



Safety of Perioperative Maintenance of Antiplatelet Agents in Elderly Patients Undergoing Lung Cancer Surgery

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Background: The maintenance of antiplatelet therapy increases the risk of bleeding during lung cancer surgery. Conversely, the perioperative interruption of antiplatelet therapy may result in serious thrombotic complications. This study aimed to investigate the safety of continuing antiplatelet therapy in the context of lung cancer surgery.

Methods: We retrospectively reviewed a cohort of 498 elderly patients who underwent surgery for lung cancer. These patients were categorized into 2 groups: group N, which did not receive antiplatelet therapy, and group A, which did. Group A was subsequently subdivided into group Am, where antiplatelet therapy was maintained, and group Ai, where antiplatelet therapy was interrupted. We compared the incidence of bleeding-related and thrombotic complications across the 3 groups.

Results: There were 387 patients in group N and 101 patients in group A (Ai: 70, Am: 31). No significant differences were found in intraoperative blood loss, thoracotomy conversion rates, transfusion requirements, volume of chest tube drainage, or reoperation rates for bleeding control between groups N and A or between groups Am and Ai. The duration of hospital stay was longer for group A compared to group N (7 days vs. 6 days, $p=0.005$), but there was no significant difference between groups Ai and Am. The incidence of cardiovascular or cerebrovascular complications did not differ significantly between groups Ai and Am. However, group Ai included a severe case of in-hospital ST-elevation myocardial infarction.

Conclusion: The maintenance of antiplatelet therapy was found to be safe in terms of perioperative bleeding and thrombotic complications in elderly lung cancer surgery patients.

Keywords: Antiplatelet agent, Lung neoplasms, Surgery, Geriatrics, Complications

Introduction

Lung cancer is the most prevalent form of cancer and the leading cause of cancer-related mortality worldwide [1]. It predominantly affects older adults, with the highest incidence observed in individuals in their eighties [2]. As the global population ages, the prevalence of lung cancer in the elderly is expected to increase. Many of these patients also have atherosclerosis in various regions of their body, which often requires antiplatelet therapy [3]. A population-based study in England reported that around 27% of lung cancer patients were taking aspirin [4]. With this trend likely to persist, the decision to either continue or discontinue anti-

platelet therapy during the perioperative period is becoming increasingly critical in an aging society.

Antiplatelet agents are prescribed for a variety of conditions, including coronary artery occlusive disease, transient ischemic attack, cerebral stroke, and peripheral artery occlusive disease [5]. These medications encompass aspirin, clopidogrel, and cilostazol, among others. Notably, aspirin and clopidogrel irreversibly inhibit platelet function, which heightens the risk of bleeding both during and after surgical procedures [6]. It is typically recommended to temporarily discontinue antiplatelet therapy in the perioperative period for major non-cardiac surgery to mitigate the risk of bleeding. However, cessation of antiplatelet therapy may



increase the likelihood of thrombotic complications stemming from underlying atherosclerosis, such as myocardial infarction and cerebral stroke [7,8]. Recent studies indicate that continuing antiplatelet therapy throughout surgery does not significantly increase the risk of postoperative bleeding when compared to its interruption [9].

Guidelines recommend maintaining antiplatelet therapy during surgery except in patients at high risk of bleeding or those with platelet function or coagulation disorders [4]. However, the evaluation of bleeding risk frequently relies on the judgment of individual surgeons, presenting thoracic surgeons with the challenge of deciding to continue or discontinue antiplatelet therapy in the face of differing guidelines.

The use of perioperative antiplatelet therapy during lung cancer surgery in elderly patients has been infrequently studied, and there is a particular lack of research on cardiovascular and cerebrovascular complications in the Korean population. This study aimed to fill this gap in knowledge by analyzing the risks of bleeding and thrombotic complications in elderly lung cancer patients who continue antiplatelet therapy throughout the perioperative period.

Methods

Patients

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (approval no., 2109-169-1261), which waived the requirement for individual informed consent. In this retrospective study, we analyzed data from 498 consecutive patients aged 60 years or older who underwent pulmonary resection for lung cancer from April 2020 to February 2021. We collected all relevant data, including patient demographics, clinicopathological characteristics, patterns of antiplatelet use, surgical details, and postoperative outcomes, by reviewing the electronic medical records of the patients. Pleural adhesion was classified based on the extent of adhesion into 3 categories: no adhesion, focal adhesion, or whole adhesion.

The standard surgical procedure for lung cancer was lobectomy with systemic lymph node dissection, performed using minimally invasive approaches such as video-assisted thoracic surgery or robot-assisted thoracic surgery. Patients on antiplatelet medications underwent preoperative evaluations by cardiologists or neurologists, depending on the underlying conditions that necessitated antiplatelet therapy. Thoracic surgeons made the decision to continue or discontinue antiplatelet therapy, considering the recom-

mendations of cardiologists or neurologists, as well as the specific condition of the individual patient.

In instances where an interruption was necessary, antiplatelet therapy was discontinued 5 to 7 days before the surgery and resumed on postoperative days 1 to 2, provided there was no evidence of bleeding. When maintenance was required, antiplatelet therapy was only omitted on the day of the operation.

