

# Safety of thoracoscopic surgery for lung cancer without interruption of anti-platelet agents

Woo Sik Yu<sup>1</sup>, Hee Suk Jung<sup>2</sup>, Jin Gu Lee<sup>2</sup>, Dae Joon Kim<sup>2</sup>, Kyung Young Chung<sup>2</sup>, Chang Young Lee<sup>2</sup>

<sup>1</sup>Department of Thoracic Surgery, Armed Forces Capital Hospital, Seongnam-si, Kyunggi-do, Republic of Korea; <sup>2</sup>Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

**Contributions:** (I) Conception and design: WS Yu, CY Lee; (II) Administrative support: CY Lee; (III) Provision of study materials or patients: JG Lee, DJ Kim, CY Lee; (IV) Collection and assembly of data: WS Yu, CY Lee, HS Jung; (V) Data analysis and interpretation: WS Yu, CY Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Chang Young Lee, MD. Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Email: CYLEECS@yuhs.ac.

**Background:** Perioperative bleeding concerns have led to the general recommendation that antiplatelet agents (APAs) be discontinued 7-10 days preoperatively, but this could increase the risk of perioperative cardiovascular events. This retrospective study aimed to evaluate the safety of APA continuation during thoracoscopic surgery for lung cancer.

**Methods:** Between January 2009 and February 2015, 164 patients taking APAs underwent curative resection. Comparisons were conducted between two groups: preoperatively interrupted APA administration (group I, n=106) and continued APA administration (group N, n=58).

**Results:** Group N had a significantly higher revised cardiac risk index (rCRI) (P=0.001). Lobectomy was performed in the majority of patients [95 (89.6%) in group I; 52 (89.7%) in group N]. There were no significant differences in intraoperative outcomes, such as the thoracotomy conversion rate, operating time, intraoperative transfusion, and amount of blood loss during the operation, or postoperative outcomes, such as postoperative bleeding and thrombotic complications, postoperative transfusions, and operative mortality. Within group N, the patients taking aspirin + clopidogrel (n=11) had significantly greater postoperative bleeding (P=0.005), and more postoperative transfusions (P=0.003) and chest tube drainage over a 3-day period (P=0.049) compared with other antiplatelet regimens.

**Conclusions:** Continued use of APAs during thoracoscopic surgery for lung cancer could be safely done in patients at high risk of cardiac or thrombotic events. However, in patients administered aspirin + clopidogrel, it may be the best to continue aspirin only because of an increased risk of postoperative bleeding and transfusion requirements.

**Keywords:** Lung cancer surgery; thoracoscopy/VATS; adult

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Primary lung cancer is the second most commonly occurring cancer and the most common cause of cancer deaths worldwide (1). Non-small cell lung cancer comprises approximately 80% of all lung cancers. Surgery is the mainstay of treatment for non-small cell lung cancer, especially in the early stages, with lobectomy as the accepted standard (2). Increasing adoption of thoracoscopic surgery

for this purpose has been observed over the previous two decades (3); the reported advantages of thoracoscopic lobectomy compared with open lobectomy include shorter chest tube durations, shorter hospital stays, decreased postoperative pain, and lower morbidity (3-5).

Antiplatelet agents (APAs) are the most frequently prescribed medications for a variety of conditions including coronary artery

occlusive disease, cerebrovascular disease, atrial fibrillation, peripheral artery occlusive disease (PAOD), prevention of venous thromboembolism, and primary prevention in high-risk patients (6). The Antithrombotic Trialists' Collaboration reported that APAs reduced the combined outcomes of any serious vascular event by approximately one quarter (non-fatal myocardial infarction by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth) (7). As a result, surgeons frequently encounter patients who have been administered antiplatelet therapy preoperatively.

Concern regarding excessive perioperative bleeding has led to the general recommendation that APAs be discontinued 7-10 days preoperatively. However, withdrawal of APAs could increase the risk of perioperative cardiovascular events (8-10). The 2012 update to the Society of Thoracic Surgeons guidelines on the use of antiplatelet drugs in patients having cardiac and noncardiac operations recommends that continuing antiplatelet monotherapy is feasible and continuing dual antiplatelet therapy can be feasible in patients undergoing noncardiac surgery unless the risk of bleeding is prohibitive (11). However, studies regarding the safety of continuing APA treatment in general thoracic surgery, especially minimally invasive surgery, are rare.

