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ORIGINAL RESEARCH

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

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BACKGROUND: Although antiplatelet therapy (APT) has been recommended to balance ischemic-bleeding risks, it has been left to an individualized decision-making based on physicians' perspectives before non-cardiac surgery. The study aimed to assess the advantages of a consensus among physicians, surgeons, and anesthesiologists on continuation and regimen of preoperative APT in patients with coronary drug-eluting stents.

METHODS AND RESULTS: A total of 3582 adult patients undergoing non-cardiac surgery after percutaneous coronary intervention with second-generation stents was retrospectively included from a multicenter cohort. Physicians determined whether APT should be continued or discontinued for a recommended period before non-cardiac surgery. There were 3103 patients who complied with a consensus decision. Arbitrary APT, not based on a consensus decision, was associated with urgent surgery, high bleeding risk of surgery, female sex, and dual APT at the time of preoperative evaluation. Arbitrary APT independently increased the net clinical adverse event (adjusted odds ratio [OR_{adj}], 1.98; 95% CI, 1.98–3.11), major adverse cardiac event (OR_{adj}, 3.11; 95% CI, 1.31–7.34), and major bleeding (OR_{adj}, 2.34; 95% CI, 1.45–3.76) risks. The association was consistently noted, irrespective of the surgical risks, recommendations, and practice on discontinuation of APT.

CONCLUSIONS: Most patients were treated in agreement with a consensus decision about preoperative APT based on a referral system among physicians, surgeons, and anesthesiologists. The risk of perioperative adverse events increased if complying with a consensus decision was failed.

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Key Words: antiplatelet therapy ■ consensus ■ drug-eluting stent ■ non-cardiac surgery ■ percutaneous coronary intervention ■ surgery

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CLINICAL PERSPECTIVE

What Is New?

- A consensus decision-making process based on an organized referral system among physicians, surgeons, and anesthesiologists was feasible and efficient to guide the management of antiplatelet therapy before non-cardiac surgery.
- Compliance with a consensus decision-making process may reduce the risks of ischemic and bleeding events in patients undergoing percutaneous coronary intervention with second-generation drug-eluting stents.

What Are the Clinical Implications?

- A consensus decision-making process can overcome biases in the management of preoperative antiplatelet therapy before non-cardiac surgery.
- This study supports the need to construct consensus decision-making pathways to guide antiplatelet therapy management before non-cardiac surgery in patients who underwent percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

APT	antiplatelet therapy
DES	drug-eluting stents
MACE	major adverse cardiac event
NACE	net adverse clinical event

With increasing age, patients are more likely to develop coronary artery disease and undergo percutaneous coronary interventions (PCI) followed by non-cardiac surgery (NCS). Previous studies have reported that ≈7% to 34% of the patients required NCS within 2 years after PCI.[1,2] Although antiplatelet therapy (APT) is a cornerstone for the prevention of subsequent ischemic events in patients with coronary stents, temporary withdrawal is occasionally inevitable before NCS, if postoperative bleeding is expected to be significant or difficult to control. As it is not clear how physicians should decide the optimal APT regimen for patients awaiting NCS, the current guidelines suggest that continuation of APT should be individualized or based on a consensus decision.[3,4] The available literature reports that APT should be continued or discontinued if the potential cardiovascular benefit outweighs the bleeding risk or vice versa. As the risk-benefit balance cannot be reliably estimated, the decision is left to intuition or agreement among the physicians. Consensus decision-making may be a good option for determining whether APT should be continued or discontinued to balance the risk-benefit ratio. Consensus yielded through various perspectives of physicians should be towards higher relevance; however, it is uncertain whether such an approach is associated with better clinical outcomes.[5,6] We recently reported that the decision to discontinue APT is commonly arrived at through a consensus decision among physicians, surgeons, and anesthesiologists as standard practice before NCS and that this discontinuation of APT, per se, may not have a significant effect on the clinical outcomes, unless APT is discontinued for an excessively prolonged period.[7] In our study, we aimed to assess whether a consensus decision on the continuation of APT would affect the risk of perioperative adverse events following NCS.

METHODS

Study Design and Population

This study was conducted using the data of a multicenter cohort archived in the KOMATE (Korean Multicenter Angioplasty Team) registry (NCT03908463), which collects information about consecutive patients undergoing PCI at the major medical centers in Korea. We retrospectively included 3582 patients who underwent NCS between May 2008 and October 2018 following PCI with second-generation drug-eluting stents (DES) from 9 institutes where the participation in the study was approved. Our study population has been described previously[7] and is shown in Figure 1. NCS includes invasive operations by laparoscopic or open procedures requiring anesthesia excluding dental or endoscopic procedures or procedures involving heart or thoracic aortic great vessel. The coronary- and procedure-related records were available from the registry, and surgery-related variables, including physicians' recommendations and practices on the duration of cessation of each antiplatelet agent, were retrospectively obtained from the investigators at each study center. The Institutional Review Board of each participating institute approved the study protocol and waived the requirement of obtaining informed consent.

Consensus Decision On Preoperative APT

Cardiology consultation before NCS was mandatory for patients undergoing PCI at all the participating institutes. Cardiologists recommended whether each antiplatelet agent should be continued or discontinued for a certain period before NCS. Surgeons and anesthesiologists took the final decision and informed whether APT should be discontinued and if required when each agent should be discontinued preoperatively. An attending surgeon was responsible for recording the preoperative APT in practice. Only the doctors working

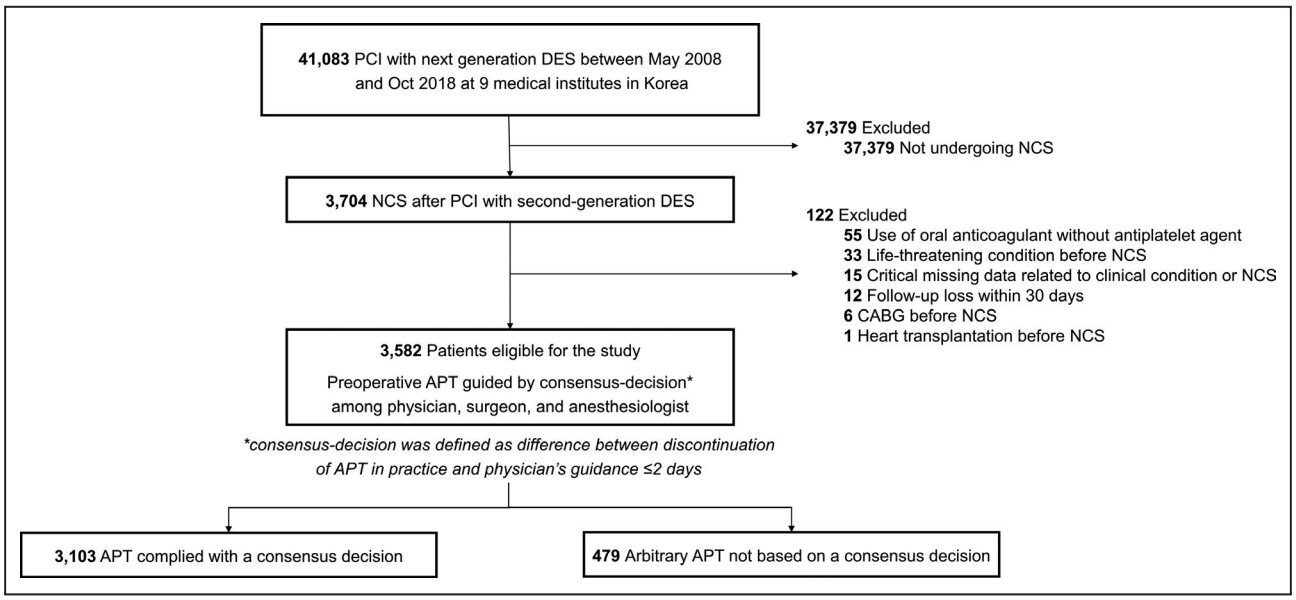

Figure 1. Study flow.
APT indicates antiplatelet therapy; CABG, coronary artery bypass graft; DES, drug-eluting stent; NCS, non-cardiac surgery; and PCI, percutaneous coronary intervention.

at each institute participated in their own referral system. An investigator at each participating institute reviewed the medical records to identify the duration of discontinuation of APT before NCS. Preoperative APT was considered to be if all the antiplatelet agents were discontinued before NCS for ≥1 day. The duration of discontinuation of APT was provided by the shortest period of each antiplatelet agent's discontinuation. Compliance with a consensus decision was defined if duration of discontinuation of APT was within 2 days of the initial recommendation. Arbitrary APT was defined if a physician's recommendation was not available or when the APT was stopped too early (longer discontinuation) or too late (shorter discontinuation) against the recommendation by ≥3 days.

