

Original Article

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Is breast cancer surgery safely performed in patients receiving antithrombotic therapy?

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Abstract

Aim: The aim of the study was to assess the safety of surgery for breast cancer in patients with antithrombotic therapy (ATT), including antiplatelet therapy (APT) and anticoagulation therapy (ACT) for thromboembolic risks.

Methods: One hundred ninety-three consecutive patients receiving breast surgery for breast cancer at our institution between 2010 and 2015 were retrospectively reviewed. Among them, ATT was regularly used in 50 patients (25.9%). Our perioperative management included maintenance of preoperative aspirin monotherapy for APT and bridging heparin for ACT in patients at high thromboembolic risks and early postoperative reinstatement in all ATT cases. The outcome variables of patients with ATT (ATT group) were compared to those of patients without ATT (non-ATT group), and the significant risk factors for postoperative complications were determined by multivariate analysis.

Results: This series included 127 mastectomy and 66 breast-conserving surgery. ATT group showed significantly high frequency of history of cerebral infarction and percutaneous coronary intervention (PCI). In the ATT group, 32 patients (16.6%) were categorized as high risk for thromboembolism, but there was neither thromboembolic event nor perioperative death in the whole cohort. Surgical blood loss and rates of intraoperative transfusion were identical between the groups. Whereas overall postoperative bleeding complication was more frequently observed in the ATT group compared to the non-ATT group (12.0% vs. 3.5%, $p=0.360$) in univariate analyses, multivariate analysis showed that neither ATT

nor preoperative aspirin continuation affected postoperative bleeding complications.

Conclusion: Even in patients undergoing ATT, surgery for breast cancer is safely performed without any increase in blood loss or postoperative bleeding, and no thromboembolism was experienced in the series. Our perioperative management of ATT patients is valid during breast surgery, although this patient population is still challenging and should be rigorously managed.

Keywords: anticoagulation; antiplatelet therapy; antithrombotic therapy; breast cancer surgery; breast-conserving surgery; mastectomy; perioperative antithrombotic management.

Abbreviations

ACT, anticoagulation therapy; APT, antiplatelet therapy; ASA, American Society of Anesthesiologists; ATT, antithrombotic therapy; CABG, coronary artery bypass graft; CDC, Clavien-Dindo classification; CHF, congestive heart failure; DES, drug-eluting coronary stent; DM, diabetes mellitus; PCI, percutaneous coronary intervention.

Introduction

More and more patients who receive [antithrombotic therapy (ATT); antiplatelet therapy (APT) and/or anticoagulation therapy (ACT)] for cardiovascular and/or cerebrovascular complications undergo many kinds of surgery, including breast surgery. In most institutions, how to manage perioperative ATT was largely determined by the individual surgeons, and there is so far no definite protocol or guideline concerning perioperative antithrombotic management. The risk of thromboembolic complications may increase when ATT is stopped; the risk of bleeding complications may increase when ATT is continued. We have conducted our perioperative antithrombotic management protocol including preoperative aspirin continuation for high thromboembolic risk patients (“Kokura Protocol”) and have shown that abdominal surgery under the Kokura Protocol could be safe and feasible [1–3]. The

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objective of this study is to compare bleeding complications after breast surgery in patients receiving ATT and patients not taking antithrombotics to assess the safety of breast surgery under the Kokura Protocol.

Materials and methods

Between January 2010 and December 2015, a total of 193 female underwent breast surgery in our institution. One hundred twenty-seven patients underwent modified radical mastectomy and 66 patients underwent breast-conserving surgery. Of those, 56 patients (29.0%) underwent axillary lymph node dissection. Patients' background and perioperative characteristics and the postoperative outcomes were collected through a standardized review of the electronic surgery database as well as hospital and clinical charts. The condition of patients' functions and symptoms with reference to need for care and ambulatory status was described according to the European Cooperative Oncology Group Scale of Performance Status (PS) [4].