This retrospective study was conducted to evaluate the safety, with regard to bleeding risk, and operative characteristics, with regard to extent of resection and dissection, of thoracoscopic surgery without interruption of APA.

## Patients and methods

### Patients

This retrospective study was approved by the institutional review board of the hospital (4-2014-0999) and the need for consent from individual patients was waived. Between January 2009 and February 2015, 1,384 patients underwent thoracoscopic surgery for curative resection of lung cancer, not including those who underwent wedge resection. Of the 164 patients that were taking APAs when the need for surgery was determined, the decision about interruption of APA for each patient was made by the surgeon, in consultation with the anesthesiologist, cardiologist, and neurologist, based on the risk of perioperative thrombotic events and bleeding. The medical records of these 164 patients were reviewed retrospectively.

### Operative technique and postoperative care

In our institution, thoracoscopic lobectomy has been performed

since 2005, and more than half of the resections for lung cancer are now performed by thoracoscopy. Thoracoscopic lobectomy or segmentectomy was performed with a 3-5 cm utility incision at the anterior axillary line of the fourth or fifth intercostal space using endoscopic instruments, without spreading the ribs, and 2-3 ports for the camera, stapler, and assistant. The operation was performed entirely with thoracoscopic visualization (12). Ultrasonic dissectors were used in most of the patients for tissue dissection and division.

One or two chest tubes were placed after the operation. Postoperative pain control was achieved using patient-controlled intravenous analgesia and supplemental intravenous opioids. An epidural was not used. APAs were readministered from postoperative day 1, if there was no postoperative bleeding complication. The last chest tube was removed when the amount of drainage was <250 mL/day and in the absence of air leaks and chyle leakage.

### Perioperative cardiac risk

The perioperative cardiac risk was calculated by the authors using Lee's revised cardiac risk index (rCRI) (13), which includes six clinical variables: high-risk surgery type (because intrathoracic procedures are classified as high-risk surgeries in the rCRI, all surgeries in this study were classified as high risk), history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine >2.0 mg/dL.

### Outcome measures

Intra/postoperative outcomes for safety comparisons included operating time, estimated blood loss, need for transfusion, amount and duration of chest tube drainage, length of hospital stay, change in hemoglobin, postoperative morbidity, and postoperative mortality. The change in hemoglobin excluded patients who received a transfusion with red blood cells during the operation or within 24 hours after the operation and was calculated as: hemoglobin on postoperative day 1—preoperative hemoglobin. To compare the oncological quality of the surgery, the extent of lung resection and lymph node dissection, number of dissected lymph nodes, and rate of complete resection were recorded.

### Statistical analysis

Continuous data are expressed as median (range) and

**Table 1** Baseline characteristics of patients with lung cancer who underwent thoracoscopic surgery, comparing those with and without interrupted antiplatelet agent administration

Characteristics	Non-Interruption (n=58)	Interruption (n=106)	P
Age (years)	69 [51-83]	70 [52-85]	0.890
Sex			
Male	39 (67.2)	67 (68.5)	0.605
BMI (kg/m <sup>2</sup> )	24.47 (18.72-32.89)	24.01 (18.74-32.89)	0.340
Smoking	39 (67.2)	63 (59.4)	0.324
Pack-years	31 [0-90]	14.35 [0-85]	0.083
FEV <sub>1</sub> (%)	95 [61-147]	101 [58-153]	0.133
ECOG	0 [0-2]	0 [0-1]	0.357
Preoperative chemotherapy	1 (1.7)	1 (0.9)	>0.999
Antiplatelet agent			
Aspirin	44 (75.9)	85 (80.2)	0.518
Clopidogrel	18 (31.0)	17 (16.0)	0.025
Aspirin + clopidogrel	11 (19.0)	6 (5.7)	0.008
Other <sup>a</sup>	9 (15.5)	13 (12.3)	0.559
rCRI	2 [1-4]	1 [1-3]	0.001
Indication for antiplatelet therapy			
Ischemic heart disease	28 (48.3)	29 (27.4)	0.007
CABG	6 (10.3)	5 (4.7)	0.199
PCI	14 (24.1)	9 (8.5)	0.006
Cerebrovascular disease	15 (25.9)	22 (20.8)	0.454
Atrial fibrillation	5 (8.6)	7 (6.6)	0.756
PAOD	3 (5.2)	2 (1.9)	0.347
Primary prevention	15 (25.9)	60 (56.6)	<0.001
Interruption duration (days)		9 [2-50]	

