0.42–0.64	<0.001
Preoperative antiplatelet therapy			
Aspirin monotherapy		(Reference)	
P2Y12 inhibitor monotherapy	1.67	1.35–2.08	<0.001
Dual antiplatelet therapy	1.25	1.05–1.49	0.014
Beta–blocker	1.24	1.07–1.44	0.004
RAS inhibitor	1.31	1.13–1.52	<0.001
Diagnosis at revascularization			
Stable angina		(Reference)	
Unstable angina	1.55	1.31–1.85	<0.001
Myocardial infarction	1.41	1.19–1.68	<0.001
High risk PCI	0.80	0.68–0.95	0.009
Duration from PCI, mo			
<6	0.31	0.25-0.38	<0.001
6–<12	0.68	0.55-0.84	<0.001
≥12		(Reference)	
Urgent surgery	0.23	0.18–0.30	<0.001
Surgery with intermediate to high cardiac risk	1.37	1.16–1.61	<0.001
Surgery with high hemorrhage risk	2.17	1.65–2.87	<0.001

The multivariate logistic regression model was adjusted covariated listed on the table. P-value for McFadden's R^2 test was 0.110 indicating that the overall model fit is good. Likelihood ratio tests between the model versus the reduce model by eliminating each single covariate indicated a better goodness of fit.

Table S5. Baseline patient and surgical characteristics according to perioperative antiplatelet therapy.

Covariates	Aspirin monotherapy	P2Y12 inhibitor monotherapy	Dual antiplatelet therapy	Discontinuation of antiplatelet therapy	*P*-value
Patients, N	843	250	739	1,750	
Age, y	69 (61–75)	69 (61–75)	69 (61–75)	69 (61–75)	.05
Male	599 (71)	167 (67)	516 (70)	1,120 (64)	.001
BMI, kg/m^{2*}	24.4 (22.4–26.5)	24.7 (22.9–26.8)	23.9 (21.9–26.2)	24.4 (22.5–26.7)	.001
Comorbidity					
Hypertension	623 (74)	181 (72)	580 (78)	1,304 (75)	.09
Diabetes mellitus	349 (41)	118 (47)	404 (55)	768 (44)	<.001
Chronic heart failure	72 (9)	20 (8)	100 (14)	145 (8)	<.001
Chronic kidney disease	109 (13)	50 (20)	206 (28)	182 (10)	<.001
Prior cerebrovascular attack	86 (10)	34 (14)	98 (13)	184 (11)	.10
Anemia[*]	137 (16)	50 (20)	195 (26)	308 (18)	<.001
Preoperative medication					
Antiplatelet therapy					<.001

Monotherapy					
Aspirin	627 (74)	0 (0)	0 (0)	610 (35)	
Clopidogrel	0 (0)	215 (86)	0 (0)	336 (19)	
Ticagrelor	0 (0)	6 (2)	0 (0)	2 (0.1)	
Prasugrel	0 (0)	0 (0)	0 (0)	1 (0.1)	
Others	0 (0)	0 (0)	0 (0)	5 (0.3)	
Dual therapy	216 (26)	29 (12)	739 (100)	796 (45)	
Duration of discontinuation before surgery, d	–	–	–	5 (4–7)	<.001
Oral anticoagulant	5 (1)	0 (0.0)	1 (0)	12 (1)	.21
Beta-blocker	345 (41)	98 (39)	359 (49)	853 (49)	<.001
Calcium channel blocker	254 (30)	79 (32)	232 (31)	576 (33)	.54
RAS inhibitor	358 (42)	106 (42)	379 (51)	926 (53)	<.001
Percutaneous coronary intervention					
Diagnosis at revascularization					<.001
Stable angina	437 (52)	131 (52)	325 (44)	708 (40)	

Unstable angina	211 (25)	50 (20)	182 (25)	547 (31)	
Myocardial infarction	195 (23)	69 (28)	232 (31)	495 (28)	
Stented vessel					
Left main	64 (8)	17 (7)	52 (7)	75 (4)	.002
Left anterior descending artery	518 (61)	153 (61)	436 (59)	1095 (63)	.42
Left circumflex artery	219 (26)	61 (24)	182 (25)	466 (27)	.71
Right coronary artery	277 (33)	94 (38)	270 (37)	621 (35)	.35
Type of DES					
Durable polymer	547 (65)	161 (64)	502 (68)	1353 (77)	<.001
Bioresorbable polymer	267 (32)	101 (40)	250 (34)	409 (23)	<.001
Polymer-free	61 (7)	1 (0)	8 (1)	18 (1)	<.001
Number of stents					.003
1	501 (59)	136 (54)	450 (61)	1036 (59)	
2	217 (26)	64 (26)	172 (23)	501 (29)	
≥3	125 (15)	50 (20)	117 (16)	213 (12)	
Maximum stent diameter, mm*					.004

