Management of Antithrombotic Agents During Surgery or Other Kinds of Medical Procedures With Bleeding: The MARK Study

Seiji Gotoh, MD, PhD; Masahiro Yasaka, MD, PhD; Asako Nakamura, MD, PhD; Takahiro Kuwashiro, MD, PhD; Yasushi Okada, MD, PhD

Background—Optimal management of antithrombotic agents during surgery has yet to be established. We performed a prospective multicenter observational study to determine the current status of the management of antithrombotic agents during surgery or other medical procedures with bleeding (MARK [Management of Antithrombotic Agents During Surgery or Other Kinds of Medical Procedures With Bleeding] study) in Japan.

Methods and Results—The participants were 9700 patients who received oral antithrombotic agents and underwent scheduled medical procedures with bleeding at 59 National Hospital Organization institutions in Japan. Primary outcomes were thromboembolic events, bleeding events, and death within 2 weeks before and 4 weeks after the procedures. We investigated the relationships between each outcome and patient demographics, comorbidities, type of procedure, and management of antithrombotic therapy. With respect to the periprocedural management of antithrombotic agents, 3551 patients continued oral antithrombotic agents (36.6%, continuation group) and 6149 patients discontinued them (63.4%, discontinuation group). The incidence of any thromboembolic event (1.7% versus 0.6%, $P<0.001$), major bleeding (7.6% versus 0.4%, $P<0.001$), and death (0.8% versus 0.4%, $P<0.001$) was all greater in the discontinuation group than the continuation group. In multivariate analysis, even after adjusting for confounding factors, discontinuation of anticoagulant agents was significantly associated with higher risk for both thromboembolic events (odds ratio: 4.55; 95% CI, 1.67–12.4; $P=0.003$) and major bleeding (odds ratio: 11.1; 95% CI, 2.03–60.3; $P=0.006$) in procedures with low bleeding risk. In contrast, heparin bridging therapy was significantly associated with higher risk for both thromboembolic events (odds ratio: 2.03; 95% CI, 1.28–3.22; $P=0.003$) and major bleeding (odds ratio: 1.36; 95% CI, 1.10–1.68; $P=0.005$) in procedures with high bleeding risk.

Conclusions—Discontinuation of oral antithrombotic agents and addition of low-dose heparin bridging therapy appear to be significantly associated with adverse events in the periprocedural period. (***J Am Heart Assoc***. 2020;9:e012774. DOI: 10.1161/JAHA.119.012774.)

Key Words: anticoagulant therapy • antiplatelet therapy • bleeding complication • discontinuation of antithrombotic agents • thromboembolism

Optimal protocols for the management of antithrombotic agents during surgery have yet to be established, despite the growing use of antithrombotic therapy to treat or prevent cardiovascular diseases in the aging Japanese population. Previous reports have found that continuation of antithrombotic agents could result in bleeding complications during the periprocedural period, although the frequency and severity of such complications vary according to the type of procedure.[1–5] The severity of thromboembolic events (TEs) is high and prognosis is poor when patients discontinue antithrombotic agents[6,7]; however, the frequency of TEs is low except in cases of surgically iatrogenic TEs, such as in cardiac surgery.[8–11] Balancing the risk of TEs with the risk of bleeding events is difficult. We previously reported that intra-arterial catheter procedures could be performed safely in patients who continue antithrombotic agents.[12] Consensus has been reached on the management of antithrombotic agents in limited fields for procedures with low bleeding risk, such as tooth extraction,[13,14] ophthalmic surgery,[9,15] and endoscopic procedures,[16,17] but such agreement remains lacking in most fields, especially for procedures with high

From the Department of Cerebrovascular Medicine and Neurology, Cerebrovascular Center and Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan.

Correspondence to: Seiji Gotoh, MD, PhD, Department of Cerebrovascular Medicine and Neurology, National Hospital Organization Kyushu Medical Center, 1-8-1 Jigyohama, Chuo-ku, Fukuoka 810-8563, Japan. E-mail: sgotoh711@gmail.com

Clinical Perspective

What Is New?

- The relationship between management of periprocedural antithrombotic therapy and thromboembolic events, major bleeding, or death was studied prospectively in a large cohort of nearly 10 000 patients.

What Are the Clinical Implications?

- Discontinuation of oral antithrombotic therapy during the periprocedural period is associated with risk not only of thromboembolism but also of major bleeding, and the addition of low-dose unfractionated heparin bridging may not fully reduce thromboembolic events while increasing the risk of major bleeding.

bleeding risk.[18] In many cases requiring high bleeding risk procedures, we consider each case individually in terms of the management of antithrombotic agents by comparing the risk of TEs and the risk of bleeding events. Heparin bridging therapy has been attempted for patients who discontinued antithrombotic agents, particularly in patients with atrial fibrillation. Randomized controlled trials and meta-analyses have shown that heparin bridging therapy increases the risk of bleeding events without decreasing the risk of TEs compared with nonheparin bridging.[19–23] However, that evidence was mainly based on the results of studies for low-molecular-weight heparin,[19–25] whereas data for unfractionated heparin (UFH), which is commonly used for heparin bridging therapy in Japan, remain limited.[26,27] In addition, although patients have generally been given various antithrombotic agents over the course of years, the effects of these agents on periprocedural complications have not been studied sufficiently. We undertook this prospective, multicenter, observational study to clarify the present conditions and issues regarding the MARK (Management of Antithrombotic Agents During Surgery or Other Kinds of Medical Procedures With Bleeding) study.

