

## Guideline for General and Gastroenterological Surgery in Patients Undergoing Antithrombotic Treatment: “Kokura Protocol 2019” with Appendix on Direct Oral Anticoagulants (DOACs)

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### ABSTRACT

In patients taking antithrombotic therapy (ATT), we have to manage two conflicting risks of bleeding and thromboembolism perioperatively. We have established our own perioperative antithrombotic management protocol for ATT-burdened patients (“Kokura Protocol”), and based on this protocol, the hospital guideline for gastroenterological and general surgery in patients receiving ATT was made and have been used. Thereafter, in consideration of newly launched anticoagulants called direct oral anticoagulants (DOACs), the guideline has been updated with appendix on DOACs. In this paper, our current updated guideline concerning perioperative ATT

management during GE and general surgery will be outlined.

**Key words:** Guideline; Gastroenterological surgery; Antithrombotic therapy; Antiplatelet therapy, Anticoagulation therapy

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### INTRODUCTION

In patients taking antithrombotic therapy (ATT), the risk of thromboembolism increases when ATT is discontinued during the perioperative period, although continuation of ATT can result in severe bleeding complications. We have to manage these two conflicting risks perioperatively. ATTs are classified into antiplatelet therapy (APT) and anticoagulation therapy (ACT); the latter consists of vitamin K antagonist (warfarin) and direct oral anticoagulants (DOACs, also known as non-vitamin K antagonist oral anticoagulants (NOACs)) (Table 1).

Our hospital is one of the most popular tertiary referral hospital in Japan regarding the treatment of severe atherosclerotic diseases, and there is a tendency for patients with atherosclerotic diseases to gather from a wide range of states. For this reason, we have to operate many cancer patients and emergency surgery cases who have concomitant high thromboembolic risks. There are also many inbound patients receiving ATT; surgery under ATT accounts for about 50% of all general and gastroenterological (GE) surgery in our department. Our hospital is, therefore, one of the leading high volume centers for such challenging surgical patient population in Japan.

We have established our own perioperative antithrombotic management protocol for ATT-burdened patients (“Kokura Protocol”) and have accumulated and assessed large numbers of ATT-received

**Table 1** Type of antithrombotic therapy (ATT) including antiplatelet therapy (APT) and anticoagulation therapy (ACT).

Types of ATT	Specific agents	Duration of action
APT		
Thienopyridine	clopidogrel (Plavix)	5-7 d <sup>1</sup>
	ticlopidine (Panardine)	
	prasugrel (Effient)	
	ticagrelor (Brilinta)	
Type 3 PDE inhibitor	cilostazol (Pretal)	2 d
Acetylsalicylic acid	aspirin (Bayaspirin, Bufferin)	7-10 d
	aspirin and clopidogrel (ConPlavin)	
	aspirin and lansoprazole (Takelda)	
Other NSAIDs	ibuprofen (Brufen, Advil)	Varies
	loxoprofen (Loxonin)	
	diclofenac (Voltaren), etc.	
Others	EPA (Epadel)	1-2 d
	dipyridamole (Persantine)	
	sarpogrelate (Anplag)	
	beraprost (Dorner)	
	limaprost (Prorenal)	
ACT		
Vitamin K antagonist	warfarin (Coumadin)	3-4 d
DOAC (NOAC)		
Direct thrombin inhibitor	dabigatran (Pradaxa)	1-2 d
Factor Xa inhibitor	rivaroxaban (Xarelto)	1-2 d
	apixaban (Eliquis)	
	edoxaban (Lixiana)	

<sup>1</sup> In ticlopidine, ticagrelor, and EPA, durations of action are 10-14 d, 3-5 d, and 7-10 d, respectively. Abbreviations: ATT: antithrombotic therapy; APT: antiplatelet therapy; ACT: anticoagulation therapy; PDE: phosphodiesterase; NSAID: non-steroidal anti-inflammatory drug; EPA: eicosapentaenoic acid; DOAC: direct oral anticoagulant; NOAC: non-vitamin K antagonist oral anticoagulant.

patients<sup>[1,2]</sup>. Based on this protocol, the hospital guideline for gastroenterological and general surgery in patients receiving ATT was established and have been used. Thereafter, in consideration of newly launched anticoagulants called DOACs, the guideline has been updated with appendix on DOACs. In this paper, our current updated guideline (“Kokura Protocol 2019”) concerning perioperative ATT management during GE and general surgery will be outlined.