Total stent length, mm*	30 (18–51)	32 (18–56)	29 (19–49)	30 (18–48)	.58
High risk PCI	202 (24)	81 (32)	305 (41)	450 (26)	<.001
Non-cardiac surgery					
Duration from PCI, mo	24 (12–5)	27 (15–48)	7 (2–15)	23 (12–41)	<.001
Urgent surgery	114 (14)	38 (15)	129 (17)	88 (5)	<.001
Risk of cardiac event					<.001
Low (<1%)	479 (57)	148 (59)	455 (62)	892 (51)	
Intermediate to high (≥1%)	364 (43)	102 (41)	284 (38)	858 (49)	
Risk of hemorrhage					<.001
Low	516 (61)	172 (69)	580 (78)	896 (51)	
Intermediate to high	247 (29)	59 (24)	119 (16)	654 (37)	
High	80 (9)	19 (8)	40 (5)	200 (11)	
Type					<.001
Orthopedic	138 (16)	35 (14)	113 (15)	358 (20)	
Major	29 (3)	8 (3)	22 (3)	78 (4)	
Minor	99 (12)	27 (11)	91 (12)	280 (16)	

Superficial	141 (17)	45 (18)	138 (19)	301 (17)
Ophthalmologic	165 (20)	54 (22)	184 (25)	147 (8)
Intraabdominal	122 (14)	25 (10)	51 (7)	317 (18)
Urologic	108 (13)	28 (11)	47 (6)	207 (12)
Major	46 (5)	11 (4)	13 (2)	109 (6)
Minor	62 (7)	17 (7)	34 (5)	98 (6)
Vascular	45 (5)	28 (11)	137 (19)	37 (2)
Spinal	54 (6)	7 (3)	21 (3)	129 (7)
Head and neck	29 (3)	14 (6)	8 (1)	87 (5)
Intrathoracic	12 (1)	2 (1)	12 (2)	37 (2)
Gynecologic	6 (1)	3 (1)	3 (0)	46 (3)
Intracranial	19 (2)	5 (2)	25 (3)	65 (4)
Breast	4 (0)	2 (1)	0 (0.0)	14 (1)
Transplantation	10 (1)	2 (1)	0 (0.0)	5 (0)

*These comparisons were performed among patients without missing values (values were missing for hemoglobin in 517 patients, BMI in 77 patients, stent diameter in 4 patients, and total stent length in 3 patients).

BMI = body mass index, DAPT = dual antiplatelet therapy, DES = drug-eluting stent, PCI = percutaneous coronary intervention, RAS = renin-angiotensin system.

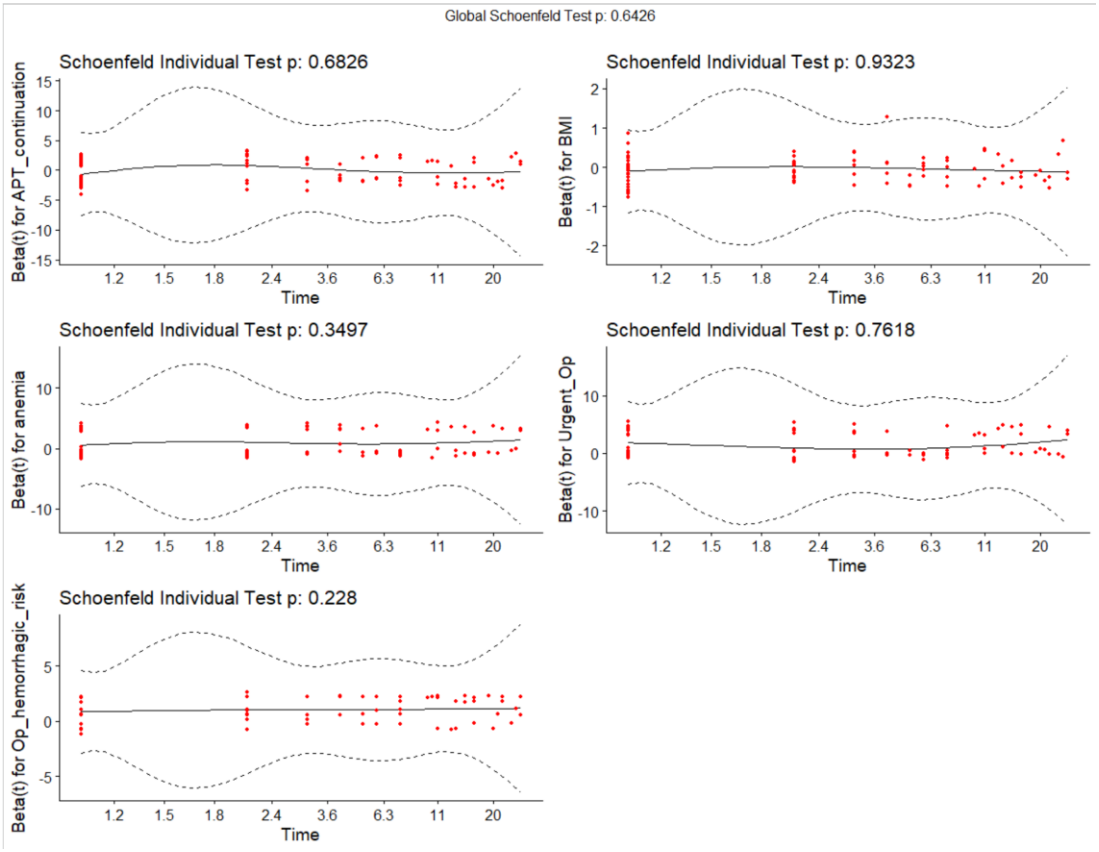
Table S6. Thirty-day incidence of adverse events after non-cardiac surgery.