Methods

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

Study Population

The MARK study was a prospective multicenter observational study involving 61 National Hospital Organization institutions in Japan. Between December 2011 and June 2014, patients who received antithrombotic agents and were scheduled to undergo surgery or other kinds of invasive medical procedures

were enrolled at 59 institutions. A total of 9992 patients consented to participate in the study. After excluding 146 patients who did not undergo any surgery or medical procedures, 78 patients who were lost to follow-up, and 68 patients who withdrew consent or were lost for other reasons, the remaining 9700 patients (6673 men, 3027 women) were enrolled in the present study.

Clinical Assessments

Data were collected prospectively at enrollment and between 2 weeks before and 4 weeks after the procedure through a review of the medical records by trained staff. In total, 165 kinds of procedures were performed for the patients, and these were classified into 10 broad categories: digestive procedures, including gastroenterologic procedures and digestive surgeries; cardiovascular procedures, including cardiologic procedures and cardiac surgeries; respiratory procedures, including respiratory medicine procedures and respiratory surgeries; neurologic procedures, including neurosurgeries; dermatologic procedures, including plastic surgeries; orthopedic procedures; dental procedures including dental and oral surgeries; urologic procedures; otorhinolaryngologic procedures; and other procedures, including anesthesiology procedures, breast surgeries, obstetrics and gynecology procedures, emergency procedures, and radiologic procedures. Standard gastrointestinal endoscopy was the most common, accounting for 16% (1585 cases) of total cases in our study. The highly invasive procedures included 749 cases of open thoracic surgery, 616 cases of laparotomy, and 86 cases of craniotomy. In addition, we classified procedures according to the risk of bleeding using the classification scheme from a previous study.[19] Procedures with low bleeding risk included gastrointestinal endoscopy and bronchoscopy (with or without biopsy), percutaneous intravascular catheterization (with or without intervention), dental or dermatologic procedures, and any other procedure lasting <1 hour. Procedures with high bleeding risk included intra-abdominal surgery, intrathoracic surgery, intracranial surgery, orthopedic surgery, peripheral arterial surgery, urologic surgery, gynecologic surgery, otorhinolaryngologic surgery, other invasive procedures at deep lesions, and any other procedure lasting ≥1 hour.

Clinical characteristics and data on vascular risk factors including age, sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking status were collected. We also investigated comorbidities and underlying target diseases for the antithrombotic agents, including cardioembolic sources such as atrial fibrillation, mitral stenosis and artificial heart valves for valvular heart disease, prior ischemic heart disease including myocardial infarction and angina pectoris, prior ischemic stroke including brain infarction and transient

ischemic attack, deep vein thrombosis including leg vein thrombus and pulmonary embolism, occlusion or stenosis of the carotid or intracranial arteries, and peripheral artery disease. Detailed data for the periprocedural antithrombotic therapies were collected, including the type and dose of oral antithrombotic agent before the procedure, and the management of antithrombotic agents at the time of the procedure, including continuation, discontinuation and alternative treatments such as heparin bridging therapy. Oral antithrombotic agents included antiplatelet and anticoagulant agents. Oral antiplatelet agents administered before the index procedure included aspirin, thienopyridines including ticlopidine or clopidogrel, cilostazol, and other antiplatelet agents including limaprost alfadex, ethyl icosapentate, sarpogrelate, beraprost sodium, and dipyridamole. Single-antiplatelet therapy was defined as taking one of the main 3 antiplatelet agents—aspirin, thienopyridines, or cilostazol—regardless of the use of other antiplatelet agents. Combination antiplatelet therapy was defined as taking 2 or all 3 of the main antiplatelet agents. Oral anticoagulant agents included vitamin K antagonists and direct oral anticoagulants. The type of heparin included intravenous or subcutaneous injection of UFH and low-molecular-weight heparin.

Primary outcomes were TEs, bleeding events, and death between 2 weeks before and 4 weeks after the procedures. TEs were defined as ischemic stroke including brain infarction and transient ischemic attack, ischemic heart disease including myocardial infarction and angina pectoris, deep vein thrombosis, and other systemic vascular embolism and thrombosis. Bleeding events were defined as brain hemorrhage, subarachnoid hemorrhage, other systemic hemorrhagic events, transfusion of whole blood or red cells, and surgical site bleeding beyond the usual level as assessed by the surgeon. Patients with symptomatic bleeding in critical areas, such as intracranial, intraspinal, retroperitoneal, pericardial, intra-articular and intramuscular sites, and/or those with bleeding of >600 mL during the procedure—which is a possible indication for transfusion at the procedure—were defined as having major bleeding (MB). We were not able to apply existing criteria, including the International Society of Thrombosis and Hemostasis criteria,[28] as a definition of MB because falls in hemoglobin values in the periprocedural period were not available in our study.

Statistical Analysis

All statistical analyses were performed using SAS v9.4 software (SAS Institute). Any patient who interrupted any oral antithrombotic agent during the periprocedural period was assigned to the discontinuation group. Twenty patients for whom the dosage of oral antithrombotic agents was reduced were also included in the discontiuation group.