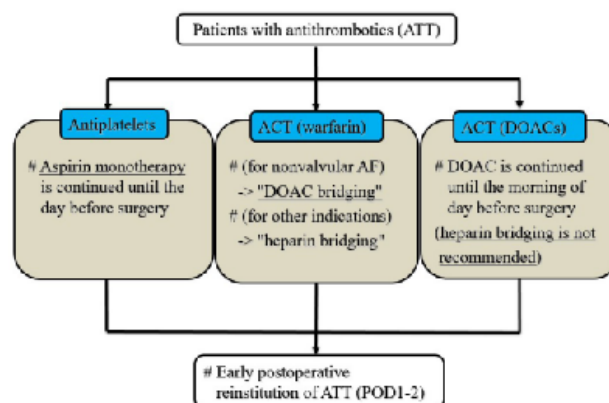
## STATEMENTS 1-8

### Statement 1

If patients receive ATT [APT and/or ACT (warfarin or DOACs)] (Table 1), and if they are managed by continuation or withdrawal of these drugs during GE surgery or general surgery, consultation with the prescribing physician or related department should be done in advance to determine the perioperative management of antithrombotics. Surgeons must explain the necessity and benefits of performing surgery, clarify the perioperative risks of bleeding and thromboembolic complications in case of taking antithrombotics, and obtain the patients’ clear consent before surgery.

### Statement 2

In case of taking antiplatelet drugs (Figure 1, the left part), aspirin monotherapy is continued until the day before surgery, stopped on the day of surgery, and resumed early after surgery (1-2 days after surgery). In patients taking multiple antiplatelet drugs, drugs other than aspirin are withdrawn and surgery under continued aspirin monotherapy is considered. If the risk of thromboembolism is high in patients taking drugs other than aspirin (e.g. thienopyridines including clopidogrel, prasugrel and



**Figure 1** Recommended perioperative management protocol for patients undergoing antithrombotic therapy in case of elective gastroenterological and general surgery (“Kokura Protocol 2019”). Abbreviations: ATT: antithrombotic therapy; ACT: anticoagulation therapy; AF: atrial fibrillation; DOAC: direct oral anticoagulant; POD: postoperative day.

ticlopidine), switch them to aspirin one week before surgery and continue aspirin monotherapy until the day before surgery (“aspirin bridging”), and resume the original drug early after surgery. If the risk of thromboembolism is low, withdrawal from a week before surgery may be considered depending on the situation, but it is desirable to continue with single aspirin therapy as much as possible.

### Further information for statement 2

Concerning the indication for APT, dealing with APT after coronary stent implantation has been a major problem. We have established the protocol of perioperative APT management including preoperative aspirin monotherapy continuation for high thromboembolic risk patients<sup>[1]</sup>, and continue to use this “Kokura Protocol” as the hospital guideline. Subsequently, the safety and feasibility of digestive laparoscopic surgery under the Kokura Protocol was shown using a large number of cases (over 1,000 cases)<sup>[1]</sup>, and the safety of open GE surgery under the protocol was also demonstrated by assessing more than 2,000 surgical patients<sup>[2]</sup>. In addition, by analyzing more than 3,000 accumulated cases of elective GE surgery during the past 14 years, preoperative discontinuation of APT was shown to be the most significant risk factor for postoperative thromboembolism, and preoperative aspirin continuation significantly reduced the occurrence of thromboembolism (paper in press).

In the clinical setting, however, some institutions may be instructed to replace heparin when it is judged by the cardiologists that the risk of thromboembolism is high in APT-received patients, probably because most surgeons and prescribed cardiologists do not recognize the option of continued aspirin monotherapy. Since heparin replacement is a strong risk factor for postoperative bleeding and should be avoided as much as possible, and because its mechanism of action is different from antiplatelet drugs, heparin replacement for antiplatelet drugs should not be used.

### Statement 3

For emergency surgery in patients taking antiplatelet drugs, surgery is performed without emergency reversal of antiplatelet action. Emergency reversal by platelet transfusion should be considered if refractory intraoperative bleeding is encountered, but if bleeding can be controlled, surgery should be performed without emergency reversal as much as possible to avoid increased risk of thromboembolism.

### Further information for statement 3

Although the number of emergency surgery for bleeding disorders has decreased with recent improvements in endoscopic hemostasis, emergency antagonism (reversal) is sometimes required for the treatment of intractable and troublesome bleeding events even though there is an increasing risk of thromboembolism. In this case, it is necessary to reverse the effect of antithrombotics according to the mechanism of each drugs. In case of

antiplatelet drug, platelet transfusion is performed.

On the other hand, in cases of emergency surgery other than surgery for intractable bleeding, the policy is not to perform emergency reversal except in situations where intraoperative bleeding cannot be controlled. Recent trends indicate that the emphasis should be placed on prevention of thromboembolism, especially in case of emergency surgery<sup>[3,4]</sup>. Even in APT-received patients, most emergency surgery can be managed by using appropriate energy devices to ensure hemostasis. However, in cases of multiple antiplatelet drugs and cases of warfarin with PT-INR overextension, it is necessary to manage with careful consideration of the bleeding risks.