Adverse event	Continuation (N=1,832)	Discontinuation (N=1,750)	P-value
Net adverse clinical event	76 (4.1)	59 (3.4)	0.257
Major adverse cardiac event	26 (1.4)	14 (0.8)	0.109
Major bleeding	47 (2.6)	50 (2.9)	0.664
Death	40 (2.2)	24 (1.4)	0.088
Cardiac	20 (1.1)	10 (0.6)	0.127
Noncardiac	20 (1.1)	14 (0.8)	0.467
Associated with bleeding	13 (0.7)	18 (1.0)	0.395
Myocardial infarction	9 (0.5)	4 (0.2)	0.303
Stent thrombosis	0 (0.0)	2 (0.1)	0.459

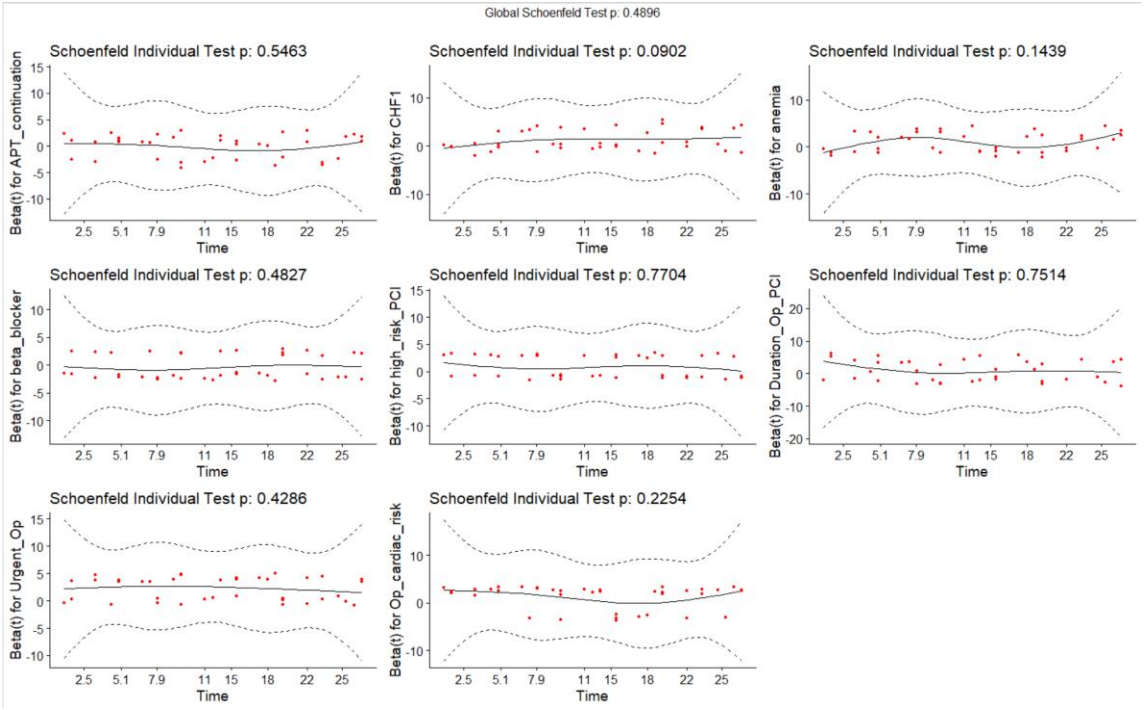
Table S7. Thirty-day incidence of adverse events after non-cardiac surgery according to perioperative antiplatet therapy.