Patients who discontinued oral antithrombotic agents before or during the periprocedural period were included in the discontinuation group; patients who changed an oral antithrombotic agent because of end point events were not included in this group. Conversely, patients who continued all antithrombotic agents at the same dosage were assigned to the continuation group. Clinical characteristics and primary outcomes between 2 weeks before and 4 weeks after the procedures were then compared between these groups. The χ^2 test or Fisher exact test was used to determine the statistical significance of differences in the frequencies of categorical variables, as appropriate. The Student t test was used to compare the mean values of continuous variables. Multivariate-adjusted odds ratios (ORs) and 95% CIs for the risk of TEs, MB, and death were calculated by a logistic regression model. Covariates included age, sex, cardiac embolic sources including atrial fibrillation and heart valvular disease, prior ischemic heart disease, prior ischemic stroke, peripheral artery disease including intracranial and carotid stenosis, hypertension, hyperlipidemia, and smoking habit in addition to types of discontinued oral antithrombotic agents and heparin bridging therapy. Two-sided values of $P<0.05$ were considered significant in all analyses.

Ethics Considerations

The study protocol was approved by the ethics committees of the National Hospital Organization Kyushu Medical Center in 2010 (KMC 10-61) and the National Hospital Organization Research Center in 2011 (NHO 0715001), and written informed consent was obtained from all participants.

Results

Among the total of 9700 patients who underwent surgery or some other kind of surgical procedure, 3551 patients (36.6%, continuation group) continued antithrombotic agents, and the remaining 6149 patients (63.4%, discontinuation group) discontinued them. Digestive procedures and cardiovascular procedures were the most common, representing 35% and 23% of the total group, respectively (Figure 1). More than 90% of patients discontinued oral antithrombotic agents when respiratory, orthopedic, or urologic procedures were planned. In contrast, 88% of patients who underwent dental procedures and 70% of patients who underwent dermatologic procedures continued their oral antithrombotic agents. The clinical characteristics of patients stratified by continuation or discontinuation of antithrombotic agents are shown in Table 1. Compared with the continuation group, the mean age and frequencies of atrial fibrillation, prior ischemic stroke, and high bleeding risk procedures were higher in the discontinuation
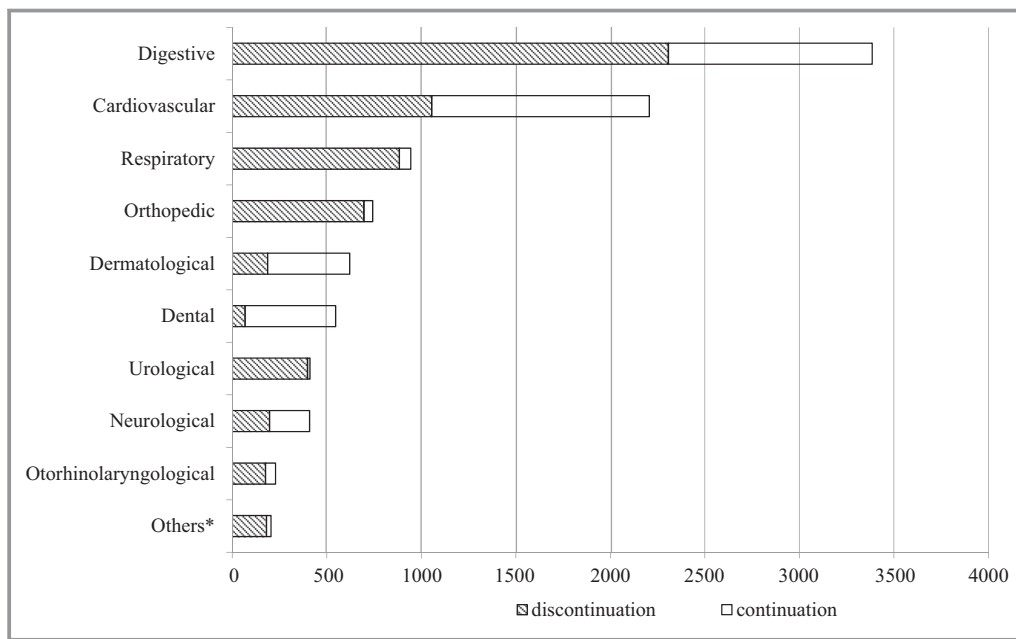
Figure 1. Number of patients and proportion of discontinuations of antithrombotic agents according to type of procedure. *Including anesthesiology procedures, breast surgeries, obstetrics and gynecology procedures, emergency procedures, and radiologic procedures.

group. In contrast, the discontinuation group showed lower frequencies of prior ischemic heart disease, diabetes mellitus, hyperlipidemia, and low bleeding risk procedures. No differences were observed between the continuation and discontinuation groups in terms of the frequencies of male sex, valvular heart disease, carotid or intracranial artery stenosis, peripheral artery disease, deep vein thrombosis, hypertension, or smoking habits. As for the use of oral antithrombotic agents before the procedures, the discontinuation group showed higher frequencies of cilostazol, other antiplatelet agents, and direct oral anticoagulants, whereas the frequencies of aspirin and thienopyridines were significantly lower in the discontinuation group than in the continuation group. Twenty percent of patients in total and 31% of the discontinuation group used heparin bridging therapy by UFH or low-molecular-weight heparin in the periprocedural period. Among the types of heparin, UFH was the most common (98%). The median dose of UFH was 10 000 U/day (95% CI, 5639–16 335). As shown in Table 2, between 2 weeks before and 4 weeks after the procedures, some form of TE or some form of bleeding event developed in 128 patients (1.3%) and 1377 patients (14.2%), respectively. Periprocedural death was observed in 65 patients (0.7%). Compared with the continuation group, rates of TEs (1.7% versus 0.6%, $P<0.001$), MB (7.6% versus 0.4%, $P<0.001$), and death (0.8% versus 0.4%, $P=0.02$) were significantly higher in the discontinuation group. The time of peak incidence varied by the type of TE in the present study (Figure 2). Periprocedural ischemic heart disease occurred most commonly on the day of the procedure and on postprocedural day 1. In contrast,

