

## **The study on the Safety and Feasibility of Gastroenterological Surgery in Patients Undergoing Antithrombotic Therapy: Study Protocol for a Multicenter Prospective Cohort Analysis (The GSATT Study)**

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### **ABSTRACT**

**BACKGROUND:** Although there are several large-scale single center cohort studies concerning gastroenterological (GE) surgery in patients receiving antithrombotic therapy (ATT), no clear evidence or guidelines based on multicenter prospective studies have not yet been established. The main purpose of this multicenter prospective cohort

study is to assess the safety and feasibility of GE surgery in ATT-received patients during the perioperative period.

**METHODS/DESIGN:** This is a multicenter, prospective cohort study conducted in Japan. Patients receiving antithrombotic therapy {antiplatelet therapy and/or anticoagulation therapy [warfarin or direct oral anticoagulants (DOACs)]}, as well as undergoing elective GE surgery (including open surgery, laparoscopic surgery, and robot-assisted surgery) are included in the current study; those undergoing emergency GE surgery are excluded. The primary endpoints include intraoperative factors including surgical blood loss, postoperative hemorrhagic complications, and thromboembolic complications; secondary endpoints include other postoperative complications, presence of re-operation, and the length of postoperative stay.

**DISCUSSION:** The present study can contribute to the determination of the safety and feasibility of elective GE surgery to ATT-received patients and is thought to establish optimal perioperative antithrombotic management for such challenging patient population.

**Key words:** Study protocol; Multicenter prospective cohort study; Gastroenterological surgery; Antithrombotic therapy; GSATT study

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### **BACKGROUND**

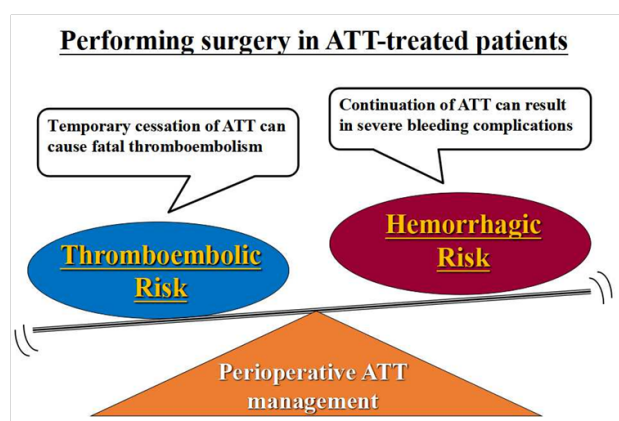
In recent years, with the arrival of an aging society, surgical cases with heart disease and cerebrovascular disease have become more common, and most of them are undergoing antithrombotic therapy (ATT; antiplatelet therapy and/or anticoagulation therapy) to prevent secondary thromboembolism. When performing surgical procedures

on patients receiving ATT, the continuation of ATT can result in severe bleeding complications during the perioperative period; temporary cessation of ATT can cause fatal thromboembolism<sup>1,2)</sup> (Figure 1). Therefore, it is important to set up optimal antithrombotic management to prevent both complications. Especially in gastroenterological (GE) surgery, there are many elderly patients who have concurrent atherosclerotic diseases, requiring resection of GE malignancy or surgery for inflammatory diseases. For this reason, GE surgery in ATT-treated patients is considered to be high risk for both bleeding and thromboembolism.

To date, there is detailed guidance regarding gastrointestinal endoscopic procedures in patients receiving ATT<sup>3-5)</sup>. On the other hand, although there are several large-scale single center cohort studies concerning GE surgery in ATT-treated patients<sup>6,7)</sup>, no clear evidence or guidelines based on multicenter prospective studies have not yet been established. The main purpose of this multicenter prospective cohort study is to assess the safety and feasibility of GE surgery in ATT-received patients during the perioperative period.

## METHODS/DESIGN

The present study is a multicenter prospective cohort study. The participants are recruited from University of Occupational and Environmental Health, Fukuoka University and Kokura



**Figure 1** The antithrombotic management of ATT-treated patients. In ATT-received patients, perioperative continuation of ATT can result in severe bleeding complications; temporary cessation of ATT can cause fatal thromboembolism. A balance between reducing the risks of both thromboembolism and bleeding must be reached for each patient. Abbreviations: ATT; antithrombotic therapy.