Adverse event	Aspirin monotherapy (N=843)	P2Y12 inhibitor Monotherapy (N=250)	Dual antiplatelet therapy (N=739)	Discontinuation (N=1,750)	P-value
Net adverse clinical event	26 (3.1)	13 (5.2)	37 (5.0)	59 (3.4)	0.094
Major adverse cardiac event	7 (0.8)	2 (0.8)	17 (2.3)	14 (0.8)	0.008
Major bleeding	16 (1.9)	10 (4.0)	21 (2.8)	50 (2.9)	0.275
Death	9 (1.1)	3 (1.2)	28 (3.8)	24 (1.4)	<0.001
Cardiac	4 (0.5)	1 (0.4)	15 (2.0)	10 (0.6)	0.001
Noncardiac	5 (0.6)	2 (0.8)	13 (1.8)	14 (0.8)	0.080
Associated with bleeding	2 (0.2)	1 (0.4)	10 (1.4)	18 (1.0)	0.069
Myocardial infarction	3 (0.4)	1 (0.4)	5 (0.7)	4 (0.2)	0.408
Stent thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0.553

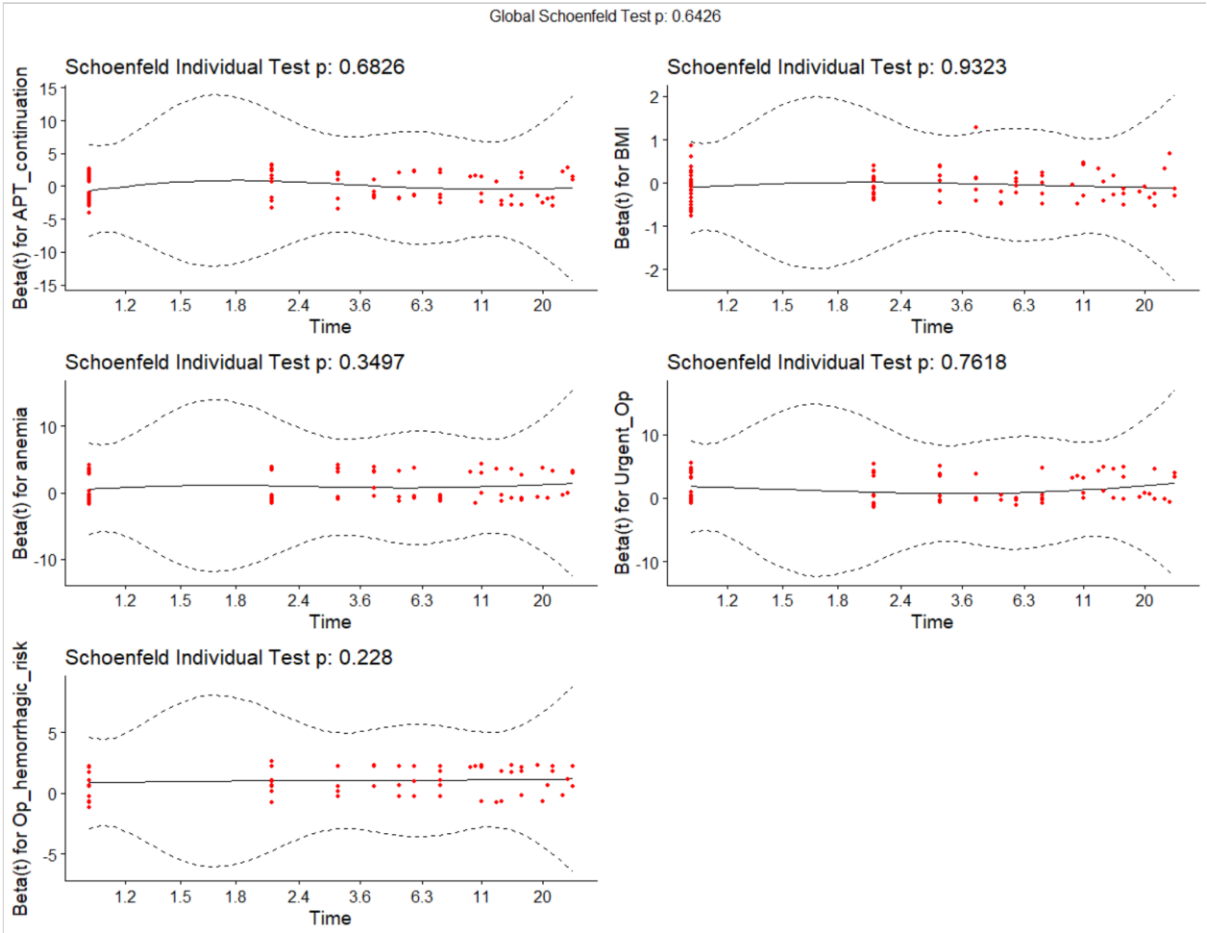
Figure S1. Diagnostic plots for the proportional hazard assumption of the Cox models with scaled Schoenfeld residuals for each covariate against time to net adverse clinical event (A), major adverse cardiac event (B), and major bleeding (C).