ischemic stroke showed peak incidence from postprocedural days 2 to 7. Most deep vein thrombosis occurred from postprocedural days 8 to 14. The rates of adverse events according to types of procedure are shown in Table 3. Compared with the continuation group, rates of TEs (1.1% versus 0.5%, $P=0.01$), MB (0.4% versus 0.1%, $P=0.03$), and death (1.0% versus 0.3%, $P=0.001$) were significantly higher in the discontinuation group with low-bleeding-risk procedures, whereas the discontinuation group showed higher frequency of MB (11.3% versus 2.5%, $P<0.001$) in high-bleeding-risk procedures, but no significant association was observed between discontinuation and other outcomes. The adverse event rates according to types of antithrombotic agent are shown in Table 4. Compared with those of the continuation group, the event rates for TEs and MB were significantly higher in the discontinuation group whether they discontinued antiplatelet agents (1.5% versus 0.8% for TE, 7.3% versus 0.4% for MB) or anticoagulant agents (1.6% versus 0.2% for TE, 7.5% versus 0.3% for MB). The association between heparin bridge therapy and adverse events is shown in Table 5. Compared with the nonbridged patients, bridged patients showed higher frequencies of TEs whether they were discontinuing antiplatelet agents (2.7% versus 1.2%, $P=0.002$) or anticoagulant agents (2.4% versus 0.6%, $P=0.02$). In contrast, in bridged patients, the discontinuation of antiplatelet agents was significantly associated with incident MB (12.9% versus 5.8%, $P<0.001$), but no significant association was observed in the nonbridged patients discontinuing anticoagulant agents (8.2% versus 7.0%, $P=0.45$). The multivariate-adjusted ORs and 95% CIs

Table 1. Baseline Clinical Characteristics of Patients With or Without Continuation of Antithrombotic Agents

	All Patients	Continuation	Discontinuation	
	N=9700	n=3551	n=6149	P Value
Age, y, mean (SD)	73 (10)	72 (11)	73 (9)	<0.001
Men, n (%)	6673 (68.8)	2482 (69.9)	4191 (68.2)	0.08
Comorbidities, n (%)				
Atrial fibrillation	2015 (20.8)	627 (17.7)	1388 (22.6)	<0.001
Valvular heart disease	332 (3.4)	134 (3.8)	198 (3.2)	0.16
Prior ischemic heart disease	3814 (39.3)	1735 (48.9)	2079 (33.8)	<0.001
Prior ischemic stroke	3019 (31.1)	940 (26.5)	2079 (33.8)	<0.001
Carotid or intracranial artery stenosis	562 (5.8)	198 (5.6)	364 (5.9)	0.43
Peripheral artery disease	927 (9.6)	328 (9.2)	599 (9.7)	0.42
Deep vein thrombosis	261 (2.7)	87 (2.5)	174 (2.8)	0.27
Vascular risk factors, n (%)				
Hypertension	7328 (75.6)	2711 (76.3)	4617 (75.1)	0.17
Diabetes mellitus	3005 (31.0)	1217 (34.3)	1788 (29.1)	<0.001
Hyperlipidemia	4586 (47.3)	1839 (51.8)	2747 (44.7)	<0.001
Smoking habit	5617 (58.1)	2065 (58.4)	3552 (58.0)	0.72
Antithrombotic agents before procedures, n (%)				
Aspirin	5640 (58.1)	2251 (63.4)	3389 (55.1)	<0.001
Thienopyridines	2496 (25.7)	1227 (34.6)	1269 (20.6)	<0.001
Cilostazol	941 (9.7)	298 (8.4)	643 (10.5)	0.001
Other antiplatelet agents	1431 (14.8)	385 (10.8)	1046 (17.0)	<0.001
VKA	2200 (22.7)	801 (22.6)	1399 (22.8)	0.84
DOAC	454 (4.7)	109 (3.1)	345 (5.6)	<0.001
Heparin bridging therapy, n (%)	1941 (20.0)	16 (0.5)	1925 (31.3)	<0.001
UFH, intravenous	1796 (18.5)	16 (0.5)	1780 (29.0)	<0.001
UFH, subcutaneous	109 (1.1)	0 (0)	109 (1.8)	<0.001
LMWH	36 (0.4)	0 (0)	36 (0.6)	<0.001
Type of procedures, n (%)				
Low bleeding risk	5112 (52.7)	3064 (86.3)	2048 (33.3)	<0.001
High bleeding risk	4588 (47.3)	487 (13.7)	4101 (66.7)	<0.001