#### Statement 4

For patients taking vitamin K antagonist [warfarin] (Figure 1, the middle part), it is recommended that surgery be performed under temporary pre-operative changes to DOAC (“DOAC bridging”) in case of non-valvular atrial fibrillation (AF). For other diseases such as valvular diseases and status after mechanical valve replacement or for patients with severe renal dysfunction, warfarin is stopped and heparin bridging is performed 3-5 days before surgery, and the drug is restarted early after surgery, and heparin bridging is finished after the PT-INR is within the therapeutic range. However, if there is a very high risk of thromboembolism such as a history of venous thrombosis (pulmonary embolism or deep vein thrombosis) or after valve replacement with a mechanical valve for valvular disease, heparin bridging under rigorous APTT monitoring from 7 days before surgery should be performed. If the risk of thromboembolism is low and the bleeding risk is considered to be high, it may be possible to consider the management of 3-5 day withdrawal without heparin bridging, but the operation should be performed with a thorough explanation of the risk of thromboembolism during the withdrawal of warfarin.

#### Further information for statement 4

So far, in patients taking warfarin, heparin replacement has been common in the perioperative period, but recent findings indicate that heparin replacement is an independent risk factor for the development of postoperative bleeding<sup>[2,5]</sup>. This suggests that heparin substitution should be avoided as much as possible.

Most importantly, a multicenter prospective cohort study was published in 2015, which showed the results of perioperative management of 1,884 warfarin-received patients for AF who underwent various treatments and operations (“BRIDGE study”)<sup>[5]</sup>. In this study, the frequency of postoperative complications was compared between the group with only warfarin withdrawal from 5 days before surgery and the group with heparin replacement. The results showed that although there was no difference in the occurrence of thromboembolism, there was a significant increase in postoperative bleeding events in the heparin replacement group. From this result, it was concluded that heparin replacement was not recommended in patients taking warfarin for AF. However, from our experience, it was quite questionable whether thromboembolism does not increase with only preoperative warfarin cessation or not. In fact, among 1,884 target cases in the BRIDGE study, most cases were minimally invasive procedures such as endoscopic procedures, and only 10 gastrointestinal surgeries were performed. Therefore, when performing highly invasive GE surgery, the results from the BRIDGE study should not be applied to the major GE surgery, and the rigorous management using heparin replacement, or alternatively using DOAC replacement, must be considered during cessation of warfarin.

A supplementary version of the guideline of ATT management for gastrointestinal endoscopy in 2017 added a description of DOACs, and it is preferable to use DOAC bridging during warfarin withdrawal in non-valvular AF cases<sup>[4]</sup>. DOACs are more effective and safer than warfarin, and we currently choose DOAC bridging as the first choice for perioperative management of warfarin patients. However, since the application of DOAC is limited to non-valvular AF, heparin replacement is planned in case of other indications (e.g. valvular AF, history of thromboembolism, or status after cardiac valve replacement) or in patients with severe renal disorders.

#### Statement 5

In the case of taking DOACs (Figure 1, the right part), DOACs are continued until the morning of the day before surgery and then stopped (for drugs administered twice a day, they are withdrawn from the evening of the day before surgery). After surgery, the drug is restarted early after surgery (1-2 days after surgery). Although heparin bridging is not necessary in general, it may be considered depending on the situation, such as when the risk of thromboembolism is very high. In patients with impaired renal function, the withdrawal period must be extended for each drug.

#### Further information for statement 5

The application of DOACs to non-valvular AF has been approved and is now available. There are currently 4 types of DOAC that can be used in the clinical setting. Only dabigatran is a direct thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors. They are “easy-to-use” drugs, with a wide range of safety. At present, a neutralizing agent can be used only for dabigatran. All four DOAC agents have strong evidence from large-scale randomized controlled trials, and the results of a meta-analysis of these four studies have been published in *Lancet*<sup>[6]</sup>. The efficacy of DOACs (inhibiting thromboembolism) is significantly higher than that of warfarin, and the safety of DOACs (inhibiting bleeding events) is similar to that of warfarin.

Concerning the perioperative management of DOAC-treated patients, heparin replacement is initially recommended in the guidelines for gastrointestinal endoscopy<sup>[7]</sup>, and it is also recommended to use heparin perioperatively during non-cardiac surgery in the 2013 guidelines for the management of AF<sup>[8]</sup>. However, DOACs have the potential advantages including rapid onset and offset of action<sup>[6,9]</sup>, and the need for perioperative heparin replacement remained questionable. Later, the major adverse effects of heparin replacement (increased postoperative bleeding) were recognized from the BRIDGE study or other studies<sup>[2,5]</sup>, and the guidelines were revised both in the United States and Europe; currently heparin replacement during perioperative DOAC withdrawal was not recommended<sup>[10,11]</sup>. Japanese guideline for gastrointestinal endoscopy was also updated in 2017, including an appendix on DOAC management, and it is described that heparin bridging during DOAC cessation is not recommended even in the setting of high bleeding risk procedures<sup>[4]</sup>.