Perioperative Adverse Event

The primary end point of the study was net adverse clinical events (NACEs) defined as a composite of all-cause mortality, major adverse cardiac events (MACEs), or major bleeding within 30 days. MACE included cardiac death, myocardial infarction, or stent thrombosis. Cardiac death was defined as death with ischemic symptoms, typical electrocardiographic ischemic patterns, or cardiac enzyme elevation, or fatal ventricular arrhythmia with no obvious non-cardiac cause of death. MI was defined according to the third universal definition as an increase in creatine kinase myocardial fraction above the upper limit of normal or in troponin-T or -I at >99th percentile of the upper limit of normal and ≥1 of the following symptoms: electrocardiographic changes or imaging, or angiographic findings indicative of myocardial infarction.[8] Stent thrombosis was defined according to the Academic Research Consortium recommendations.[9] Major bleeding was defined according to the International Society of Thrombosis and Hemostasis.[10] An independent adjudication was performed for each event and obtained a good agreement between adjudicators.[7]

Coronary Revascularisation and Surgical Risk

Details of standardized strategies on procedures and APT following coronary revascularization was previously described elsewhere.[7] High-risk PCI was defined as a left main stenting, 3 stents or long total stent length (≥60 mm), a stent with small-diameter (<2.5 mm), 2 stents at the bifurcation, or chronic total occlusion.[11,12] Urgent surgery was defined as surgery that should be performed within 30 days for a condition that had the potential to deteriorate quickly and become an emergency.[13] The cardiac risk of each surgery was classified as low (<1%) or intermediate to high (≥1%), according to the ≈30-day risk of cardiovascular death or myocardial infarction.[4,14] The bleeding risk of each NCS was categorized into 3 groups (low, intermediate, or high), according to Rossini et al.[12]

Statistical Analysis

Continuous variables were reported as median and quartiles and compared using the Mann-Whitney *U* test because of their skewed distribution. Categorical

variables were reported as number and percentage and compared using the χ^2 or Fisher exact test. The multivariable logistic regression model was used to find independent risk factors for arbitrary APT. Backward elimination was applied by including covariates identified by univariable analysis and sequential exclusion by $P \leq 0.1$ and the efficacy of the final model was diagnosed by McFadden's R^2 statistics. The association between a consensus decision and clinical outcome was inferred using doubly robust estimation, which allows for both propensity score-based weighting and outcome regression to offer more robustness than a single model approach of exposure or outcome modeling.[15,16] To control for potential confounding, exposure modeling was adjusted for the covariates including age, sex, body mass index, comorbidities, PCI-related factors, medication, and surgical risks to estimate the propensity of compliance with a consensus decision. Outcome regression was constructed by using a multivariable logistic regression model adjusting for determined covariates. The regression model for NACE was adjusted for diabetes mellitus, chronic heart failure, chronic kidney disease, anemia, high-risk PCI, preoperative medication of dual APT and beta-blockers, urgent surgery, and surgery risk for cardiac and hemorrhagic events. The regression model for MACE and major bleeding was also adjusted for covariates as previously described.[7] The overall goodness-of-fit was determined based on the Hosmer–Lemeshow method for the logistic regression models. Non-linear effect of the difference in discontinuation of APT between physician's guide and practice on clinical outcome was demonstrated by a restricted cubic regression spline and conventional logistic regression model, in which the difference was categorized into 7 periods; ≤−5; −4 or −3; −2 or −1; 0; 1 or 2; 3 or 4; and ≥5 days. Five complete data sets were generated using multiple imputations by chained equation approach, assuming missingness is at random which was tested by conditional distribution of the missing data, to impute missing values. We used all the analyses described above for the imputed data sets, and then we pooled the coefficients.[17] Two-sided tests were performed, and $P<0.05$ were considered statistically significant. All statistical analyses were performed using R Statistical Software (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Compliance With a Consensus Decision

A total of 479 (13%) patients were not complied with a consensus decision on preoperative APT (Figure 1). Dual APT before surgery was more frequent in patients not complied with a consensus decision. Urgent or high-risk surgeries were also more common in patients not guided by a consensus decision (Table 1). Physicians guided 55% of patients to continue APT before NCS, in whom the consensus rate was 93%. Non-compliance was more common in patients guided to discontinue APT, and longer discontinuation (302 patients, 63%) was more frequent than shorter discontinuation (54 patients, 11%) as a pattern of non-compliance (Table 2, Figure S1). When a higher bleeding risk of surgery was expected, more patients were recommended to discontinue APT before NCS (Figure S2). Also, the incidence of major bleeding was more common in the patients recommended to discontinue APT compared with those recommended to continue APT (1.8% versus 3.1%, $P=0.015$). Sufficient withdrawal of APT (discontinuation for 4–7 days) was recommended before NCS for 27% of patients with low bleeding risk and 46% of patients undergoing NCS with high bleeding risk. A consensus decision was less feasible for patients undergoing NCS with high bleeding risk, mostly because of the unavailability of physician's recommendation or non-compliance with the recommendation of proper discontinuation. Arbitrary APT was independently associated with urgency and bleeding risk of surgery, women, and dual APT. Urgency, cardiac and bleeding risk of surgery, and dual APT were related to shorter discontinuation of APT than guidance, while high-risk PCI, <6 months since PCI, and urgent surgery were related to longer discontinuation of APT with lower risk than guidance (Table S1).

Clinical Outcomes

Patients guided by a consensus decision on preoperative APT had less of NACE following NCS compared with those not complied with a consensus (2.9% versus 9.2%). The incidences of MACE (0.8% versus 2.9%), major bleeding (1.9% versus 7.7%), and all-cause mortality (1.2% versus 5.8%) were lower in patients under consensus-guidance than in those without (Table 3). Figure 2 shows a combined plot of a restrictive spline curve and the result of the logistic regression model for the association between NACE and the difference in APT duration between physician's guidance and practice. The risk of NACE increased according to the increase of the difference. The risk of NACE was significant if there was a difference of ≥5 days between physician's guidance and practice in both shorter (adjusted odds ratio [OR_{adj}], 5.62; 95% CI, 1.96–16.1) and longer discontinuations (OR_{adj}, 2.44; 95% CI, 1.26–4.75). While shorter discontinuation did not