Valvular heart disease includes mitral stenosis and artificial heart valve. Ischemic heart disease includes previous myocardial infarction and angina pectoris. Ischemic stroke includes previous brain infarction and transient ischemic attack. Deep vein thrombosis includes leg vein thrombus and pulmonary embolism. Thienopyridines include clopidogrel and ticlopidine. Other antiplatelet agents include limaprost alfadex, ethyl icosapentate, sarpogrelate, beraprost sodium, and dipyridamole. DOAC indicates direct oral anticoagulants; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonists.

for risks of adverse events are shown in Table 6. Discontinuation of anticoagulant agents was significantly associated with higher risk for both TEs (OR: 4.55; 95% CI, 1.67–12.4; P=0.003) and MB (OR: 11.1; 95% CI, 2.03–60.3; P=0.006) in low-bleeding-risk procedures, whereas discontinuation of antiplatelet agents was significantly associated with death (OR: 2.43; 95% CI, 1.10–5.36; P=0.03). In contrast, heparin bridging therapy was significantly associated with higher risk for both TEs (OR: 2.03; 95% CI, 1.28–3.22; P=0.003) and MB (OR: 1.36; 95% CI, 1.10–1.68; P=0.005) with high-bleeding-risk

procedures. In addition, discontinuation of antithrombotic agents was also associated with higher risk for MB whether the discontinued agents were anticoagulant agents (OR: 1.47; 95% CI, 1.07–2.01; P=0.02) or antiplatelet agents (OR: 1.81; 95% CI, 1.36–2.40; P<0.001).

Discussion

Using the data from the prospective multicenter observational MARK study in Japan, we examined the present conditions for

Table 2. Rates of Adverse Events During the Periprocedural Period

	All Patients	Continuation	Discontinuation	
	N=9700	n=3551	n=6149	P Value
Any TE, n (%)	128 (1.3)	23 (0.6)	105 (1.7)	<0.001
Ischemic stroke	58 (0.6)	15 (0.4)	43 (0.7)	0.10
Ischemic heart disease	18 (0.2)	4 (0.1)	14 (0.2)	0.23
Deep vein thrombosis	31 (0.3)	0 (0)	31 (0.5)	<0.001
Other TE	25 (0.3)	4 (0.1)	21 (0.3)	0.04
Any bleeding complications, n (%)	1377 (14.2)	321 (9.0)	1056 (17.2)	<0.001
MB	485 (5.0)	15 (0.4)	470 (7.6)	<0.001
Transfusion of whole blood or red cells	670 (6.9)	30 (0.8)	640 (10.4)	<0.001
Hemorrhagic stroke	14 (0.1)	4 (0.1)	10 (0.2)	0.59
Other bleeding events	397 (4.1)	57 (1.6)	340 (5.5)	<0.001
Increased surgical site bleeding	886 (9.1)	257 (7.2)	629 (10.2)	<0.001
Death, n (%)	65 (0.7)	15 (0.4)	50 (0.8)	0.03

MB indicates major bleeding; TE, thromboembolism.

use of antithrombotic therapy in the periprocedural period and risk factors affecting periprocedural TEs, MB, and death. As a result, we found that management of antithrombotic therapy, including discontinuation of oral antithrombotic agents and addition of heparin bridging therapy, was associated with adverse events in the periprocedural period.

Some form of TE and ischemic stroke were observed in 1.3% and 0.6% of all participants in this study. The frequency of ischemic stroke was reported as ≈0.7% for noncardiac and nonvascular surgeries in previous studies.[29,30] Our results were comparable to those reports. As for the time from the procedure to the development of ischemic stroke and ischemic heart disease, a previous report found that the incidence peaked early after surgery and decreased over a matter of days.[31,32] The timing of peak incidence varied by the type of TE in the present study. The surgical procedure itself
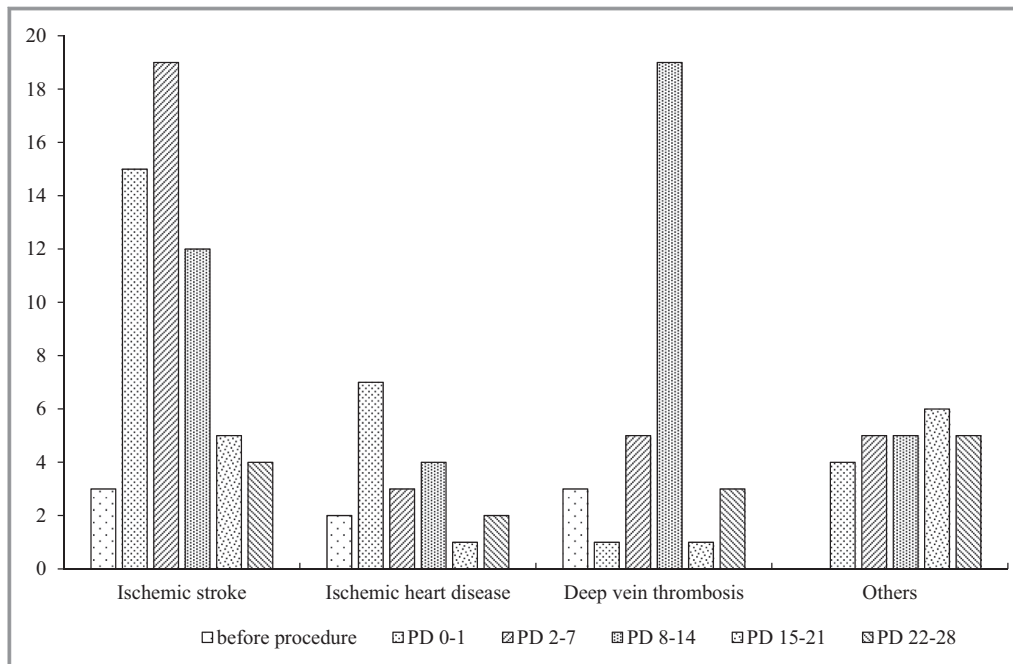
Figure 2. Number of thromboembolic events according to the periprocedural time and type of thromboembolism. PD indicates postprocedural day.