The categorization of postoperative complications was achieved using the Clavien-Dindo classification (CDC) [5]. Postoperative bleeding complications included bloody drainage, formation of hematoma, and subcutaneous hemorrhage. Bleeding complications with CDC class 1 or more were defined overall bleeding complications; those with CDC class 2 or more were defined major complications. Both bleeding complications were regarded as primary outcomes. Background characteristics, perioperative conditions, and outcome variables were compared between patients with ATT (ATT group) and those without ATT (non-ATT group).

Perioperative antithrombotic management

After discussing with cardiologists, cerebrovascular surgeons, and anesthesiologists, we have established our perioperative antithrombotic management protocol (Kokura Protocol [1]; Figure 1). High thromboembolic risk patients were defined as follows: (1) patients undergoing drug-eluting coronary stent (DES) implantation, (2) patients undergoing bare metal coronary stent implantation within 2 months, (3) patients undergoing cerebrovascular reconstruction within 3 months, (4) patients having recent-onset cerebral stroke or transient ischemic attack, (5) patients with regular oral anticoagulation for chronic atrial fibrillation or those with previous thrombosis, and (6) patients having cardiovascular or cerebrovascular diseases who were recognized as high risk by cardiac/cerebral specialists. The flowchart generally consists of interrupting ATT 5–7 days before surgery and postoperative early reinstatement in low thromboembolic risk patients. In contrast, preoperative aspirin monotherapy is continued for APT patients and ACT was substituted by bridging heparin in high thromboembolic risk patients.

Statistical analysis

The categorized data was compared by χ^2 or Fisher's exact probability test. Continuous variables in the characteristics were expressed as a median with range and compared by one-way analysis of variance

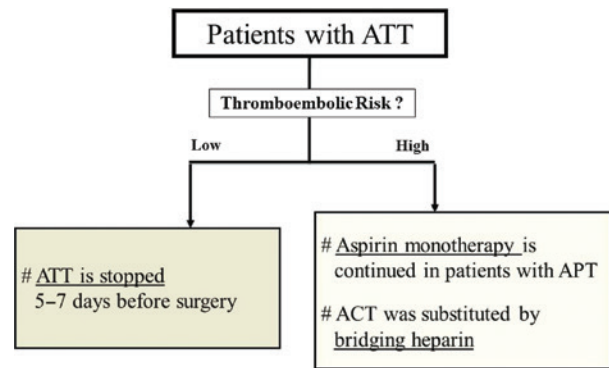


Figure 1: Perioperative management protocol (Kokura Protocol) for patients undergoing ATT in case of elective surgery [1–3].

The management generally consists of interrupting ATT 5–7 days before surgery in low thromboembolic risk patients. In patients with high thromboembolic risk, aspirin monotherapy is continued in patients with APT, and/or ACT was substituted by bridging heparin, and both were reinstated postoperatively as soon as possible.

(ANOVA) or Kruskal-Wallis test. Nonparametric variables were also compared using Kruskal-Wallis test with Scheffe's F-test. Multivariate logistic regression analyses were performed to determine risk factors that affect postoperative bleeding complications. Statistical significance was set at $p < 0.20$. Data were analyzed using the SPSS package software.

This study was approved by our institutional review board.

Results

In this cohort, ATT was regularly used in 50 patients (25.9%). The patients in the study were all Asians. APT was used in 35 patients and ACT was used in 21 patients. Both APT and ACT were used in 6 patients. In total, 32 patients (16.5%) were regarded as high risk for thromboembolism. Table 1 shows the background characteristics of patients in each group. Age above 75 years, diabetes mellitus (DM), American Society of Anesthesiologists (ASA) scores 3–4, history of congestive heart failure (CHF), history of coronary artery bypass graft (CABG), history of percutaneous coronary intervention (PCI), and history of cerebral infarction were more common in the ATT group. There was no difference between the groups in the rates of hemodialysis or morbid obesity [body mass index (BMI) ≥ 30 kg/m²].