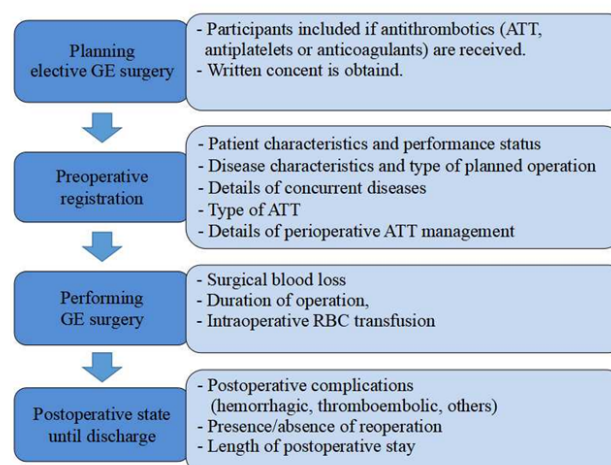
Memorial Hospital in Japan. We obtain written informed consent by investigators from all study patients prior to any screening or inclusion procedures. The trial is organized by the Department of Surgery, Kokura Memorial Hospital, Fukuoka, Japan (Figure 2).

### Study schedule

The present study was registered as UMIN000038280 on October 12, 2019. Registration started on October 2019. Since this study does not constitute a study aimed at verifying hypotheses, we will not design the number of cases based on statistical considerations. In this study, the evaluation items are summarized in an exploratory manner. A total of 1,000 cases will be enrolled during the study enrollment period. It is anticipated that registration will be completed in two years from the preliminary survey. The estimated study completion date is 2021 (final data collection, date for primary outcome measurement). Outcome results will be collected for 90 days after registration.

### Inclusion criteria (Table 1)

Participants are included if all following criteria are met: (1) Patients receiving antithrombotic therapy (antiplatelet therapy and/or anticoagulation therapy), (2) Those undergoing elective GE surgery (including open surgery, laparoscopic surgery, and robot-assisted surgery), and (3) Those being able to submit written consent before the study.



**Figure 2** The summary of patient enrollment and data collection in the current GSATT study. Abbreviations: GE; gastroenterological, ATT; antithrombotic therapy, RBC; red blood cell.

**Table 1** Patient selection criteria and objectives in the current GSATT study.

Patient selection criteria	
Inclusion criteria: (1) and (2) and (3)	Exclusion criteria: (1) or (2) or (3)
(1) Patients receiving antithrombotic therapy: - antiplatelet therapy; - anticoagulation therapy (warfarin, DOACs)	(1) Urgent surgery
(2) Those undergoing elective GE surgery: - open surgery; - laparoscopic surgery; - robot-assisted surgery	(2) Being difficult to obtain consent for explanations (e.g. consciousness levels and examples of cognitive decline)
(3) Written consent being obtained before the study	(3) Written consent being not obtained
Objectives	
Primary endpoints	Secondary endpoints
(1) Intraoperative factors including surgical blood loss, duration of operation, intraoperative RBC transfusion	(1) The presence or absence of other postoperative complications
(2) postoperative hemorrhagic complications including luminal (e.g. GI) bleeding, abdominal bleeding, abdominal wall hematoma	(2) The presence of postoperative re-operation
(3) postoperative thromboembolic complications including cerebral infarction, myocardial infarction, pulmonary embolism, etc.	(3) The length of postoperative stay

Abbreviations: DOAC; direct oral anticoagulant, GE; gastroenterological, GI; gastrointestinal.

**Table 2** Details of GE surgery type and antithrombotics included in the GSATT study.

Type of GE surgery included	
(1) GE surgery for malignant tumor	(a) GI tract surgery: esophageal resection, gastric resection, colorectal resection, etc.
	(b) HBP surgery: liver resection, biliary tract resection, pancreatic resection.
	(c) Other GE surgery
(2) GE surgery for benign diseases	(a) Biliary diseases: cholecystectomy, choledocolithotomy, choledochojunostomy, etc.
	(b) GI diseases: appendectomy, resection of of small intestine, gastrojejunostomy, etc.
	(c) Other GE surgery
Type of antithrombotics included	
(1) Antiplatelet agents	(a) Acetylsalicylic acid (aspirin)
	(b) Thienopyridines (clopidogrel, ticlopidine, prasugrel, ticagrelor)
	(c) Type III PDE (cilostazol)
	(d) Others (EPA, dipyridamole, sarpogregrate, beraprost, limaprost, etc)
(2) Anticoagulant agents	(a) Vitamin K antagonist (warfarin)
	(b) Direct oral anticoagulants (DOACs): - Direct thrombin inhibitor (dabigatran); - Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

**Exclusion criteria (Table 1)**

Exclusion criteria were as follows: (1) urgent surgery, (2) being difficult to obtain consent for explanations, such as consciousness levels and examples of cognitive decline, and (3) written consent being not obtained. The number of such patients is reported separately.