Table 3. Rates of Adverse Events According to Type of Procedures

	Incident TEs			Incident MB			Death		
	Continuation	Discontinuation	P Value	Continuation	Discontinuation	P Value	Continuation	Discontinuation	P Value
Bleeding risk, n/n (%)									
Low	14/3064 (0.5)	22/2048 (1.1)	0.02	3/3064 (0.1)	8/2048 (0.4)	0.03	9/3064 (0.3)	20/2048 (1.0)	0.002
High	9/487 (1.9)	83/4101 (2.0)	0.87	12/487 (2.5)	462/4101 (11.3)	<0.001	6/487 (1.2)	30/4101 (0.7)	0.27
Type of procedures, n/n (%)									
Digestive	5/1078 (0.5)	15/2307 (0.7)	0.63	1/1078 (0.1)	53/2307 (2.3)	<0.001	4/1078 (0.4)	12/2307 (0.5)	0.79
Cardiovascular	3/1151 (0.3)	31/1055 (2.9)	<0.001	8/1151 (0.7)	333/1055 (31.6)	<0.001	4/1151 (0.4)	13/1055 (1.2)	0.03
Respiratory	0/60 (0)	9/884 (1.0)	1.00	0/60 (0)	7/884 (0.8)	1.00	1/60 (1.7)	19/884 (2.2)	1.00
Orthopedic	1/47 (2.1)	29/696 (4.2)	1.00	4/47 (8.5)	30/696 (4.3)	0.26	1/47 (2.1)	2/696 (0.3)	0.18
Dermatologic	4/434 (0.9)	3/187 (1.6)	0.44	0/434 (0)	2/187 (1.1)	0.09	2/434 (0.5)	0/187 (0)	1.00
Dental	0/479 (0)	1/68 (1.5)	0.12	0/479 (0)	1/68 (1.5)	0.12	0/479 (0)	0/68 (0)	. . .
Urologic	0/13 (0)	3/398 (0.8)	1.00	1/13 (7.7)	18/398 (4.5)	1.00	0/13 (0)	0/398 (0)	. . .
Neurologic	10/212 (4.7)	6/197 (3.1)	0.45	1/212 (0.5)	18/197 (9.1)	<0.001	3/212 (1.4)	3/197 (1.5)	1.00
Otorhinolaryngologic	0/53 (0)	1/176 (0.6)	1.00	0/53 (0)	2/176 (1.1)	1.00	0/53 (0)	0/176 (0)	. . .
Other procedures	0/24 (0)	7/181 (3.9)	1.00	0/24 (0)	6/181 (3.3)	1.00	0/24 (0)	1/181 (0.6)	1.00

may directly influence the development of TEs, whereas most TEs occurred after the second postprocedural day in our study. In recent years, although the occurrence of surgically iatrogenic TEs may have decreased given improved surgical techniques and anesthetic management, the association of periprocedural management, including management of comorbidities and antithrombotic therapies of the patients, and TEs may have increased along with the widespread use of oral antithrombotic agents and the growth of the elderly population in Japan. Compared with those in the continuation group, the event rates for deep vein thrombosis were significantly higher in the discontinuation group, whereas the event rates of other ischemic events were not significantly different between the 2 groups, and deep vein thrombosis occurred later than other ischemic events. These facts probably relate to the poor management of changes in antithrombotic agents after heparin bridging and the time required for the development of deep vein thrombosis.

Table 4. Rates of Adverse Events According to Type of Antithrombotic Agents

	Incident TEs			Incident MB			Death		
	Continuation	Discontinuation	P Value	Continuation	Discontinuation	P Value	Continuation	Discontinuation	P Value
Antiplatelet agents, n/n (%)	20/2646 (0.8)	68/4420 (1.5)	0.004	11/2646 (0.4)	321/4420 (7.3)	<0.001	9/2646 (0.3)	29/4420 (0.7)	0.09
SAPT*	11/1542 (0.7)	48/3088 (1.6)	0.02	9/1542 (0.6)	217/3088 (7.0)	<0.001	5/1542 (0.3)	18/3088 (0.6)	0.28
CAPT[†]	7/1012 (0.7)	14/716 (2.0)	0.02	6/1012 (0.6)	83/716 (11.6)	<0.001	4/1012 (0.4)	9/716 (1.3)	0.049
Anticoagulant agents, n/n (%)	1/615 (0.2)	18/1148 (1.6)	0.006	2/615 (0.3)	86/1148 (7.5)	<0.001	6/615 (1.0)	9/1148 (0.8)	0.79
VKA	1/547 (0.2)	18/928 (1.9)	0.003	1/547 (0.2)	84/928 (9.1)	<0.001	6/547 (1.1)	12/928 (1.3)	0.81
DOAC	0/83 (0)	2/268 (0.8)	1.00	1/83 (1.2)	8/268 (3.0)	0.69	0/83 (0)	0/268 (0)	. . .
Antiplatelet plus anticoagulant agents[‡]	3/361 (0.8)	16/431 (3.7)	0.009	5/361 (1.4)	53/431 (12.3)	<0.001	1/361 (0.3)	8/431 (1.9)	0.04

CAPT indicates combination antiplatelet therapy; DOAC, direct oral anticoagulants; MB, major bleeding; SAPT, single antiplatelet agents; TE, thromboembolic event; VKA, vitamin K antagonists.