Table 1. Baseline Clinical Characteristics

Characteristics	All (n=3582)	Consensus Decision		
		Yes (n=3103)	No (n=479)	*P* Value
Age, y	69 (61–75)	69 (61–75)	70 (62–76)	0.052
Women	1180 (33)	1003 (32)	177 (37)	0.051
BMI, kg/m²*	24.3 (22.3–26.5)	24.2 (22.4–26.5)	24.4 (22.2–26.6)	0.960
Comorbidity				
Hypertension	2688 (75)	2339 (75)	349 (73)	0.259
Diabetes mellitus	1639 (46)	1424 (46)	215 (45)	0.717
Chronic heart failure	337 (9)	298 (10)	39 (8)	0.349
Chronic kidney disease	547 (15)	482 (16)	65 (14)	0.297
Prior cerebrovascular attack	402 (11)	335 (11)	67 (14)	0.047
Anemia*	607 (20)	580 (19)	109 (23)	0.042
Percutaneous coronary intervention				
Diagnosis				<0.001
Stable angina	1601 (45)	1415 (46)	186 (39)	
Unstable angina	990 (28)	816 (26)	174 (36)	
Myocardial infarction	991 (28)	872 (28)	119 (25)	
High-risk PCI	877 (24)	771 (25)	106 (22)	0.219
Duration between PCI and NCS, mo	20 (8–39)	20 (8–39)	21 (10–39)	0.165
Medication at preoperative evaluation				
Antiplatelet therapy				<0.001
Monotherapy				
Aspirin	1237 (35)	1102 (36)	135 (28)	
Clopidogrel	551 (15)	484 (16)	67 (14)	
Others	14 (0)	10 (0)	4 (1)	
Dual therapy	1780 (50)	1507 (49)	273 (57)	
Oral anticoagulant	18 (1)	14 (0)	4 (1)	0.448
Beta-blockers	1655 (46)	1420 (46)	235 (49)	0.194
Calcium channel blockers	1141 (32)	982 (32)	159 (33)	0.533
RAS inhibitors	1769 (49)	1532 (49)	237 (49)	>0.999
Urgent surgery	369 (10)	299 (10)	70 (15)	0.001
Surgery with intermediate to high cardiac risk	1608 (45)	1350 (44)	258 (54)	<0.001
Surgical with bleeding risk				<0.001
Low	2164 (60)	1934 (62)	230 (48)	
Intermediate	1079 (30)	932 (30)	147 (31)	
High	339 (9)	237 (8)	102 (21)	

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

*Comparisons were performed after omitting missing values for hemoglobin (517 patients, 14%) and BMI (77 patients, 2%).

impact on the risk of MACE, longer discontinuation led to increased risk (Figure S3). The risk of major bleeding was influenced by both shorter and longer discontinuation (Figure S4). Arbitrary APT was independently associated with NACE (OR_{adj}, 1.98; 95% CI, 1.98–3.11), MACE (OR_{adj}, 3.11; 95% CI, 1.31–7.34), and major bleeding (OR_{adj}, 2.34; 95% CI, 1.45–3.76; Figure 3, Figures S5 and S6). The risk of arbitrary APT for NACE and major bleeding was consistent across the different subsets according to the surgical risk, physician's guidance, and practice on discontinuation of APT. Arbitrary APT had a great impact on the risk of MACE in patients who discontinued APT (OR_{adj}, 10.0; 95% CI. 2.25–44.6; *P* for interaction=0.03) while such an association did not emerge in patients who continued APT in practice (Figure S5). Series of sensitivity analyses supported consistency of the significant association between arbitrary APT and perioperative adverse event (Data S1, Figure S7, Tables S2–S10).

Table 2. Guidance, Practice, and Consensus on Preoperative Antiplatelet Therapy

Characteristics	All (n=3582)	Consensus Decision		
		Yes (n=3103)	No (n=479)	*P* Value
Physician's guidance				<0.001
Continuation	1953 (55)	1815 (58)	138 (29)	
Discontinuation				
1–3 d	301 (8)	279 (9)	22 (5)	
4–7 d	1205 (34)	1009 (33)	196 (41)	
Not available	123 (3)	…	123 (26)	
Preoperative APT in practice				<0.001
Continuation	1832 (51)	1748 (56)	84 (18)	
Aspirin monotherapy	836 (23)	810 (26)	26 (5)	
P2Y12 inhibitor monotherapy	250 (7)	243 (8)	7 (1)	
Dual APT	746 (21)	695 (22)	51 (11)	
Discontinuation	1750 (49)	1355 (44)	395 (82)	
1–3 d	358 (10)	327 (11)	31 (6)	
4–8 d	1131 (32)	1004 (32)	127 (27)	
≥9 d	261 (7)	24 (1)	237 (49)	
Non-compliance with the guidance*				NA
Shorter discontinuation	54 (2)	…	54 (11)	
Longer discontinuation	302 (8)	…	302 (63)	

Data are expressed as number (percentage). APT indicates antiplatelet therapy.
*Non-compliance is counted if the difference in duration of discontinuation of APT between practice and physician's guidance is ≥3 d.

DISCUSSION

In this observational study using pooled data from an all-comer PCI registry, we found that arbitrary APT was more frequent when surgery was considered riskier or urgent. The present analysis indicates that arbitrary APT doubled the risk of a 30-day perioperative NACE. Arbitrary APT was also associated with MACE as well as major bleeding. Arbitrary APT has a consistently deleterious effect on NACE irrespective of the surgical risk, physician's recommendation, and practice of the discontinuation of APT.

A major strength of this study is that the consensus decision, an unperceived but increasingly indispensable step for decision-making in complicated medical situations, is considered as a process of preoperative risk modification for patients receiving coronary stents currently used. Major studies about risk modification for patients with cardiac risk have focused on specific pharmacological treatments such as beta-blockers, statins, or APT.[7,18–23] However, the results of recent studies have been in disagreement in terms of the efficacy and safety of APT,[7,19,21–23] which could be inconsistent and largely dependent upon each

Table 3. Perioperative Adverse Event According to a Consensus Decision

Adverse Event	All (n=3582)	Consensus Decision		
		Yes (n=3103)	No (n=479)	*P* Value
Net adverse clinical event	135 (3.8)	91 (2.9)	44 (9.2)	<0.001
Major adverse cardiac event	40 (1.1)	26 (0.8)	14 (2.9)	<0.001
Major bleeding	97 (2.7)	60 (1.9)	37 (7.7)	<0.001
Death	64 (1.8)	36 (1.2)	28 (5.8)	<0.001
Cardiac	30 (0.8)	20 (0.6)	10 (2.1)	0.003
Non-cardiac	34 (0.9)	16 (0.5)	18 (3.8)	<0.001
Associated with bleeding	31 (0.9)	10 (0.3)	21 (4.4)	<0.001
Myocardial infarction	13 (0.4)	9 (0.3)	4 (0.8)	0.150
Stent thrombosis	2 (0.1)	0 (0.0)	2 (0.4)	0.010

Data are expressed as number (percentage). APT indicates antiplatelet therapy.