The perioperative characteristics and postoperative morbidity in each group are shown in Table 2. Concerning the type of surgery, there were no differences in the rates of modified radical mastectomy, axillary dissection, neoadjuvant chemotherapy, or bilateral breast surgery between the groups. One patient in the ATT group needed intraoperative transfusion because of preexisting anemia.

Table 1: Background characteristics of patients in the cohort.

Variables	Total (n=193)	ATT (n=50)	Non-ATT (n=143)	p-Value
Age (years), median (range)	65 (35–89)	60 (35–89)	74 (37–89)	<0.001
ASA class, n (%)				
3–4	27 (14.0)	21 (42.0)	6 (4.2)	<0.001
0–2	166 (86.0)	29 (58.0)	137 (95.8)	
CHF, n (%)				
Yes	19 (9.8)	17 (34.0)	2 (1.4)	<0.001
No	174 (90.2)	33 (66.0)	141 (98.6)	
CABG, n (%)				
3–4	5 (2.6)	5 (10.0)	0 (0)	<0.001
0–2	188 (97.4)	45 (90.0)	143 (100)	
PCI, n (%)				
Yes	13 (6.7)	13 (26.0)	0 (0)	<0.001
No	180 (93.3)	37 (74.0)	143 (100)	
CI, n (%)				
Yes	8 (4.1)	7 (14.0)	1 (0.7)	<0.001
No	185 (95.9)	43 (84.0)	142 (99.3)	
DM, n (%)				
Yes	24 (12.4)	15 (30.0)	9 (6.3)	<0.001
No	169 (87.6)	35 (70.0)	134 (93.7)	
HD, n (%)				
Yes	2 (1.0)	1 (2.0)	1 (0.7)	0.452
No	191 (99.0)	49 (98.0)	49 (98.0)	
BMI, n (%)				
≥ 30	21 (10.9)	4 (8.0)	17 (11.9)	0.600
< 30	172 (89.1)	46 (92.0)	126 (88.1)	
WF, n (%)				
Yes	21 (10.9)	21 (42.0)	0 (0)	<0.001
No	172 (89.1)	29 (58.0)	143 (100)	
Continuation of APT, n (%)				
Yes	14 (7.3)	14 (28.0)	0 (0)	<0.001
No	179 (92.7)	36 (72.0)	143 (100)	
APT, n (%)				
Yes	35 (18.1)	35 (70.0)	0 (0)	<0.001
No	158 (81.9)	15 (30.0)	143 (100)	

CI, cerebral infarction; HD, hemodialysis; WF, warfarin.

No intraoperative massive blood loss (≥ 500 mL) was experienced in this study.

There was no thromboembolic complication in the whole cohort. Overall and major postoperative bleeding complications occurred in 11 (5.7%) and 5 (2.6%) patients, respectively. The ATT group included more patients with both overall and major postoperative bleeding.

Univariable and multivariable analyses for overall and major bleeding complications in this study were performed and are shown in Tables 3 and 4, respectively. DM, ASA scores 3–4, history of CHF, history of CABG, and ATT use were associated with overall bleeding complications on the univariable analyses. Using multivariable analyses, however, no factor turned out to be significant for overall bleeding complications. Concerning major bleeding complications, DM, ASA scores 3–4, history of CHF, and

history of PCI were associated in the univariable analyses, although there were also no associated risk factors detected by multivariable analyses. Either ATT use or preoperative aspirin continuation was not associated with overall/major bleeding complications.

Discussion

Some reports showed that APT might increase perioperative complications in several procedures (neurosurgical procedures, hip arthroplasty, transurethral prostatectomy, tonsillectomy, endoscopic large polyp resection, and transbronchial biopsy) [6–9]. Chetlen et al. showed that no clinically significant hematomas or bleeding

Table 2: Factors concerning operative procedures and postoperative morbidity.