A. Net adverse clinical event



B. Major adverse cardiac event



C. Major bleeding

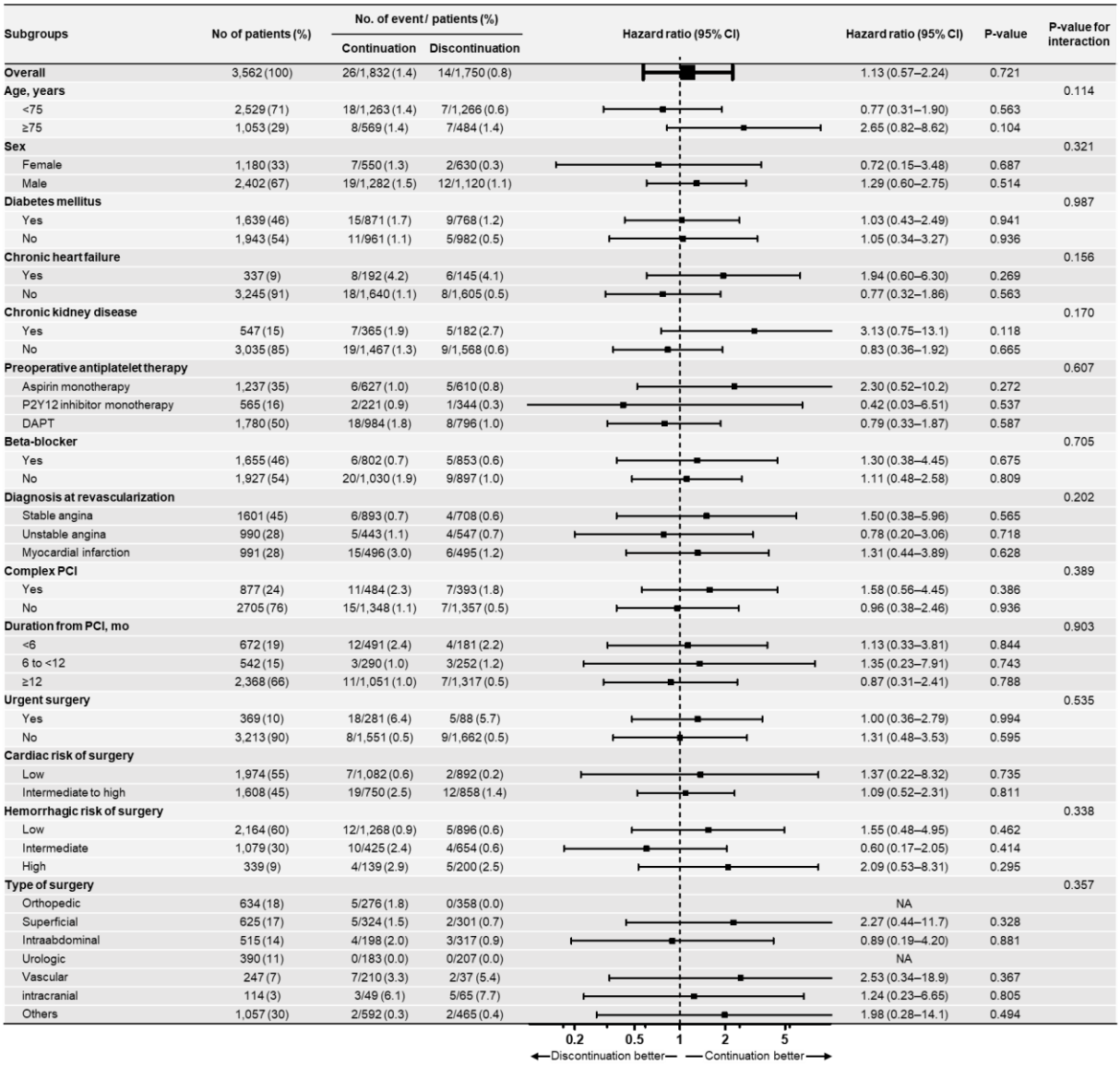


Figure S2. Forest plot of adjusted hazard ratio of discontinuation of antiplatelet therapy for major adverse cardiac event in subgroup analysis. Cox proportional hazard model for net adverse clinical event was adjusted with chronic heart failure, anemia, high risk PCI, preoperative use of beta–blocker, urgent surgery and surgical risk for cardiac event. Center dots and whiskers indicate hazard ratios and 95% confidence intervals, respectively. CI = confidence interval, DAPT = dual antiplatelet therapy, PCI = percutaneous coronary intervention