<sup>a</sup>, other antiplatelet agents included cilostazol (n=8), sarpogrelate (n=7), and triflusal (n=7). Data are expressed as median (range) or n (%). BMI, body mass index; CABG, coronary artery bypass graft; ECOG, eastern cooperative oncology group; FEV<sub>1</sub>, forced expiratory volume in 1 second; PAOD, peripheral artery occlusive disease; PCI, percutaneous coronary intervention; rCRI, revised cardiac risk index.

categorical data as n (percentage). The patients were placed into two groups for comparisons: preoperatively interrupted APA administration (group I) and continued APA administration (group N). Within group N, comparisons were also conducted between those administered aspirin + clopidogrel and those administered other APAs (aspirin only, clopidogrel only, other single APA, and aspirin + other APA). Continuous variables were compared between the groups using the Mann-Whitney U test, and categorical variables were compared using the Chi-squared tests or Fisher's exact tests. All tests were two-sided, and a P value <0.05 was considered statistically significant. All statistical

analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

## Results

### Baseline characteristics

Group I consisted of 106 patients (64.6%), with a median duration of APA interruption of 9 [2-50] days. Group N consisted of 58 (35.3%) patients. The baseline characteristics of the patients are summarized in *Table 1*. Group N had significantly higher rCRI scores (P=0.001). Significantly more patients in group N were administered

**Table 2** Characteristics of lung cancer in patients who underwent thoracoscopic surgery, comparing those with and without interrupted antiplatelet agent administration

Characteristics	Non-interruption (n=58)	Interruption (n=106)	P
Location of tumor			0.081
RUL	18 (31.0)	28 (26.4)	
RML	4 (6.9)	18 (17.0)	
RLL	12 (20.7)	18 (17.0)	
LUL	17 (29.3)	18 (17.0)	
LLL	7 (12.1)	24 (22.6)	
Histology			0.250
Adenocarcinoma	38 (65.5)	80 (75.5)	
Squamous cell carcinoma	18 (31.0)	21 (19.8)	
Other	2 (3.4)	5 (4.7)	
pTstage			0.770
0	0 (0.0)	1 (0.9)	
is	0 (0.0)	3 (2.8)	
1a	26 (44.8)	37 (34.9)	
1b	11 (19.0)	25 (23.6)	
2a	16 (27.6)	32 (30.2)	
2b	2 (3.4)	2 (1.9)	
3	3 (5.2)	6 (5.7)	
pNstage			0.422
0	53 (91.4)	89 (84.0)	
1	2 (3.4)	8 (7.5)	
2	3 (1.8)	9 (8.5)	

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe. Data are expressed as n (%).

clopidogrel (P=0.025) or aspirin + clopidogrel (P=0.008). Significantly more patients in group I were administered APAs for primary intervention (P<0.001). Significantly more patients in group N had ischemic heart disease (P=0.007) and underwent percutaneous coronary intervention (PCI) (P=0.006).

#### **Characteristics of lung cancer and operation parameters**

Characteristics of lung cancer and operative data are summarized in *Tables 2,3*. The groups were not significantly different in terms of lung cancer characteristics or extent of lung resection and lymph node dissection, number of dissected lymph nodes, rate of complete resection, rate of thoracotomy conversion, rate of transfusion, amount of blood loss during the operation, or operating time. Thoracotomy conversion was performed because of

bleeding from the pulmonary artery in 4 patients (2 in each group), descending thoracic aorta rupture by linear stapler tip in 1 patient (group N), invasion to mediastinal pleura by tumor in 1 patient (group I) and severe pleural adhesion in 1 patient (group I).