Variables	Total (n=193)	ATT (n=50)	Non-ATT (n=143)	p-Value
Surgery type, n (%)				
Mastectomy	127 (65.8)	33 (66.0)	94 (65.7)	1.000
Breast-conserving	66 (34.2)	17 (34.0)	49 (34.3)	
Ax, n (%)				
Yes	56 (29.0)	16 (32.0)	40 (28.0)	0.591
No	137 (71.0)	34 (68.0)	103 (72.0)	
NAC, n (%)				
Yes	11 (6.0)	3 (6.0)	8 (5.6)	1.000
No	182 (94.0)	47 (94.0)	135 (94.4)	
Bilateral, n (%)				
Yes	5 (2.6)	0 (0)	5 (3.5)	0.330
No	188 (97.4)	50 (100)	138 (96.5)	
Surgical blood loss (mL), median (range)	30 (0–350)	35 (0–350)	20 (1–175)	1.000
Intra-RBC Transf, n (%)				
Yes	1 (0.5)	1 (2.0)	0 (0.0)	0.259
No	192 (99.5)	49 (98.0)	143 (100)	
TC, n (%)				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	–
No	193 (100.0)	50 (100.0)	143 (100.0)	
Overall BC, n (%)				
Yes	11 (5.7)	6 (12.0)	5 (3.5)	0.360
No	182 (94.3)	44 (88.0)	138 (96.5)	
Major BC, n (%)				
Yes	5 (2.6)	3 (6.0)	2 (1.4)	0.111
No	188 (97.4)	47 (94.0)	141 (98.6)	

Ax, axillary dissection; BC, bleeding complication; Intra-RBC Transf, intraoperative red blood cell transfusion; NAC, neoadjuvant chemotherapy; TC, thromboembolic complication.

complications after the breast core needle biopsy were found on patients undergoing ATT [10]. However, there are no detailed reports about bleeding complications after breast surgery in patients undergoing ATT. Our study demonstrated that 25.9% of the patients undergoing breast surgery were receiving ATT, but no patients suffered from thromboembolic complications. The rates of overall and major postoperative bleeding complications on the ATT group were 12.0% and 6.0%, respectively. Multivariable analyses showed that either ATT use or preoperative continuation of aspirin did not increase the risk of bleeding complications.

ACT and APT for secondary prevention of cardiovascular or cerebrovascular diseases are widespread and are increasing as the elderly ages [11–15]. More and more patients with ATT receive major noncardiac surgery [16, 17]. In patients with ATT, we are worried about perioperative bleeding and thromboembolic complications. The discontinuation of ATT may cause thromboembolic complications, whereas the continuation of APT or bridging heparin may increase the risk of bleeding complications [18]. The Kokura Protocol, which classifies patients according to the risk of thromboembolic complications and chooses perioperative management of ATT, should be

adequate to minimize the risk of both bleeding and thromboembolism [1–3].

We have to balance bleeding risks against thromboembolic risks in patients receiving ATT, but several updated guidelines [19–24] clearly show that the prevention of thromboembolism is more important, as it might cause severe sequela and death. In case of coronary stent implantation, especially in patients with DES implantation, the discontinuation of antiplatelet medications significantly increases the risk of coronary stent thrombosis, which may cause acute myocardial infarction and death [25]. For that reason, some guidelines said that we should continue antiplatelet medications in the perioperative period for high thromboembolic risk patients [14, 26–28], but in practice, most institutions choose to stop APT in case of major noncardiac surgery with bleeding risks. Our study demonstrated that not only open or laparoscopic abdominal surgery but also breast surgery, either mastectomy or breast conserving surgery, can be safely performed under the continuation of aspirin monotherapy or heparin bridging.

Concerning patients with ACT, heparin bridging is the common management for ACT [29]. Recently, the BRIDGE study recommended to stop warfarin therapy 5 days before an elective operative procedure and to resume

Table 3: Univariate analysis of overall and major postoperative bleeding complications in the cohort (n=193).