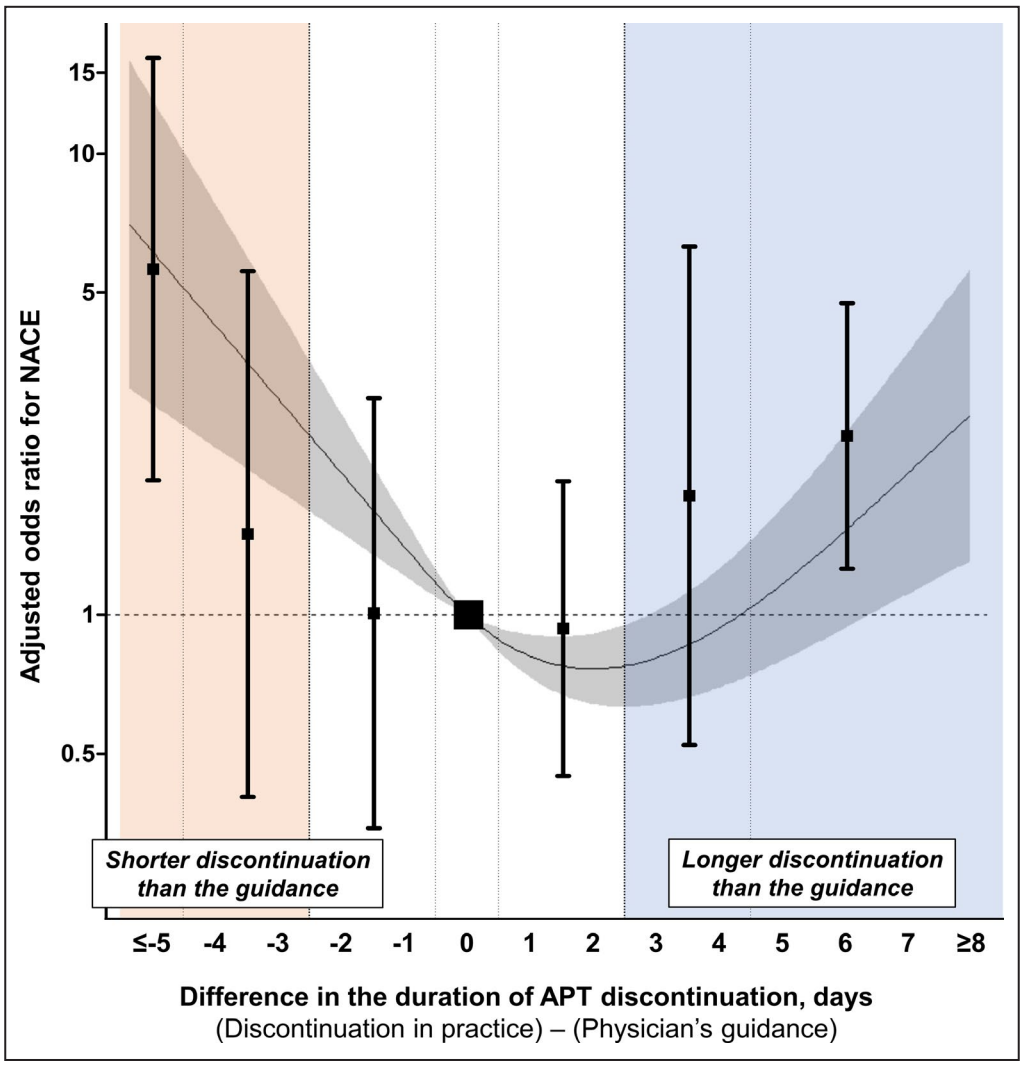

Figure 2. Impact of difference in discontinuation of antiplatelet therapy between the guidance and practice on net adverse clinical events.
Non-linear association was depicted by a restricted cubic regression spline, in which the grey area indicates 95% CI. A dot-and-whisker indicates the adjusted odds ratio and 95% CI. The discrepancy is calculated as the duration of discontinuation of APT in practice minus the duration guided by a physician. A minus value indicates shorter (later) discontinuation which might cause less sufficient withdrawal (or continuation) of platelet inhibition than expected, by a physician. APT indicates antiplatelet therapy; and NACE, net adverse clinical event.

patent's clinical characteristics and surgical risks. Therefore, individualized evaluation and management should be essential, based on clinician's perspectives as the current guidelines recommend.[3,4] Our study demonstrated that women, dual APT, urgent surgery, and higher bleeding risk of surgery were independent factors for arbitrary APT. As it has been known in previous investigations,[24,25] sex differences in patients undergoing PCI were shown that female patients were older and had higher incidence of anemia compared with male patients in our cohort. Considering that longer discontinuation that a physician's guidance was more frequent as a pattern of arbitrary APT, bleeding risk would be more concerned rather than ischemic risk in patients not complied with a consensus-based APT. As physicians, surgeons, and anesthesiologists see from a different perspective the risk of surgery and the post-surgical outcome, it is important to find common ground on the risk-benefit balance of the perioperative APT.[26] Our study comes up with evidence supporting the benefit of a consensus decision based on an organized referral system.

We previously demonstrated that discontinuation of APT did not impact on both ischemic and bleeding outcomes after NCS unless it was inappropriately prolonged.[7] POISE-2 (Perioperative Ischaemic Evaluation-2) is a randomized controlled study that evaluated the effect of aspirin compared

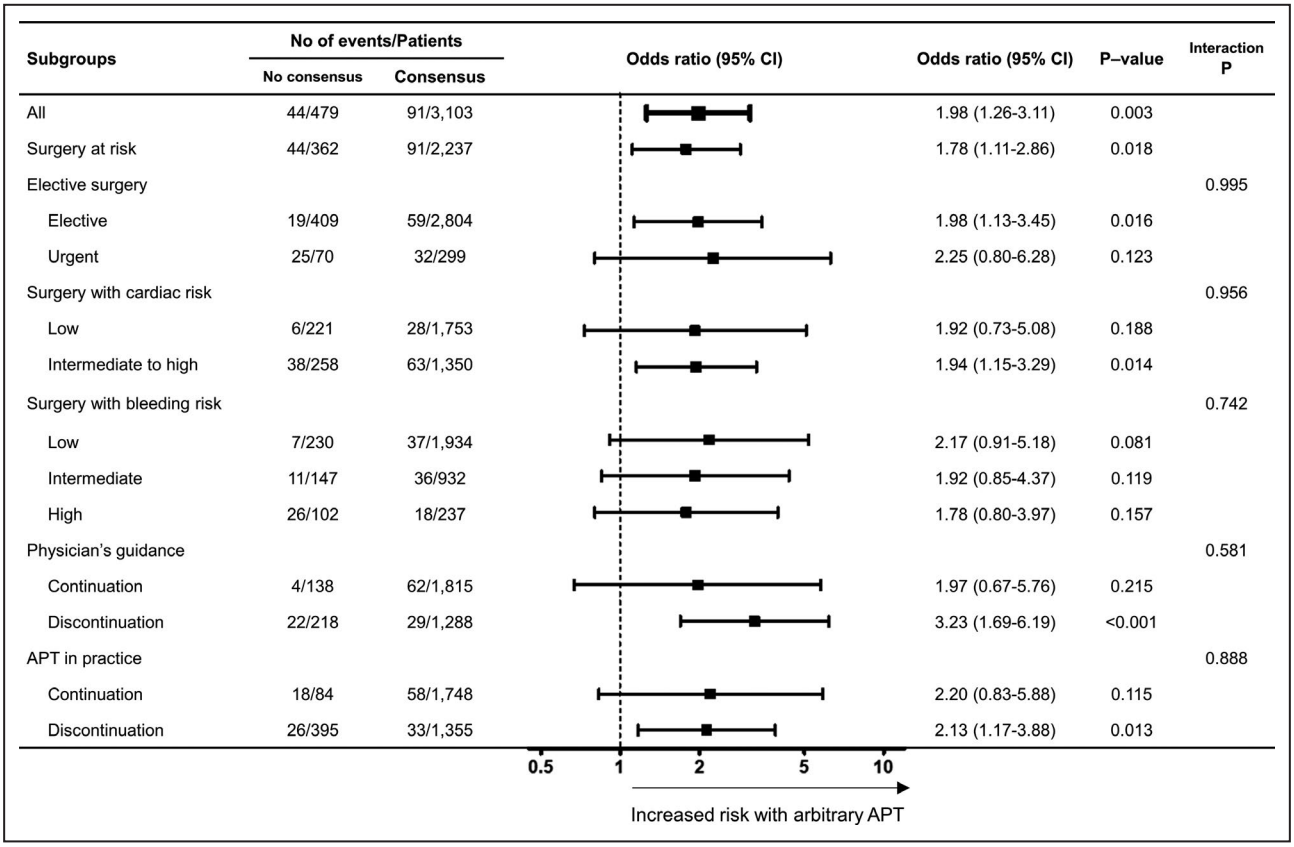

Figure 3. Adjusted odds ratio of arbitrary antiplatelet therapy for net adverse clinical event according to subgroups.
Surgery at risk excludes any type of surgery associated with no perioperative adverse event. APT indicates antiplatelet therapy.