#### **Postoperative outcomes**

Postoperative outcomes are described in *Table 4*. The groups were not significantly different in the number of patients requiring transfusion within 30 days postoperatively, change in hemoglobin, amount of chest tube drainage over a period of 3 days, the length of hospital stay, postoperative bleeding and thrombotic complications, or operative mortality. Duration of chest tube drainage was little longer in patient group N (4 days in group N vs. 3.5 day in group I, P=0.036).

Postoperative bleeding occurred in 5 patients (3 in

**Table 3** Operative characteristics of thoracoscopic surgery in patients with lung cancer, compared between those with and without interrupted antiplatelet agent administration

Operative characteristics	Non-interruption (n=58)	Interruption (n=106)	P
Extent of resection			0.496
Bilobectomy	0 (0.0)	3 (2.8)	
Lobectomy	52 (89.7)	95 (89.6)	
Segmentectomy	6 (10.3)	8 (7.5)	
Extent of LN dissection			0.423
LN sampling	1 (1.7)	6 (5.7)	
LN dissection	57 (98.3)	100 (94.3)	
Number of dissected LN	27.5 [7-47]	26 [5-57]	0.375
Complete resection (R0)	57 (98.3)	102 (96.2)	0.657
Adhesion	23 (39.7)	39 (36.8)	0.718
Thoracotomy conversion	3 (5.2)	4 (3.8)	0.699
Intraoperative transfusion	2 (3.4)	2 (1.9)	0.615
Blood loss (mL)	50 (10-2,900)	50 [10-3,900]	0.158
Bleeding >500 cc	5 (8.6)	3 (2.8)	0.132
Operating time (min)	136 [54-307]	141 [60-360]	0.265

LN, lymph node. Data are expressed as median (range) or n (%).

**Table 4** Postoperative outcomes of thoracoscopic surgery in patients with lung cancer, comparing those with and without interrupted antiplatelet agent administration

Postoperative outcomes	Non-interruption (n=58)	Interruption (n=106)	P
Postoperative transfusion (within 30 days postoperative)	5 (8.6)	3 (2.8)	0.132
ΔHb (mg/dL)	-1.10 (-5.20-2.10)	-1.00 (-3.30-1.70)	0.592
Chest tube drainage over a 3-day period (mL)	695 (140-2,280)	720 (90-3,080)	0.870
Duration of chest tube (days)	4 [2-114]	3.5 [1-18]	0.036
Length of hospital stay (days)	6 [3-140]	5 [2-19]	0.064
Postoperative complications (all)	13 (22.4)	14 (13.2)	0.129
Bleeding complication	3 (5.2)	3 (2.8)	0.667
Postoperative bleeding	3 (5.2)	2 (1.9)	0.357
Postoperative bleeding requiring reoperation	0 (0.0)	1 (0.9)	>0.999
Bronchopulmonary hemorrhage	0 (0.0)	1 (0.9)	>0.999
Cerebrovascular accident	1 (1.7)	0 (0.0)	0.354
Pneumonia	5 (8.6)	3 (2.8)	0.132
Prolonged air leak (>7 days)	3 (5.2)	3 (2.8)	0.667
Bronchopulmonary fistula	2 (3.4)	0 (0.0)	0.124
Vocal cord palsy	1 (1.7)	2 (1.9)	>0.999
Chylothorax	0 (0.0)	1 (0.9)	>0.999
Wound dehiscence	0 (0.0)	2 (1.9)	0.540
Readmission	1 (1.7)	2 (1.9)	>0.999
Operative mortality	1 (1.7)	0 (0.0)	0.354

ΔHb, hemoglobin on postoperative day 1—preoperative hemoglobin, excluding patients who received a transfusion with red blood cells during the operation or within 24 hours after the operation (n=7). Data are expressed as median (range) or n (%).