Variable	No	Major bleeding complication		Overall bleeding complication	
		Present (%)	Univariate p	Present (%)	Univariate p
Age, n (%)					
≥ 75	44	1 (2.3)	1.000	1 (2.3)	0.461
< 75	149	4 (2.7)		10 (6.7)	
ASA, n (%)					
3–4	27	2 (7.4)	0.144	3 (11.1)	0.186
0–2	166	3 (1.8)		8 (4.8)	
CHF, n (%)					
Yes	19	3 (15.8)	0.007	3 (15.8)	0.081
No	174	2 (1.1)		8 (4.6)	
CABG, n (%)					
3–4	5	1 (20.0)	0.124	1 (20.0)	0.257
0–2	188	4 (2.1)		10 (5.3)	
PCI, n (%)					
Yes	13	1 (7.7)	0.297	3 (23.1)	0.029
No	180	4 (2.2)		8 (4.4)	
CI, n (%)					
Yes	8	0 (0)	1.000	0 (0)	1.000
No	185	5 (2.7)		11 (5.9)	
DM, n (%)					
Yes	24	2 (8.3)	0.177	4 (16.7)	0.034
No	169	3 (1.8)		7 (4.1)	
WF, n (%)					
Yes	21	1 (4.8)	0.441	3 (15.8)	1.000
No	172	4 (2.3)		8 (4.6)	
Continued APT, n (%)					
Yes	14	1 (7.1)	0.317	4 (28.6)	0.004
No	179	4 (2.2)		7 (3.9)	
APT, n (%)					
Yes	35	3 (8.6)	0.042	3 (23.1)	0.006
No	158	2 (1.3)		8 (4.4)	
ATT, n (%)					
Yes	50	3 (6.0)	0.111	6 (12.0)	0.036
No	143	2 (1.4)		5 (3.5)	

CI, cerebral infarction; WF, warfarin.

Table 4: Multivariate logistic regression analysis for major and overall bleeding complications after breast surgery (n=193).

Variable	Major bleeding complication		Overall bleeding complication	
	Multivariate p	Odds ratio (95% confidence interval)	Multivariate p	Odds ratio (95% confidence interval)
ASA 3 or 4	0.725	1.637 (0.105–25.388)	0.999	1.001 (0.1756–5.692)
CHF	0.55	16.903 (0.936–305.245)	0.532	1.876 (0.261–13.465)
CABG	0.968	0.934 (0.032–27.401)	–	–
PCI	–	–	0.993	0.989 (0.101–9.643)
DM	0.864	1.274 (0.079–20.544)	0.481	1.873 (0.326–10.752)
ATT	0.728	0.566 (0.023–14.045)	0.936	1.088 (0.142–8.341)
Continued APT	0.794	1.59 (0.049–51.822)	0.137	6.264 (0.558–70.374)

therapy 12–24 h after low bleeding risk surgery; heparin bridging was not recommended due to increased bleeding risks [30]. However, this study included few numbers of major noncardiac surgery, so we could not conclude

that heparin bridging is not necessary in major general or abdominal surgery. The current study suggested that, even in patients with heparin bridging, breast surgery is safe and feasible without any increase of bleeding events.

This study has some limitations. This is a retrospective review from a single institution, which weakens the impact of the conclusion. A follow-up study and a multi-institutional prospective study are expected. We continue to use the same ATT, so we will collect more patients to prove that the Kokura Protocol is feasible and safe on breast surgery.

Conclusion

Our study suggests that it is safe to perform breast surgery in patients receiving ATT when we properly manage them in the perioperative period. To minimize the risk of thromboembolism, preoperative aspirin continuation for antiplatelets and heparin bridging for anticoagulation should be considered when patients with high thromboembolic risks undergo breast surgery.

Author Statement

Research funding: Authors state no funding involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals. Ethical approval: The condition of patients' functions and symptoms with reference to need for care and ambulatory status was described according to the European Cooperative Oncology Group Scale of Performance Status.

Author Contributions

Norio Emoto: Design of the study; Data retrieval; Data analysis; Statistical analysis; Writing of the manuscript; Analysis of literature. Takahisa Fujikawa: Design of the study; Data retrieval; Data analysis; Statistical analysis; Revision of the manuscript. Yasunori Yoshimoto: Approval of the manuscript. Hiroshi Kawamoto: Statistical analysis; Approval of the manuscript. Akira Tanaka: Approval of the manuscript.