with a placebo in 10 000 patients undergoing NCS. Although the findings of the main study demonstrated that aspirin increases the risk of major bleeding without a significant effect on lowering ischemic events,[21] a subgroup analysis in patients with prior PCI claimed that there is a potential benefit of aspirin in decreasing the risk of death or myocardial infarction by half, without significant effect on major bleeding.[22] These findings imply that the benefit of APT may be determined by the balance among ischemic-bleeding risks. The sub-study of POISE-2 included more than half of patients treated with bare-metal stents and only 25% of patients treated with DES. Considering lower risk of stent thrombosis of the second-generation DES compared with bare-metal stents as well as first-generation DES,[27] it is uncertain whether the modest thrombotic risk associated with the second-generation DES would be significantly modified by the unconditional use of an antiplatelet agent. It should be also noted that about 50% of patients with prior PCI in the POISE-2 study were not receiving any APT ≤7 days before NCS. They could be at a higher risk of the cardiac event because they would discontinue APT for 7 more days even after surgery if they were assigned to take a placebo. In contrast, we recommended to the patients to continue APT as early as possible. The Registre des patients porteurs d'Endoprothèses Coronaires, Opérés de chirurgie non cardiaque (RECO) observation study, including patients with PCI mostly with bare-metal stent and first-generation DES, showed that prolonged discontinuation is a significant factor for ischemic event occurrence after NCS.[19] In a recent observational study, dual APT seems to increase the risk of both MACE and bleeding while monotherapy is comparable with no APT.[23] However, the processes of decision-making on preoperative APT were not available in previous studies. Based on the results of our study, we are convinced that the dilemma of whether APT should be continued or discontinued is no longer the most fundamental solution to reduce the risk of perioperative adverse events and an individualized decision through an appropriate process must be emphasized. According to the results of previous studies on NCS after PCI, the incidence of perioperative MACE ranged from 0.6% to 20%, which was a wide range and varied by the study population of interest.[1,28–32] It may refer that indiscriminate recommendations on antiplatelet

regimen for other patients would not be appropriate for patients with coronary stents awaiting NCS.

Although a consensus decision through referral processes of cardiological consultation and decision-making for preoperative APT was well-conducted as a usual practice for most patients in our study, multidisciplinary approaches including patient's participation and interactive communication through counter-referral systems or roundtable discussions would be more effective to facilitate this decision.[12] As we included only the patients who underwent NCS after PCI in each site, patients who were referred to other hospitals or those who underwent NCS at other hospitals were not the subjects of our study. The relevance of a decision process on preoperative APT for such patients would not have been the same as that for the participants in our study. A facilitated referral system may be required to ensure a consensus decision among doctors and its efficacy should be studied in the future. Also, any differences in the reasons for arbitrary APT may be also concerned during a progress of consensus decision-making and further investigation of the detailed process would be valuable.

Limitations

We retrospectively identified eligible patients who underwent NCS and collected surgery-related covariates as the prospective PCI cohort was not initially purposed to assess perioperative outcomes after NCS. Therefore, it was unavailable to identify the reasons for arbitrary APT, which may be contributed to the disagreement between physicians and surgical staff, or patients' non-compliance caused by unattributable intention, misunderstanding, or careless instruction of medical personnel. Because detailed clinical course during a consensus decision-making was not available, it would be limited to reveal the precise causality of arbitrary APT in the study. Nevertheless, we have demonstrated that arbitrary APT was consistently deleterious irrespective of urgency and different risks of surgery, and the subject of the recommendation. As the process of decision-making for preoperative APT was not influenced by the study enrollment, our retrospective approach may be more efficient to describe real-practice and assess the clinical influence of arbitrary APT which inadvertently occurred.

CONCLUSIONS

A consensus decision on preoperative APT has highly adhered to the patients who underwent NCS in the hospitals based on an organized referral system among physicians, surgeons, and anesthesiologists. Arbitrary APT not based on a consensus decision was shown to be associated with an increased risk of perioperative adverse events including NACE, MACE, and major bleeding. Our findings suggest that a consensus decision should be desirable in patients receiving coronary stenting to balance ischemic and bleeding risks. The results should be interpreted with caution in interpretation of causality and in consideration of the potential for selection bias.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S10
Figures S1–S7

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Supplemental Material

Data S1.

Supplemental Methods

We performed a series of sensitivity analyses to evaluate the robustness of our findings and how the effects might be affected by various inference models. First, we carried out both exposure modeling using the inverse probability of treatment weighting with trimming at 0.01 and 0.05 and outcome modeling using multivariate logistic regression. Second, we conducted analyses in patients without any missing values. Third, we adopted 0, 1, or 3 days as a new criterion for a consensus decision regarding the difference in the duration of discontinuation. Finally, the estimates were calculated after exclusion of each participating site.

Supplemental Results

In the analyses adjusted by doubly robust estimation as a primary statistical method, logistic regression, and inverse probability of treatment weighting, OR_{adj} of arbitrary APT, were similar regarding each clinical outcome, including NACE, MACE, and major bleeding (Figure S7). The results of the analyses in patients without a missing value were like our main results and consistent across the statistical methods used (Tables S2–4). OR_{adj} of arbitrary APT was 1.53 (1.02–2.28) and 1.94 (1.23–3.06) for NACE when a consensus was defined as 0 or ≤3 days difference between physician's guidance and practice, respectively (Table S5). Arbitrary APT was also significant for MACE and major bleeding when criteria were defined at 0 or 3 days' difference (Tables S6, 7). OR_{adj} of the arbitrary APT was ranged from 1.73 to 2.26 for NACE when excluding each participating site (Table S8). Estimations of OR_{adj} of arbitrary APT for MACE and major bleeding were also not far apart from each other in such analyses (Table S9, 10).

Table S1. Independent risk factors for arbitrary antiplatelet therapy.

Covariate	Adjusted odds ratio (95% CI)	*P*–value
All patients not complied with a consensus decision		
Female	1.36 (1.10-1.67)	0.004
Dual antiplatelet therapy	1.49 (1.19-1.86)	<0.001
Urgent surgery	1.39 (1.04-1.85)	0.027
Surgery with bleeding risk		
Intermediate	1.30 (1.04-1.63)	0.021
High	3.69 (2.80-4.86)	<0.001
**Shorter discontinuation*		
Dual antiplatelet therapy	2.28 (1.16-4.49)	0.017
Urgent surgery	4.87 (2.64-8.99)	<0.001
Surgery with bleeding risk		
Intermediate	5.17 (2.26-11.8)	<0.001
High	14.4 (5.85-35.7)	<0.001
Surgery with intermediate to high cardiac risk	2.42 (1.09-5.38)	0.03
**Longer discontinuation*		
High risk PCI	0.73 (0.55-0.99)	0.042
<6 months since PCI	0.56 (0.38-0.80)	0.002
Urgent surgery	0.12 (0.05-0.33)	<0.001

Final parsimonious models excluded insignificant covariates with P>0.10 by backward elimination and covariates in the table were adjusted for each model. *Shorter or longer discontinuation is counted if the difference in duration of discontinuation of APT between practice and physician's recommendation is ≥3 days. CI = confidence interval, PCI = percutaneous coronary intervention.