**Table 5** Outcomes in patients with lung cancer who underwent thoracoscopic surgery, comparing those administered aspirin + clopidogrel and those who received other single or dual antiplatelet agents

Outcomes	Aspirin + clopidogrel (n=11)	Other than aspirin + clopidogrel <sup>a</sup> (n=47)	P
Blood loss during operation (mL)	145 [10-1,300]	50 [10-2,900]	0.441
Blood loss during operation (>500 mL)	2 (18.2)	3 (6.4)	0.237
Intraoperative transfusion	0 (0.0)	2 (4.3)	>0.999
Operating time (min)	130 [94-307]	137 [54-307]	0.743
Postoperative transfusion (within 30 days after operation)	4 (36.4)	1 (2.1)	0.003
ΔHb (mg/dL)	-1.5 (-5.2-2.1)	-1.0 (-5.1-1.4)	0.571
Chest tube drainage over a 3-day period (mL)	1,140 (430-2,280)	690 [140-2,030]	0.049
Duration of chest tube (days)	5 [3-14]	4 [2-114]	0.095
Length of hospital stay (days)	6 [4-18]	5 [3-140]	0.154
Postoperative bleeding	3 (27.3)	0 (0.0)	0.005
Cerebrovascular accident	1 (9.1)	0 (0.0)	0.190
Postoperative complications (all)	4 (36.4)	9 (19.1)	0.244

<sup>a</sup>, this group included aspirin only (n=32), clopidogrel only (n=6), other single APA (n=7), aspirin + other APA (n=1), and clopidogrel + other APA (n=1); ΔHb, hemoglobin on postoperative day 1—preoperative hemoglobin, excluding patients who received a transfusion with red blood cells during the operation or within 24 hours after the operation (n=4). Data are expressed as median (range) or n (%).

group N, 2 in group I; 1 reoperation was performed in the group I patient. The other patients were managed conservatively). One patient in group I experienced hemoptysis, with pulmonary infiltration on chest radiography (bronchopulmonary hemorrhage). He recovered without intervention and was discharged on postoperative day 11. There was one cerebrovascular accident in a group N patient who was administered aspirin + clopidogrel preoperatively for a cerebral infarction. Neurologic deficit was apparent immediately after the operation and acute cerebral infarction was confirmed using brain magnetic resonance imaging. There were no other cardiac or thrombotic complications.

Operative mortality occurred in one patient in group N. After the right lower lobe lobectomy, he was discharged on postoperative day 7 without any complications. He was readmitted with pneumonia, empyema, and a bronchopulmonary fistula on postoperative day 14 and died on postoperative day 89.

Table 5 provides the results of the comparisons between aspirin + clopidogrel and other APAs within group N. Patients administered aspirin + clopidogrel had significantly more postoperative bleeding (P=0.005), more chest tube drainage over a 3-day period (P=0.028), longer duration of chest tube drainage (P=0.028), and longer hospital stays

(P=0.030). In addition, more patients required postoperative transfusion (P=0.001). Reoperation for bleeding was not required in any of the patients.

Transfusion was required for eight patients during and/or within 30 days after the operation (group I, n=3; group N, n=5) (Table 6). Most of these patients had pleural adhesion.

## Discussion

The present results indicate that thoracoscopic surgery for lung cancer without interruption of APAs can be performed without an increase in the thoracotomy conversion rate, operating time, estimated blood loss during the operation, transfusion requirement, or postoperative bleeding complications.

APAs are administered for a variety of conditions, including coronary artery occlusive disease, cerebrovascular disease, atrial fibrillation, PAOD, prevention of venous thromboembolism, and primary prevention in high-risk patients (6). In the present study, approximately 10% of the patients who underwent thoracoscopic surgery for lung cancer were taking APAs, while in a population-based cohort study, approximately 26% of patients diagnosed with lung cancer were aspirin users (14). Concerns regarding the discontinuation of APAs include the resulting rebound