*Taking one of the main 3 antiplatelet agents: aspirin, thienopyridines, or cilostazol.

[†]Taking ≥2 of the main 3 antiplatelet agents: aspirin, thienopyridines, or cilostazol.

[‡]Taking ≥1 of the main antiplatelet agents (aspirin, thienopyridines, or cilostazol) plus an anticoagulant agent.

Table 5. Rates of Adverse Events in Discontinued Patients With or Without Heparin Bridging Therapy

	Incident TE			Incident MB			Death		
	No Bridge	Bridge	P Value	No Bridge	Bridge	P Value	No Bridge	Bridge	P Value
Antiplatelet agents, n/n (%)	43/3500 (1.2)	25/920 (2.7)	0.002	202/3500 (5.8)	119/920 (12.9)	<0.001	18/3500 (0.5)	11/920 (1.2)	0.04
SAPT*	32/2521 (1.3)	16/567 (2.8)	0.01	143/2521 (5.7)	74/567 (13.1)	<0.001	13/2521 (0.5)	5/567 (0.9)	0.35
CAPT†	6/405 (1.5)	8/311 (2.6)	0.42	43/405 (10.6)	40/311 (12.9)	0.41	5/405 (1.2)	4/311 (1.3)	1.00
Anticoagulant agents, n/n (%)	3/502 (0.6)	17/706 (2.4)	0.02	35/502 (7.0)	58/706 (8.2)	0.45	7/502 (1.4)	5/706 (0.7)	0.25
VKA	2/358 (0.6)	16/570 (2.8)	0.01	31/358 (8.7)	53/570 (9.3)	0.81	7/358 (2.0)	5/570 (0.9)	0.23
DOAC	1/136 (0.7)	1/132 (0.8)	1.00	4/136 (2.9)	4/132 (3.0)	1.00	0/136 (0)	0/132 (0)	...
Antiplatelet plus anticoagulant agents‡	5/170 (2.9)	11/261 (4.2)	0.61	18/170 (10.6)	35/261 (13.4)	0.45	4/170 (2.4)	4/261 (1.5)	0.72

CAPT indicates combination antiplatelet therapy; DOAC, direct oral anticoagulants; MB, major bleeding; SAPT, single antiplatelet agents; TE, thromboembolic event; VKA, vitamin K antagonists.

*Taking one of the main 3 antiplatelet agents: aspirin, thienopyridines, or cilostazol.

†Taking ≥2 of the main 3 antiplatelet agents: aspirin, thienopyridines, or cilostazol.

‡Taking ≥1 of the main 3 antiplatelet agents (aspirin, thienopyridines, and cilostazol) plus an anticoagulant agent.

In the present study, discontinuation of anticoagulant agents was significantly associated with periprocedural TEs in low-bleeding-risk procedures. However, in high-bleeding-risk procedures, significant association was not observed between discontinuation of antithrombotic agents and TEs; however, heparin bridging therapy was significantly associated with higher risk for TEs. The results showing that discontinuation of anticoagulant agents and addition of heparin bridging therapy were associated with the risk for periprocedural TEs are in accordance with previous reports.[6–11,20] In these reports, in low-bleeding-risk procedures such as dental surgery and endoscopy, TEs developed in ≈1% of patients who discontinued vitamin K antagonist, and the event rate for stroke increased in the more complex patients, including those

requiring urgent procedures.[7,8] In addition, a subanalysis of the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial showed that bridged patients with vitamin K antagonist interruption experienced more episodes of any TE than those without bridging.[20] Although it is not clear why the association between management of antithrombotic agents and TEs varied according to the type of procedure in our study, some possible explanations would be as follows. Because oral anticoagulant agents have short duration of action and patients with atrial fibrillation, valvular heart disease, or other conditions who are taking these agents are often at high risk for thromboembolism, TE risk may increase even for patients with low bleeding risk who discontinue oral anticoagulants for a short time. In such cases, short-term,

Table 6. Multivariate-Adjusted ORs and 95% CIs for Adverse Events

	Incident TEs		Incident MB		Death	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Low-bleeding-risk procedure						
Discontinuation of anticoagulant agents	4.55 (1.67–12.4)	0.003	11.1 (2.03–60.3)	0.006	2.22 (0.70–7.07)	0.18
Discontinuation of antiplatelet agents	1.56 (0.77–3.14)	0.21	0.86 (0.20–3.74)	0.84	2.43 (1.10–5.36)	0.03
Heparin bridging therapy	1.82 (0.69–4.78)	0.22	2.44 (0.50–12.0)	0.27	1.25 (0.40–3.88)	0.70
High-bleeding-risk procedure						
Discontinuation of anticoagulant agents	1.29 (0.65–2.56)	0.47	1.47 (1.07–2.01)	0.02	1.07 (0.38–3.07)	0.89
Discontinuation of antiplatelet agents	1.23 (0.68–2.23)	0.49	1.81 (1.36–2.40)	<0.001	1.02 (0.43–2.44)	0.96
Heparin bridging therapy	2.03 (1.28–3.22)	0.003	1.36 (1.10–1.68)	0.005	1.03 (0.49–2.16)	0.94