Table S2. Adjusted odds ratio of arbitrary antiplatelet therapy for net adverse clinical event among patients without a missing value.

Statistical method	Adjusted odds ratio (95% CI)	P–value
Doubly robust estimate	2.11 (1.26-3.52)	0.004
Logistic regression	2.00 (1.22-3.27)	0.006
IPTW (trimming at 0.05)	2.44 (1.51-3.94)	<0.001
IPTW (trimming at 0.01)	2.57 (1.58-4.19)	<0.001

CI = confidence interval, IPTW = inverse probability of treatment weighting

Table S3. Adjusted odds ratio of arbitrary antiplatelet therapy for major adverse cardiac event among patients without a missing value.

Statistical method	Adjusted odds ratio (95% CI)	P–value
Doubly robust estimate	4.01 (1.67-9.63)	0.002
Logistic regression	3.96 (1.85-8.51)	<0.001
IPTW (trimming at 0.05)	4.35 (1.98-9.57)	<0.001
IPTW (trimming at 0.01)	4.87 (2.18-10.9)	<0.001

CI = confidence interval, IPTW = inverse probability of treatment weighting

Table S4. Adjusted odds ratio of arbitrary antiplatelet therapy for major bleeding among patients without a missing value.

Statistical method	Adjusted odds ratio (95% CI)	P–value
Doubly robust estimate	2.49 (1.45-4.28)	0.001
Logistic regression	2.33 (1.37-3.97)	0.002
IPTW (trimming at 0.05)	2.53 (1.46-4.38)	0.001
IPTW (trimming at 0.01)	2.66 (1.51-4.68)	0.001

CI = confidence interval, IPTW = inverse probability of treatment weighting

Table S5. Adjusted odds ratio of arbitrary antiplatelet therapy for net adverse clinical event according to different criteria for a consensus.

Difference between physician's guidance and practice as a criterion for the consensus	Adjusted odds ratio (95% CI)	P–value
0 day	1.53 (1.02-2.28)	0.040
≤1 day	1.64 (1.07-2.53)	0.024
≤2 days (criterion of the study)	1.98 (1.26-3.11)	0.003
≤3 days	1.94 (1.23-3.06)	0.004

CI = confidence interval

Table S6. Adjusted odds ratio of arbitrary antiplatelet therapy for major adverse cardiac event according to different criteria for a consensus.

Difference between physician's guidance and practice as a criterion for the consensus	Adjusted odds ratio (95% CI)	P–value
0 day	2.17 (1.00-4.73)	0.050
≤1 day	2.22 (0.98-5.06)	0.057
≤2 days (criterion of the study)	3.11 (1.31-7.34)	0.010
≤3 days	2.98 (1.28-6.93)	0.011

CI = confidence interval

Table S7. Adjusted odds ratio of arbitrary antiplatelet therapy for major bleeding according to different criteria for a consensus.

Difference between physician's guidance and practice as a criterion for the consensus	Adjusted odds ratio (95% CI)	P–value
0 day	1.76 (1.14-2.72)	0.011
≤1 day	1.95 (1.24-3.09)	0.004
≤2 days (criterion of the study)	2.34 (1.45-3.76)	<0.001
≤3 days	2.36 (1.45-3.82)	0.001

CI = confidence interval

Table S8. Adjusted odds ratio of arbitrary antiplatelet therapy for net adverse clinical event after excluding each participating site.

Subgroup	Adjusted odds ratio (95% CI)	P–value
- (Hospital A)	1.73 (1.02-2.93)	0.043
- (Hospital B)	2.04 (1.22-3.41)	0.006
- (Hospital C)	1.95 (1.22-3.11)	0.005
- (Hospital D)	2.05 (1.28-3.30)	0.003
- (Hospital E)	1.92 (1.17-3.15)	0.01
- (Hospital F)	2.00 (1.23-3.22)	0.005
- (Hospital G)	1.88 (1.19-2.97)	0.007
- (Hospital H)	2.26 (1.42-3.61)	0.001
- (Hospital I)	2.01 (1.26-3.19)	0.003

CI = confidence interval

Table S9. Adjusted odds ratio of arbitrary antiplatelet therapy for major adverse cardiac event after excluding each participating site.

Subgroup	Adjusted odds ratio (95% CI)	P–value
- (Hospital A)	3.00 (1.11-8.14)	0.031
- (Hospital B)	2.63 (0.99-6.98)	0.052
- (Hospital C)	3.00 (1.20-7.54)	0.019
- (Hospital D)	3.63 (1.51-8.74)	0.004
- (Hospital E)	3.39 (1.37-8.37)	0.008
- (Hospital F)	2.59 (1.00-6.73)	0.051
- (Hospital G)	2.85 (1.19-6.83)	0.019
- (Hospital H)	3.29 (1.37-7.88)	0.008
- (Hospital I)	3.33 (1.37-8.09)	0.008

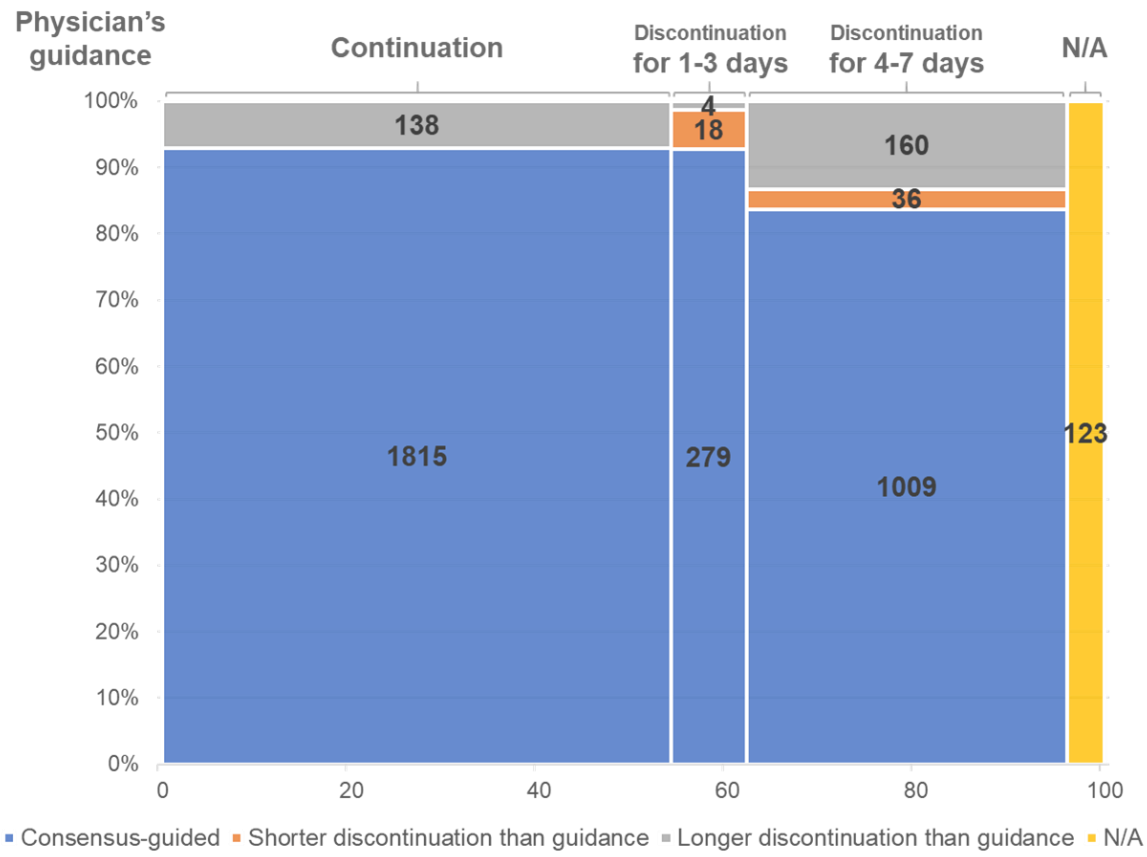
CI = confidence interval

Table S10. Adjusted odds ratio of arbitrary antiplatelet therapy for major bleeding after excluding each participating site.