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Supplemental Material: The article (DOI: 10.1515/iss-2017-0001) offers reviewer assessments as supplementary material.

Reviewer Assessment

Open Access

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Reviewers' Comments to Original Submission

Reviewer 1: Wulf Siggelkow

Jan 21, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	80
Custom Review Questions	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	4
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	5 - High/Yes
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

The present publication of Emoto et al. addresses the question of safety of antithrombotic procedures in patients undergoing several types of breast surgery. The question is by far relevant as more than 6 million patients in the US receive long-term anticoagulation/ antiplatelet therapy for cardiovascular reasons. Annually 10% of patients taking antithrombotic therapy require surgical procedure that temporarily discontinuates antithrombotic therapy.

The present paper examines 193 patients undergoing several types of breast surgery in one institution between 2010 and 2015. The majority of them (127) receives a modified radical mastectomy, 66 patients underwent breast conserving therapy, 29 % of these patients underwent axillary lymph node dissection. The perioperative characteristics are given in the material section. Categorization of postoperative complications was achieved using the Clavien-Dindo classification. Postoperative bleeding complications were comprehended as class 1, class 2 or more major complications.

An interdisciplinary antithrombotic perioperative management protocol (Kokura Protocol) was used defining high thrombotic risk patients. In general ATT was interrupted 5-7 days before surgery and postoperative early reinstatement in low thrombotic risk patients. Perioperative aspirin is continued for APT patients and ACT was substituted by bridging in high thrombotic risk patients.

The cohort includes 35 APT patients and 21 ACT patients. Both, APT and ACT were used in 6 patients.

32 patients (16.5%) were regarded as high risk for thrombembolism. Cardiovascular background characteristics were shown in Table 1. Perioperative complication and postoperative morbidity showed no differences between several types of breast surgery, status after neoadjuvant chemotherapy or bilateral procedures. No intraoperative blood loss more than 500ml occurred. There was no thrombotic complication in the whole cohort. The ATT group included more patients with both overall and postoperative bleeding.

On the univariable analysis, DM, ASA Score 3-4, history of CHF, history of CABG and ATT use were associated with overall bleeding complications. Using multivariate analysis, no factor was turned to be significant for overall bleeding complications. Either ATT use or perioperative aspirin continuation were not associated with overall/ major bleeding complications.

The results are reflected by some papers addressing the safety of breast-biopsies in ATT-patients. The present study is, so far, the first investigation of APT- and ATT patients undergoing breast surgery procedures.

The study has some weaknesses. It is not appropriate to confirm the Kokura Protocol and its feasibility for the safety of breast surgery patients. The study displays surgical risks of APT- and ATT patients undergoing breast surgery within the risk classification and the management suggestions of the protocol. The present Study does not add new aspects in the question of balancing bleeding risks against thrombotic risks beyond established guidelines.

As single institution study the impact of the results is weakened.

In summary the study has scientific relevance to display the safety of breast surgery patients in anticoagulation and antiplatelet therapy in a relevant number of patients and an appropriate method. It confirms established guidelines for the prevention of thrombembolism in APT- and ATT-patients in the field of breast surgery. The present paper is recommended for publication in Innovative Surgical Sciences.

There are no suggestions for revisions.

Reviewer 2: anonymous

Jan 20, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	60
Custom Review Questions	Response
Is the subject area appropriate for you?	3
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	3
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	3
Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	3
Please rate the practical significance.	3
Please rate the accuracy of methods.	3
Please rate the statistical evaluation and quality control.	3

Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

This is a nicely presented study. However, the Information is not completely new. It is well known that surgery can be performed with adequate safety in patients receiving antithrombotic therapy. Therefore, the study adds only Little new Information. Despite these limitations, the paper should be published because there are still some institutions and surgeons interrupting antithrombotic therapy which may be a risk factor for These patients.