**The type of GE surgery included (Table 2)**

The type of surgery included in the current study is as follows: (1) GE surgery for malignant tumor (e.g. resection of esophageal cancer, gastric cancer, colorectal cancer, liver cancer, biliary tract cancer, pancreatic cancer), and (2) GE surgery for benign diseases, including cholecystectomy, choledocholithotomy, appendectomy, and resection of small intestine.

**Treatment**

The treatment policy (selection of surgical procedure, necessity of conversion in the case of laparoscopic and robotic surgery, postoperative treatment policy, etc.) is conducted in the same fashion as the daily surgical treatment.

**Objectives**

The Primary endpoint is as follows: (1) intraoperative factors including surgical blood loss, duration of operation and intraoperative red blood cell (RBC) transfusion, (2) postoperative hemorrhagic complications including luminal (e.g. gastrointestinal) bleeding, abdominal bleeding, and abdominal wall hematoma, and (3) postoperative thromboembolic complications (e.g. cerebral infarction, myocardial infarction, mesenteric infarction, pulmonary embolism).

The secondary endpoint is as follows: (1) The presence or absence of other postoperative complications, (2) The presence of postoperative re-operation, and (3) The length of postoperative stay. The definition and classification Postoperative complications are defined and classified by the JCOG postoperative complication criteria (Clavien-Dindo classification)<sup>[8]</sup>.

**Observation and examination contents**

**Before surgery:** (1) Patient characteristics: gender, age at surgery, height, weight. (2) Disease characteristics: malignant diseases (esophageal cancer, stomach cancer, colon cancer, liver cancer, biliary tract cancer, pancreatic cancer, etc.) or benign diseases (cholelithiasis, gallbladder polyps, appendicitis, small intestinal tumors, etc.). (3) The type and mode of surgical procedures planned (Table 2): the type

includes elective GE surgery for both malignant and benign diseases, and the mode includes laparoscopic, robot-assisted or open-fashioned surgery. (4) Physical findings: ECOG scale of performance status (PS)<sup>[9]</sup>. (5) Details of concurrent diseases: history of congestive heart failure and left ventricular dysfunction, history of coronary artery disease (percutaneous coronary intervention and coronary artery bypass graft surgery), history of stroke and transient ischemic attack, hypertension, diabetes, maintenance dialysis, or other pre-existing conditions. (6) Details of antithrombotic drugs (Table 2): antiplatelet drugs (aspirin, clopidogrel, ticlopidine, prasugrel, cilostazol, etc.) and/or anticoagulant agents [warfarin, direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban)]. (7) Perioperative antithrombotic therapy management: (a) antiplatelet drugs; preoperative discontinuation, preoperative aspirin continuation, heparin replacement, etc, (b) warfarin; preoperative discontinuation, heparin replacement, DOAC replacement, etc, (c) DOAC; preoperative discontinuation, heparin replacement, etc.

**After surgery:** (1) Date of operation. (2) Surgical procedures performed: laparoscopic, robot-assisted, or open-fashioned. (3) Presence/absence of conversion to open surgery in case of laparoscopic or robotic surgery. (4) Reason for conversion to open surgery in the case of laparoscopic or robotic surgery. (5) Operative time. (6) Presence/absence of drain. (7) Amount of surgical blood loss. (8) Intraoperative RBC transfusion. (9) Presence of intraoperative accidents.

**At discharge:** (1) Antithrombotic drug resumption time: antiplatelet agents, warfarin, DOACs. (2) Postoperative complications. (3) Existence of re-operation. (4) Content of complications: date of onset, type, grade, outcome. (5) Length of postoperative stay. (6) Presence/absence of death: cause.

**Data collection**

The researchers at each hospital conduct investigations using case report forms (CRF) and registration forms. The registration slip will be forwarded to the data center at Kokura Memorial Hospital by fax or email before the surgery begins. The CRF will be completed within two weeks after discharge of the registered patient and sent to the data center. Alternatively, it will be collected at a meeting (scheduled to be held every six months) where relevant facilities participating in this study participate. All data are collected by Kokura Memorial Hospital. The data sharing process within the study is supervised

by the data center. Clinical data entry, central monitoring, and data management is also performed.