Subgroup	Adjusted odds ratio (95% CI)	P–value
- (Hospital A)	1.93 (1.11-3.35)	0.020
- (Hospital B)	2.55 (1.50-4.34)	0.001
- (Hospital C)	2.45 (1.51-3.98)	<0.001
- (Hospital D)	2.40 (1.46-3.97)	0.001
- (Hospital E)	2.22 (1.32-3.75)	0.003
- (Hospital F)	2.40 (1.45-4.00)	0.001
- (Hospital G)	2.16 (1.33-3.50)	0.002
- (Hospital H)	2.72 (1.63-4.54)	<0.001
- (Hospital I)	2.31 (1.42-3.77)	0.001

CI = confidence interval

Figure S1. Physician's guidance and antiplatelet therapy in practice regarding duration of discontinuation.



Each dimension of mosaic plot stands for number of patients corresponding to physician's guidance and practice regarding discontinuation of antiplatelet therapy (APT). Among patients who were guided to continue APT, to discontinue ≤3 days, or to discontinue 4 to 7 days by physician, 93%, 93%, and 84% patients complied with the guidance, respectively.

Figure S2. Physician's guidance and antiplatelet therapy in practice regarding duration of discontinuation accoridng to surgical risk of bleeding.

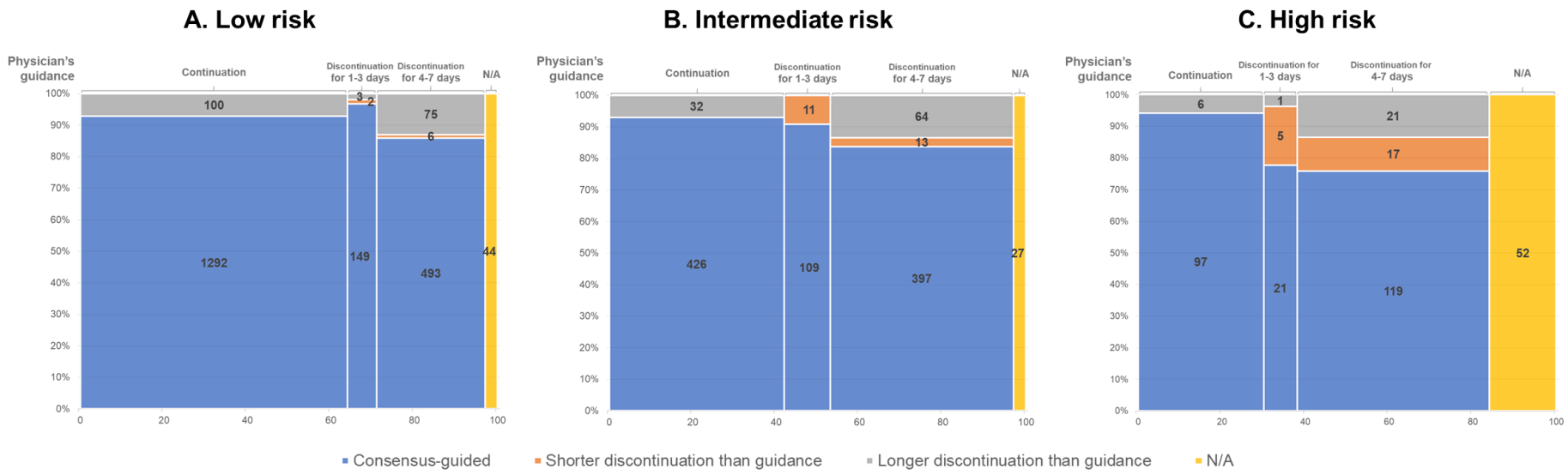


Figure S3. Impact of discrepancy in discontinuation of antiplatelet therapy between guidance and practice on 30-day perioperative MACE.

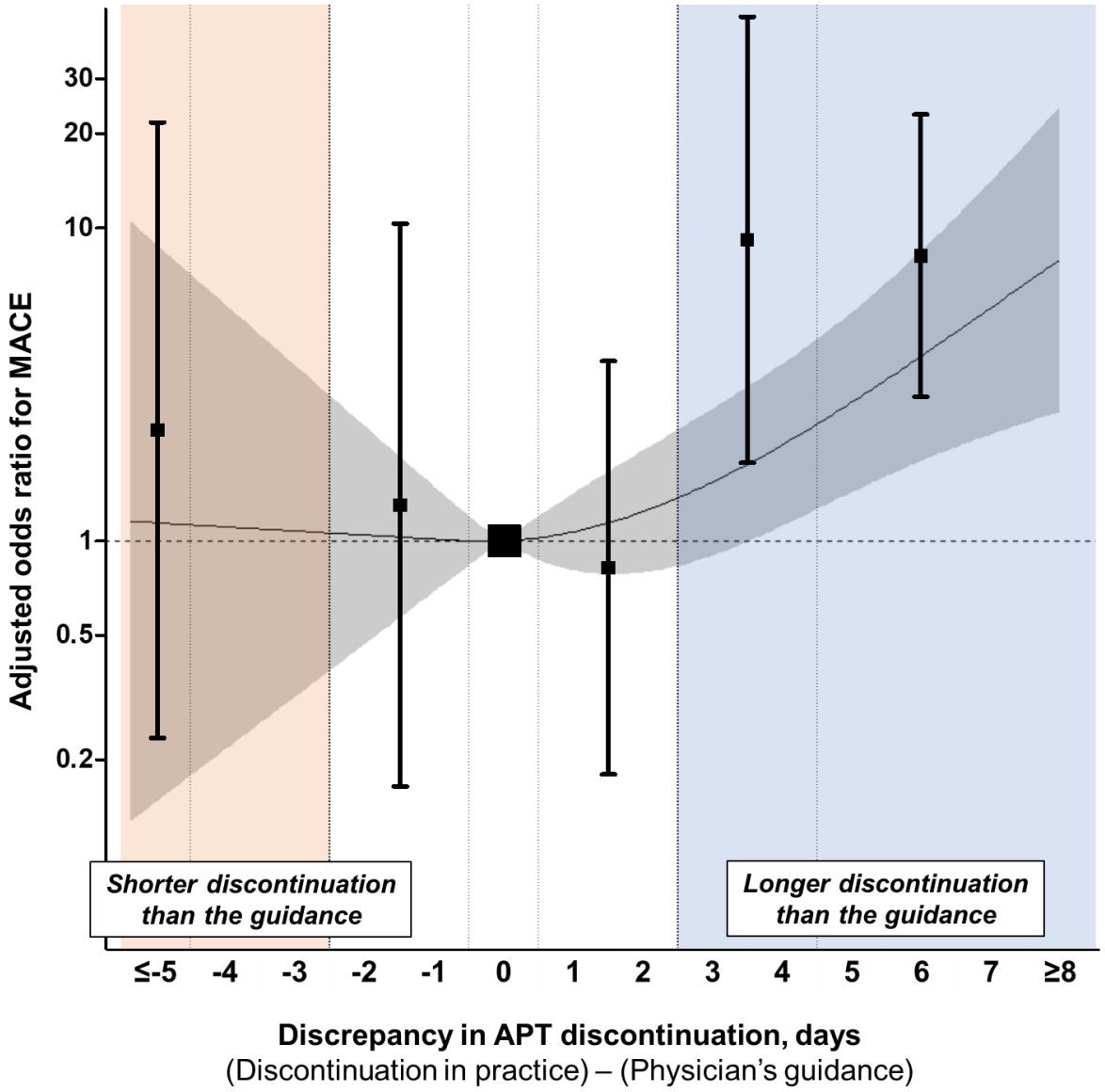


Figure S4. Impact of discrepancy in discontinuation of antiplatelet therapy between guidance and practice on 30-day perioperative major bleeding.