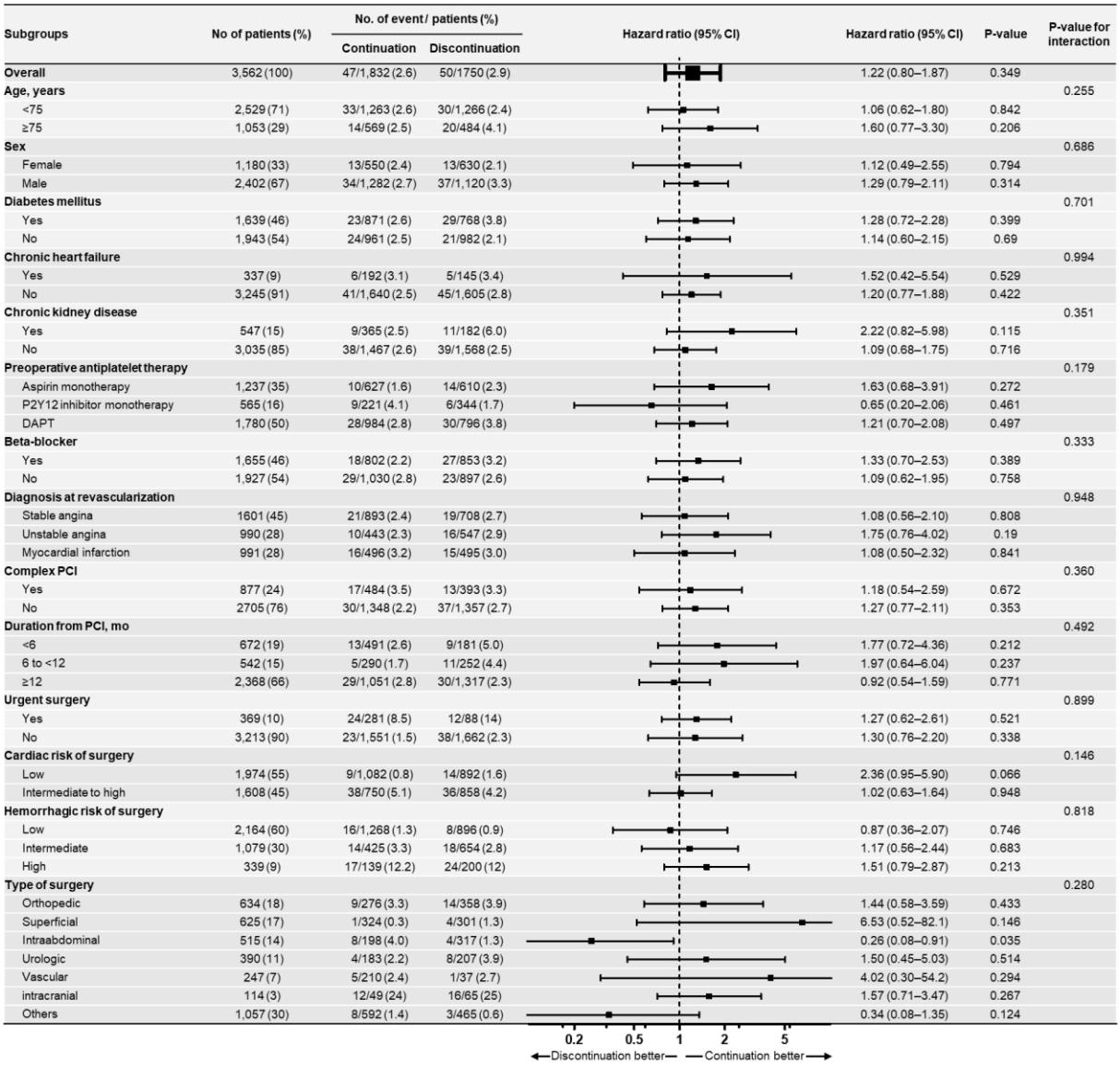


Figure S3. Forest plot of adjusted hazard ratio of discontinuing antiplatelet therapy for major bleeding in subgroup analysis. Cox proportional hazard model for net adverse clinical event was adjusted with body mass index, anemia, urgent surgery and surgical risk for hemorrhagic