#### Statement 6

During emergency surgery in patients taking anticoagulants, PT-INR is monitored for warfarin and emergency reversal is performed as necessary (administration of prothrombin complex concentrate (Kcentra), vitamin K2, or fresh frozen plasma). In case of DOAC, surgery can be performed without emergency reversal unless the bleeding tendency is clinically significant. However, if control of bleeding is difficult, surgery is performed after emergency reversal with fresh frozen plasma, or neutralization with idarucizumab (Prizbind) in the case of dabigatran.

#### Further information for statement 6

In patients receiving ACT, emergency antagonism (reversal) is also required in some situation such as the case of intraoperative intractable bleeding events. It is necessary to reverse the effect of anticoagulants according to the mechanism of each drug types. In case of warfarin, if PT-INR is excessively prolonged, the first choice is administration of prothrombin complex concentrate (Kcentra) plus vitamin K2. If Kcentra is not available, fresh frozen plasma is alternatively used. In case of DOACs, only a neutralizer against the effect of dabigatran is currently used (idarucizumab), and it can be applied only for the bleeding events during dabigatran treatment. At the moment, there is no neutralizer for Xa factor inhibitor and the reversal by fresh frozen plasma is considered.

Again, recent trends indicate that the emphasis should be placed on prevention of thromboembolism, especially in case of emergency surgery<sup>[4]</sup>. Even in ACT-received patients, most emergency surgery can be managed by using appropriate energy devices to ensure hemostasis. However, especially in cases of over-extension of PT-INR during warfarin treatment, it is necessary to manage with careful consideration of the bleeding risks and proper management with emergency reversal should be applied.

**Statement 7**

In surgery for patients taking antithrombotic drugs, indications for laparoscopic/thoracoscopic surgery should follow the institution's indication criteria, but are carefully applied with sufficient explanation to the patient, taking into account the risks of both bleeding and thrombotic complications.

**Further information for statement 7**

Many GE and general operations are currently performed laparoscopically. Several reports have shown advantages of laparoscopic digestive surgery, including early recovery of digestive function, reduction of body wall destruction, reduction of postoperative pain, less postoperative complications, and rapid return to daily life<sup>[12-16]</sup>. During laparoscopic surgery, minimizing surgical blood loss to maintain a dry operative field is exclusively important. Improvement of several techniques and new surgical devices such as ultrasonic coagulating shears or saline-linked soft-coagulation system led us to perform various types of advanced laparoscopic digestive operations including colorectal resection, esophagogastrectomy, and hepato-biliary-pancreas surgery. However, optimal management of patients receiving ATT during laparoscopic digestive surgery is still controversial.

One systematic review summarized results of various types of laparoscopic digestive surgery in patients receiving ATT<sup>[17]</sup>, showing that the risk of hemorrhagic or thromboembolic complications during or after these procedures in patients with continued APT or heparin bridging was not significantly higher than in patients with no ATT or interrupted APT. The retrospective cohort study using a large number of cases (more than 1,000 cases) for various types of laparoscopic surgery demonstrated that there was no significant difference in postoperative bleeding events between who continued APT and other patients<sup>[18]</sup>. Fujikawa *et al.* conducted a retrospective cohort study using liver resection cases (including laparoscopic and open surgery)<sup>[19]</sup>. The authors found that neither intraoperative nor postoperative bleeding complications increased in the case of laparoscopic liver resection, even with aspirin monotherapy for APT and/or heparin bridging for ACT. In two studies of laparoscopic colorectal cancer resection, the effect of APT on bleeding complications was assessed, and the authors found that APT continuation did not significantly affect bleeding complications<sup>[20,21]</sup>. Although the assessment of various types of laparoscopic surgery is still ongoing, laparoscopic surgery in patients receiving ATT can be safely performed.

**Statement 8**

Postoperatively, it is confirmed that there are no signs of bleeding, and resumes early after the operation (1-2 days after the operation). In the case of taking two or more antithrombotics, early reinstatement is performed in stages while confirming the presence or absence of postoperative bleeding.

**Further information for statement 8**

Continuing single aspirin therapy through the perioperative period is not associated with a higher risk of serious bleeding complications<sup>[22]</sup>. On the other hand, the use of multiple APT or combination of APT and ACT in surgical patients is more complicated. In a metaanalysis of large studies in medical patients, dual APT with aspirin and clopidogrel therapy was associated with an increased risk of significant bleeding (odds ratio = 1.8)<sup>[23]</sup>. Therefore, in case of taking multiple antithrombotics, early reinstatement should be performed, not once in all but in stages, while confirming the absence of bleeding events.

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