Adjustment was made for age, sex, cardiac embolic sources including atrial fibrillation and heart valvular disease, prior ischemic heart disease, prior ischemic stroke, peripheral artery disease including intracranial and carotid stenosis, hypertension, hyperlipidemia, smoking habit, types of discontinued oral antithrombotic agents, and heparin bridging therapy. MB indicates major bleeding; OR, odds ratio; TE, thromboembolic event.

low-dose heparin bridging therapy may have only a small effect on incident TEs. In contrast, the association between heparin bridging therapy and TEs in procedures with high bleeding risk may have been due to heparin-bridged patients discontinuing oral antithrombotic agents for a long time and thus having a higher potential risk of TEs than nonbridged patients. In Japan, intravenous injections of UFH at low doses of ≈10 000 U might not achieve a sufficient inhibition of thrombogenesis and at the same time might increase the risk of TEs. Moreover, the discontinuation of antiplatelet agents was significantly associated with periprocedural death in low-bleeding-risk procedures in our study. The patients who discontinued antiplatelet agents despite undergoing minimally invasive procedures might have had serious underlying diseases other than those being targeted by the antiplatelet agents or the minimally invasive procedures.

We found that discontinuation of oral anticoagulant agents for low-bleeding-risk procedures was significantly associated with not only risk of TEs but also risk of MB. In addition, for high-bleeding-risk procedures, discontinuation of any antithrombotic agents and addition of heparin bridging therapy were also significantly associated with higher risks for MB. Some possible explanations for the finding that discontinuation of antithrombotic agents was associated with the risk of MB are as follows. Patients requiring the discontinuation of oral antithrombotic agents might have extensive atherosclerotic lesions with high bleeding risk and might undergo more invasive procedures than those who continue these agents. In addition, procedures, especially in emergency situations, might have been performed before the antithrombotic effect disappeared because discontinuation and its timing were left to the physician's discretion in our observational study setting. Our result that heparin bridging therapy was associated with higher risk of MB supports the findings of some meta-analyses and randomized control trials.[19–23] Those studies failed to confirm any protective efficacy of periprocedural TEs with heparin bridging therapy, whereas the risk of bleeding complications increased. The IST (International Stroke Trial) demonstrated that the protection against ischemic events conferred by heparin is offset by bleeding complications.[33] Furthermore, heparin bridging therapy may not be appropriate in the periprocedural period, when bleeding risk is increased.

The strengths of our study include its enrollment of nearly 10 000 patients due to a multicenter prospective design; this large study population may have suitably reflected the present conditions for the management of periprocedural antithrombotic therapy in Japan. However, several limitations should also be discussed. First, our findings were based on an observational study. The management of antithrombotic therapy, including continuation or discontinuation of antithrombotic therapy and the use of heparin bridging therapy in the periprocedural period, was not randomized but rather was entrusted to the decision of the physicians. The ability to interpret the direction of causality between the management of antithrombotic therapy and periprocedural complications was thus limited. Further studies, including interventional studies, will be needed to determine the optimal management of antithrombotic therapy in the periprocedural period. Second, we could not distinguish emergency procedures from elective procedures. The frequencies of adverse events might be higher in patients undergoing emergency than patients undergoing elective surgery, and thus the frequencies of adverse events in our study might have been higher than those in studies for elective surgery. However, because we accumulated cases that were determined to be operable in clinical practice, our findings would seem to reflect the present real-world conditions for the periprocedural management of antithrombotic therapy. Third, regarding the definition of MB, we could not adopt the definition use by other studies—namely, a decrease in hemoglobin >2 mg/dL—because hemoglobin values were not available in our study. In place of this criterion, we defined MB as bleeding >600 mL during the procedure in addition to symptomatic bleeding in critical areas. Fourth, when we stratified the participants, the statistical power to detect differences between the management of antithrombotic therapy and adverse events in these groups was limited because the numbers of adverse events for a particular patient group, especially in patients who took direct oral anticoagulant or underwent low bleeding risk procedures, were relatively small. Finally, data on the severity of underlying diseases and hematologic disorders such as thrombocytopenia, coagulation disorders, and anemia, which also seem to influence periprocedural complications, were unavailable in the present study. Although we attempted to account for possible risk factors in the multivariate analysis, some confounding factors may have remained.

Conclusions

Our findings suggest that the frequency of discontinuation of oral antithrombotic agents depends on the type of procedure. With respect to the timing of periprocedural thromboembolic events, the peak incidence varies by the type of thromboembolism. The discontinuation of oral antithrombotic agents and addition of heparin bridging therapy are associated with adverse events in the periprocedural period. Low-dose heparin bridging therapy is associated with bleeding events and may not actually reduce the risk of thromboembolism.

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