event. Center dots and whiskers indicate hazard ratios and 95% confidence intervals, respectively. CI = confidence interval, DAPT = dual antiplatelet therapy, PCI = percutaneous coronary intervention

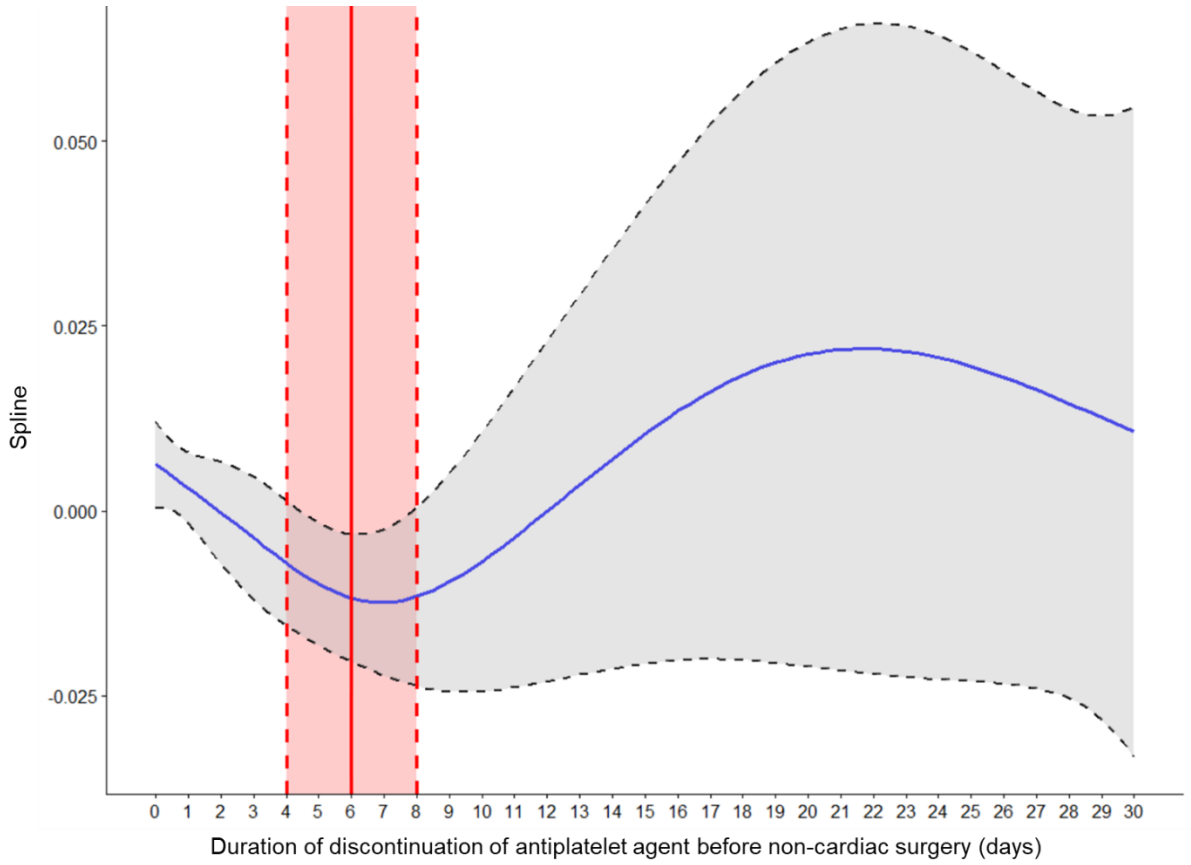
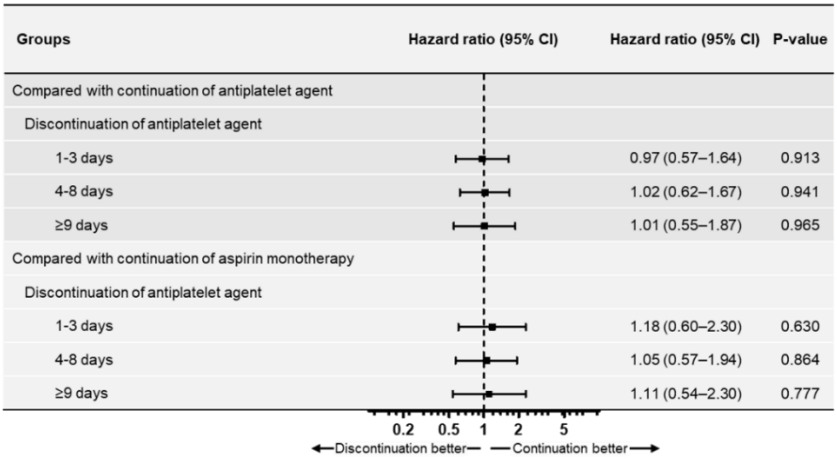
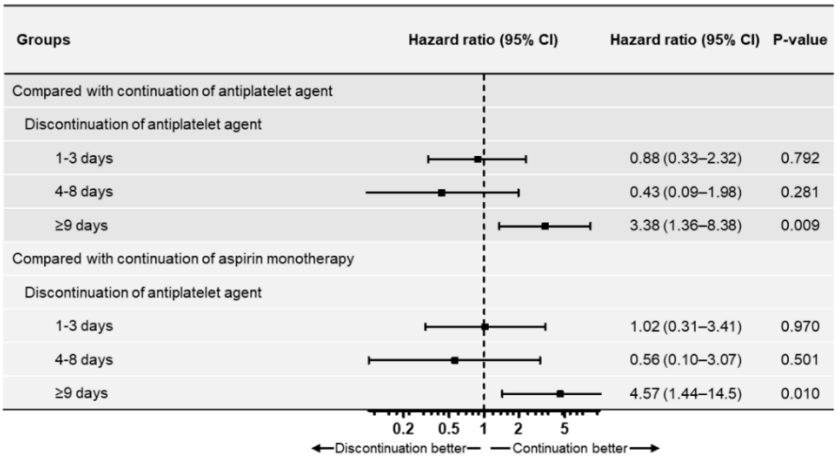