### Statistical analysis

All patients enrolled in the present study are subject to the analysis. After enrollment, ineligible patients are excluded from the present study. Risk factors of excessive intraoperative blood loss, postoperative hemorrhagic complication, and thromboembolic complication are evaluated by both univariate or multivariate analyses. For univariate comparisons, Fisher's exact probability test is used to evaluate categorical variables; alternatively, continuous variables are analyzed by 1-way ANOVA and Kruskal-Wallis tests for normally and nonnormally distributed data, respectively. For multivariate analysis, logistic regression analysis is conducted to determine the independent risk factors. All P-values are two sided and P-values less than 0.05 are considered statistically significant.

## DISCUSSION

ATT includes two types of medications, classified as antiplatelets and anticoagulants. Antiplatelets decrease aggregation of platelets and prevent thrombus formation, and are commonly used for primary and secondary prevention of cardiovascular and cerebrovascular diseases. Antiplatelets include aspirin, thienopyridines, type III phosphodiesterase inhibitor, and other antiplatelet agents<sup>[6,10,11]</sup>. On the other hand, anticoagulants interfere with the native clotting cascade and prevent the blood clotting, and are generally used for atrial fibrillation, deep vein thrombosis, cardiac endoprostheses<sup>[3,4,11]</sup>, and acute coronary syndrome. These include vitamin K antagonists and DOACs (direct thrombin inhibitor and factor Xa inhibitors)<sup>[3,4]</sup>.

Recently updated guidelines concerning antithrombotic management during non-cardiac surgery showed that the prevention of thromboembolic events is more important than bleeding complications, as it might cause death or severe sequelae<sup>[3-5,12,13]</sup>. Concerning antiplatelet therapy after implantation of coronary stent, recent AHCC/AHA and ESC guideline said that we should continue antiplatelet medications, at least aspirin monotherapy, in the perioperative period for patients with high risk of thromboembolism<sup>[14]</sup>, but most institutions practically choose to discontinue antiplatelets in case of major digestive surgery with bleeding risks. Although some studies such as POISE-2 study have reported that a modest increase in bleeding risk was observed in single antiplatelet-continued patients during non-cardiac surgery<sup>[15,16]</sup>, most of other studies showed that there was no increase in the significant bleeding events<sup>[17,18]</sup>.

Concerning patients receiving anticoagulation therapy, DOACs are increasingly prescribed for the purpose of preventing arterial or venous thromboembolism. In large clinical trials, DOACs have been demonstrated to have lower rates of intracranial hemorrhage compared to warfarin<sup>[19-22]</sup>. This difference is primarily due to the difference in mechanism of action in the blood clotting cascade. Recently published review article and ongoing prospective study suggests safety and feasibility of perioperative management of DOACs during noncardiac surgery, which is rather simple and requires no heparin bridging in general<sup>[23,24]</sup>. Still, there is so far scarce evidence concerning the safety of DOAC-treated patients during the more specific types of surgery such as GE surgery.

Concerning warfarin therapy, heparin bridging is the common management for warfarin<sup>[25]</sup>. Recently, large-scale randomized controlled trial (BRIDGE study) showed that heparin bridging was not recommended in the case of low bleeding risk surgery due to increased bleeding risks<sup>[26]</sup>. However, this study included relatively

small numbers of GE surgery, and it is not concluded that heparin bridging is unnecessary in major GE surgery. Especially in case of high thromboembolic risks, rigorous perioperative antithrombotic management including heparin bridging, or alternatively DOAC bridging, should be considered to avoid critical thromboembolic complications.

The recently-published review article summarized the outcomes of various types of laparoscopic GE surgery in patients receiving ATT for prevention of thromboembolism<sup>[11]</sup>. The risk of hemorrhagic or thromboembolic complications during or after these procedures in patients with continued antiplatelets or heparin bridging was not significantly higher than in patients with no ATT or interrupted antiplatelets. The review concluded that there are some promising results for both basic and laparoscopic surgery, although there is scarce evidence concerning the safety of advanced laparoscopic surgery such as colorectal resection or liver resection.

Although there are several large-scale single center cohort studies concerning GE surgery in ATT-treated patients<sup>[6,7]</sup>, no clear evidence or guidelines based on multicenter prospective studies have not yet been established. In this meaning, the current study may contribute to investigate the safety and feasibility of GE surgery in ATT-treated patients using the large-scale real world data. The definite protocol or guidelines will be established using the reliable studies with good design like the current study.

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