**Table 6** Characteristics of transfused patients with lung cancer who underwent thoracoscopic surgery

Patient	Age (years)	Sex	Procedure	Antiplatelet agent	Interruption (duration)	Intraoperative event(s)	Thoracotomy conversion	Transfusion <sup>a</sup> (intraoperative/postoperative)	Reoperation for bleeding	Hospital stay (days)
1	78	M	RML lobectomy	Aspirin, clopidogrel	Yes (16 days)	PA tearing	Yes	5-2-0/2-4-0	No	12
2	72	M	LLL lobectomy	Aspirin	Yes (14 days)	Pleural adhesion	Yes	1-0-0/3-0-0	No	8
3	62	F	RML lobectomy	Aspirin, clopidogrel	Yes (3 days)	No	No	0-0-0/5-2-6	Yes	5
4	78	F	LUL lobectomy	Aspirin	No	Pleural adhesion, PA tearing	Yes	5-0-0/0-0-0	No	10
5	72	M	RUL lobectomy	Aspirin, clopidogrel	No	Pleural adhesion, PA tearing	Yes	0-0-0/2-0-0	No	11
6	60	M	RUL lobectomy	Aspirin, clopidogrel	No	Pleural adhesion, pleural tenting	No	0-0-0/3-0-0	No	6
7	71	F	RUL lobectomy	Aspirin, clopidogrel	No	Pleural adhesion	No	0-0-0/0-0-6	No	5
8	73	M	RUL lobectomy	Aspirin, clopidogrel	No	Pleural adhesion	No	0-0-0/0-2-0	No	18
9	64	M	LLL lobectomy	Aspirin	No	Pleural adhesion descending thoracic aorta rupture	Yes	5-3-0/1-2-0	No	140

<sup>a</sup>, transfused blood products are shown as packed red blood cells-fresh frozen plasma-platelets. LLL, left lower lobe; LUL, left upper lobe; PA, pulmonary artery; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

effect and potentially increased coagulability from a systemic inflammatory reaction to surgery. The average postoperative myocardial infarction rate and mortality due to stent thrombosis during the re-endothelialization phase of a coronary stent are reportedly 35% and 20-40%, respectively. In addition, the treatment for postoperative myocardial infarction, including emergency PCI and thrombolysis, is more difficult and is associated with greater risk (15).

Aspirin does not appear to significantly increase bleeding complications (16,17), based on the results of two randomized clinical trials. The first, a multicenter, blinded study regarding the impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after non-cardiac surgery reported no differences in bleeding events between the aspirin (n=145) and placebo (n=146) groups at postoperative day 7 (n=9, 6.2% and n=8, 5.5%, respectively, P=0.81) or day 30 (n=10, 6.9% and n=10, 6.8%, respectively, P=0.99) (16). In the second, a double-blind study involving 220 patients, a 7.2% absolute

risk reduction (95% confidence interval, 1.3-13%) in postoperative major adverse cardiac events was observed, without an increase in bleeding complications. Interestingly, a subjective assessment of intraoperative bleeding by the attending surgeon indicated no difference between the aspirin and placebo groups (17).

The effects of clopidogrel have typically been investigated for cardiac surgeries, resulting in increased blood loss, reoperations for bleeding, transfusion rate, and length of stay in the intensive care unit (15,18,19). However, in the study regarding the safety of general thoracic surgery in patients taking clopidogrel by Cerfolio *et al.*, the risk of bleeding after primary thoracotomy or minimally invasive thoracic surgery was not increased (20). Although 12 lobectomies (11 open, 1 robot-assisted) and 6 thoracoscopic procedures were included, none of the patients underwent thoracoscopic lobectomy.

In addition to the reported advantages of shorter chest tube durations, shorter hospital stays, decreased

postoperative pain, and lower morbidity with thoracoscopic lobectomies (3-5), decreased blood loss during the operation has also been reported (12). A few studies have recently reported that minimally invasive surgery in other surgical areas could be safely performed in patients taking APAs without an increase in bleeding complications (21,22). To the best of our knowledge, the present study is the first to suggest that a complex thoracoscopic procedure such as lobectomy can be performed safely, without increasing bleeding complications, blood loss, transfusion requirements, perioperative morbidity, or mortality.

In the present study, continuation of aspirin + clopidogrel was associated with increased postoperative bleeding, transfusion requirements, amount of chest tube drainage over a period of 3 days, duration of chest tube drainage, and length of hospital stay. Of the 11 patients taking aspirin + clopidogrel, 4 (36.4%) patients received transfusions postoperatively, and all had severe pleural adhesions (Table 6). This is consistent with the results of the study by Cerfolio *et al.*, in which patients administered both aspirin and clopidogrel who underwent a redo thoracotomy for subsequent lung cancer needed reoperation because of postoperative bleeding. It appears to be more difficult to control bleeding from the chest wall secondary to the takedown of adhesions in patients taking aspirin + clopidogrel (20).