Figure S4. Nonparametric smoothing plot using generalized additive model of duration of antiplatelet therapy before non-cardaic surgery. The plot indicates that discontinuing antiplatelet therapy for 6 days was associated with the lowest risk of net adverse clinical event in patients undergoing non-cardiac surgery. Time interval from 4 to 8 days would be defined as optimal duration for discontinuation of antiplatelet agent before non-cardiac surgery in the analysis. Dashed lines and the shaded area indicate the 95% confidence intervals. The y-axis represents the effect of discontinuation duration on net adverse clinical event.

A. Net adverse clinical event



B. Major adverse cardiac event



C. Major bleeding

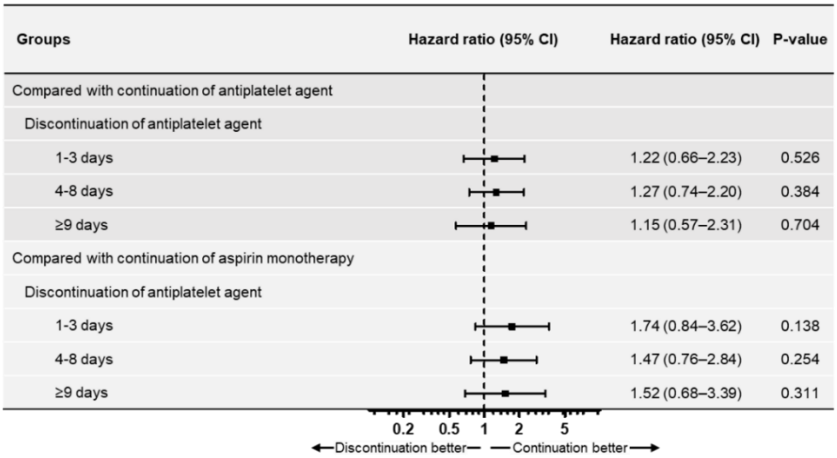


Figure S5. Adjusted hazard ratio of discontinuing antiplatelet therapy for net adverse clinical event, major adverse cardian event and major bleeding. Center dots and whiskers indicate hazard ratios and 95% confidence intervals, respectively. CI = confidence interval.A.