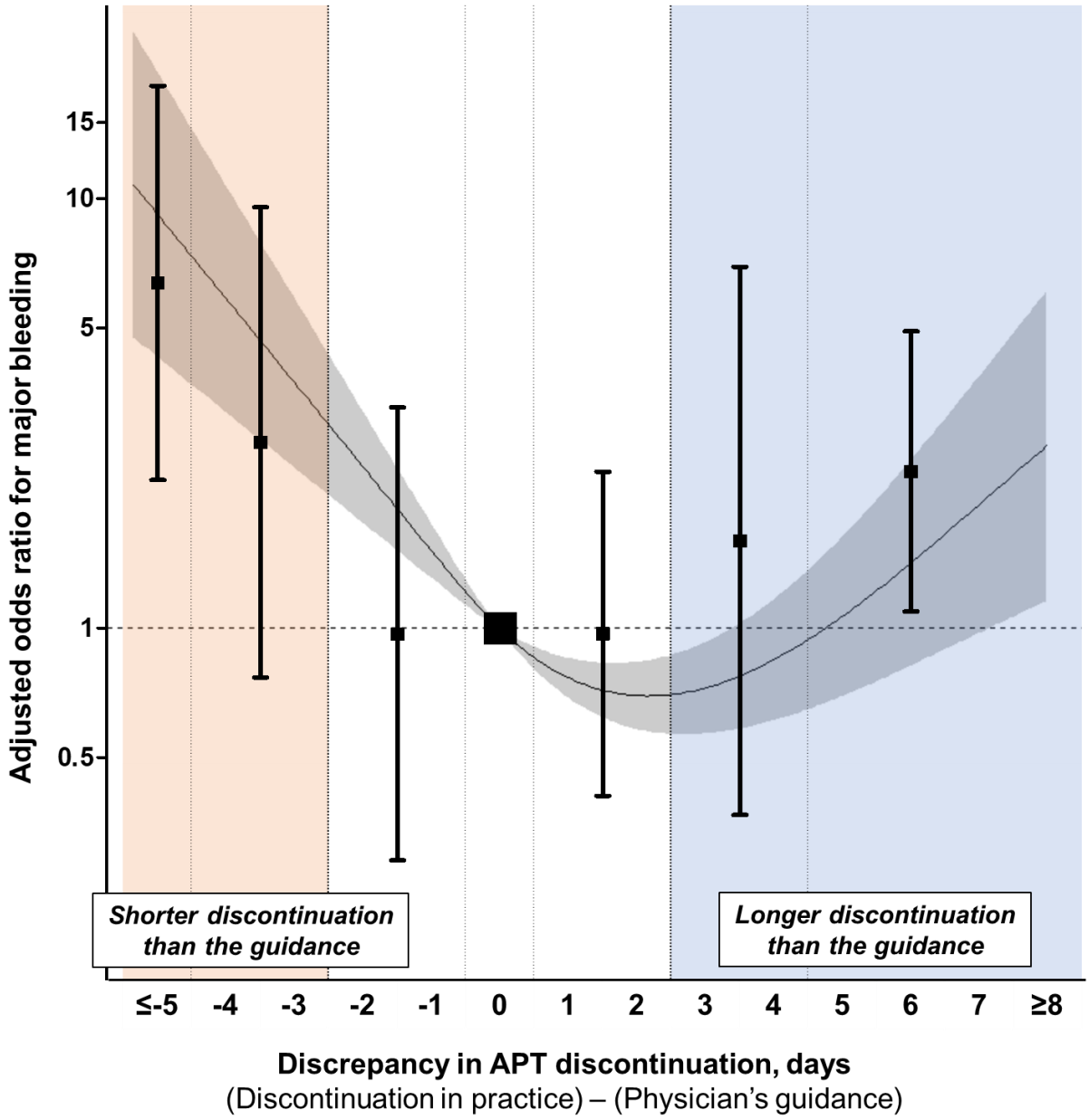


Figure S5. Odds ratio of arbitrary antiplatelet therapy for 30-day major adverse cardiac event.

Subgroups	No of events/Patients		Odds ratio (95% CI)	Odds ratio (95% CI)	P–value	Interaction P
	No consensus	Consensus				
All	14/479	26/3,103		3.11 (1.31-7.34)	0.010	
Surgery at risk	14/362	26/2,237		2.61 (1.03-6.59)	0.043	
Elective surgery						0.081
Elective	7/409	10/2,804		6.12 (2.06-18.2)	0.001	
Urgent	7/70	16/299		0.92 (0.12-6.89)	0.932	
Surgery with cardiac risk						0.704
Low	2/221	7/1,753		5.08 (0.86-30.0)	0.073	
Intermediate to high	12/258	19/1,350		2.84 (1.06-7.57)	0.038	
Physician's guidance						0.564
Continuation	2/138	23/1,815		5.59 (1.08-29.0)	0.040	
Discontinuation	7/218	3/1,288		19.8 (2.99-130)	0.002	
APT in practice						0.030
Continuation	4/84	22/1,748		0.90 (0.26-3.15)	0.865	
Discontinuation	10/395	4/1,355		10.0 (2.25-44.6)	0.002	

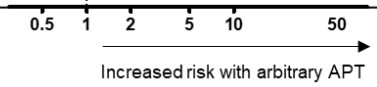


Figure S6. Odds ratio of arbitrary antiplatelet therapy for 30-day major bleeding.

Subgroups	No of events/Patients		Odds ratio (95% CI)	P–value	Interaction P
	No consensus	Consensus			
All	37/479	60/3,103	2.34 (1.45-3.76)	<0.001	
Surgery at risk	37/362	60/2,237	2.20 (1.34-3.61)	0.002	
Elective surgery					0.234
Elective	15/409	46/2,804	1.90 (1.02-3.54)	0.045	
Urgent	22/70	14/299	3.29 (1.04-10.4)	0.043	
Surgery with bleeding risk					0.554
Low	5/230	19/1,934	2.57 (0.87-7.6)	0.089	
Intermediate	7/147	25/932	1.75 (0.7-4.37)	0.228	
High	25/102	16/237	2.15 (0.99-4.7)	0.055	
Physician's guidance					0.340
Continuation	2/138	33/1,815	1.25 (0.27-5.87)	0.773	
Discontinuation	19/218	27/1,288	2.80 (1.42-5.54)	0.003	
APT in practice					0.415
Continuation	16/84	31/1,748	2.90 (1.03-8.19)	0.044	
Discontinuation	21/395	29/1,355	1.94 (1.03-3.66)	0.040	

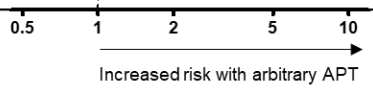


Figure S7. Adjusted odds ratio of arbitrary antiplatelet therapy for perioperative adverse events according to different statistical analyses.