This study has several limitations. It was a retrospective study performed in a single institution with a small sample of patients. Patients of group N seem to have more cardiac or thrombotic risk and they could be performed simpler procedure for lung cancer. In fact, patients continuing clopidogrel tend to have recent cerebrovascular disease, recent PCI or CABG, or multiple risk factor (Table S1). Because of the small sample of patients and few thromboembolic events, the effect of continued use APAs on perioperative thromboembolic events cannot be evaluated. In addition, we only compared postoperative outcomes but not the long-term oncologic outcomes of the perioperative use of APAs. However, there were no differences in the extent of resection and lymph node dissection, rate of complete resection, or number of dissected lymph nodes between the groups.

In conclusion, continued use of APAs during thoracoscopic surgery for lung cancer could be safely done in patients at high risk of cardiac or thrombotic events. However, in patients administered aspirin + clopidogrel, it may be the best to continue aspirin only because of an increased risk of postoperative bleeding and transfusion requirements.

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## Footnote

*Conflicts of Interest:* The authors have no conflict of interest to declare.

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Table S1 Characteristics of patients continued clopidogrel

Patient	Age (years)	Sex	Antiplatelet agent	BMI (kg/m <sup>2</sup> )	Smoking (pack-years)	Indication for continuing antiplatelet therapy	Lung cancer histology/pStage
1	73	M	Aspirin, clopidogrel	20.28	38	Cerebrovascular disease (7 months ago)	SCC/pT3N0
2	72	M	Aspirin, clopidogrel	28.02	82	Cerebrovascular disease (4 months ago)	SCC/pT2aN0
3	71	F	Aspirin, clopidogrel	20.03	0	Cerebrovascular disease (2 months ago)	ADC/T1aN0
4	69	M	Aspirin, clopidogrel	26.44	30	Ischemic heart disease (s/p PCI, 2 months ago)	SCC/T1bN0
5	75	F	Aspirin, clopidogrel	26.49	40	Ischemic heart disease (s/p PCI, 2 years ago); DM with insulin	ADC/T2aN0
6	70	M	Aspirin, clopidogrel	27.51	23	Ischemic heart disease (s/p PCI, 1 month ago)	ADC/T1aN0
7	70	M	Aspirin, clopidogrel	23.32	10	Ischemic heart disease (s/p CABG, 2 years ago)	ADC/T1aN0
8	60	M	Aspirin, clopidogrel	22.96	15	Ischemic heart disease (s/p CABG, 1 month ago)	ADC/T1aN0
9	64	M	Aspirin, clopidogrel	26.42	50	Ischemic heart disease (s/p PCI, 1 month ago)	LCC/T2N2
10	65	M	Aspirin, clopidogrel	25.24	1.5	Ischemic heart disease (s/p CABG, 2 months ago)	ADC/T1aN0
11	71	F	Aspirin, clopidogrel	19.63	0	Cerebrovascular disease (2 months ago)	ADC/T1bN0
12	79	M	Clopidogrel	20.82	90	Atrial fibrillation	SCC/T1aN0
13	76	M	Clopidogrel	31.74	40	Ischemic heart disease (s/p PCI, 5 years ago); DM with insulin, CRF	ADC/T1aN0
14	80	M	Clopidogrel	26.41	52	Ischemic heart disease (s/p PCI, 3 years ago); DM without insulin, PAOD	SCC/T1aN0
15	78	M	Clopidogrel	24.09	60	Cerebrovascular disease (Unknown onset); DM without insulin	SCC/T3N0
16	65	M	Clopidogrel	24.31	65	Cerebrovascular disease (Unknown onset); DM with insulin	ADC/T2aN0
17	68	M	Clopidogrel	22.55	68	Cerebrovascular disease (5 years ago)	SCC/T2bN1
18	56	M	Clopidogrel, cilostazol	24.46	56	Ischemic heart disease (s/p CABG, 3 years ago); DM with insulin, CRF, PAOD	ADC/T1bN0

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; DM, diabetes mellitus; CRF, chronic renal failure; PAOD, peripheral artery occlusive disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; LCC, large cell carcinoma.