Outcome measurements

The parameters of surgical outcomes were operation time (minutes), amount of estimated intraoperative blood loss (mL), intraoperative transfusion volume (packs), postoperative transfusion volume (packs), total amount of chest tube drainage (mL), duration of chest tube maintenance (days), and length of hospital stay (days). The incidence of postoperative complications—namely, postoperative transfusion, reoperation for bleeding control, cardiovascular events, cerebrovascular events, pneumonia, prolonged air leak, vocal fold palsy, and chylothorax—was also investigated.

Cardiovascular complications included postoperative atrial fibrillation and ST-elevation myocardial infarction (STEMI), while cerebrovascular events included stroke, cerebral hemorrhage, and transient ischemic attacks. Pneumonia was recorded when a patient received antibiotics treatment based on clinical symptoms, radiologic findings, and elevated inflammatory markers, irrespective of pathogen isolation.

Statistical analysis

Patients were categorized into 2 groups: group N (no antiplatelet therapy) and group A (antiplatelet therapy). group A was further subdivided into group Am (antiplatelet maintenance) and group Ai (antiplatelet interruption). If a patient continued 1 of 2 antiplatelets, they were assigned to group Am. Patient characteristics were compared using the independent t-test for continuous variables and the chi-square test for categorical variables. Continuous data are presented as median (range), while categorical data are expressed as the number (percentage). Statistical analyses were performed using SAS statistical software for Windows ver. 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

Among a total of 498 patients, 397 (79.7%) were in group N, and 101 (20.3%) were in group A. In group A, 70 patients (69.3%) were in group Ai, while 31 patients (30.7%) were in group Am (Fig. 1).

Compared to group N, group A included older patients, more men, more ex- or current smokers, and fewer stage I cases. The approach methods and extents of pulmonary resection were similar between groups A and N. The incidence of pleural adhesion was not significantly different between the groups (Table 1).

The characteristics of patients in group Ai and group Am showed no statistically significant differences. Similarly, the approaches and extents of pulmonary resection were comparable between the 2 groups (Table 1). In both groups, lobectomy was the predominant procedure (n=44, 62.9%) in group Ai versus (n=19, 61.3%) in group Am.

Antiplatelet medications

The antiplatelets used included aspirin in 53 patients (52.5%), clopidogrel in 30 patients (29.7%), dual antiplatelet therapy (aspirin and clopidogrel) in 9 patients (8.9%), cilostazol in 6 patients (5.9%), and sarpogrelate in 3 patients (3.0%). The underlying conditions necessitating antiplatelet therapy were cerebrovascular disease in 32 patients (31.7%) and cardiovascular disease in 36 patients (35.6%). The remaining 34 patients (33.7%) were prescribed antiplatelets for prophylactic purposes, predominantly due to hypertension. There was no significant difference in the distribution of underlying diseases or the types of antiplatelets used be-

tween groups Ai and Am (Table 2).

In group Ai, antiplatelets were discontinued a median of 5 days (range, 2–30 days) prior to surgery and resumed a median of 3 days (range, 1–11 days) after surgery.

Surgical outcomes

Group A showed no statistically significant differences from group N in terms of intraoperative blood loss (100 mL versus 60 mL, $p=0.76$), operation time (125 minutes versus 115 minutes, $p=0.56$), or the volume of chest tube drainage (667 mL versus 528 mL, $p=0.58$). For patients with whole pleural adhesion, the intraoperative blood loss was comparable between group A and group N. The rate of thoracotomy conversion was also similar for both groups (group N: n=23 [5.8%] versus group A: n=9 [8.9%]; $p=0.23$). Only 3 patients required reoperation for bleeding control, with no significant difference in incidence rates between the 2 groups. However, the duration of hospital stay was significantly longer for group A than for group N (Table 3).

There were also no statistically significant differences in surgical outcome parameters between groups Ai and Am (Table 3).

Postoperative complications

In group Ai, there was 1 cardiovascular event (STEMI) that necessitated the insertion of a percutaneous stent. The incidence rates of STEMI were significantly different between groups N and A, with rates of 0% and 1.0%, respectively ($p=0.047$). However, the STEMI rates between groups Ai and Am did not show a statistically significant difference, with rates of 1.4% and 0%, respectively ($p=0.5$). The incidence rates of atrial fibrillation were significantly higher in group A than in group N (5.9% versus 1.0%, $p=0.002$). However, there was no statistically significant difference in the rate of atrial fibrillation between group Ai and group Am (4.3% versus 9.7%, $p=0.29$). Two patients in the entire cohort suffered cerebrovascular events: 1 patient in group N experienced a transient ischemic attack, and 1 patient in group Am had an ischemic cerebral stroke preceded by atrial fibrillation. The incidence rates of cerebrovascular events did not differ significantly between groups A and N (1.0% versus 0.3%, $p=0.38$) or between groups Ai and Am (0% versus 3.2%, $p=0.14$).

Pneumonia was the most common postoperative complication, with similar incidence rates observed between group A and group N (7.9% versus 5.3%, $p=0.31$). Although the incidence of pneumonia was numerically higher in

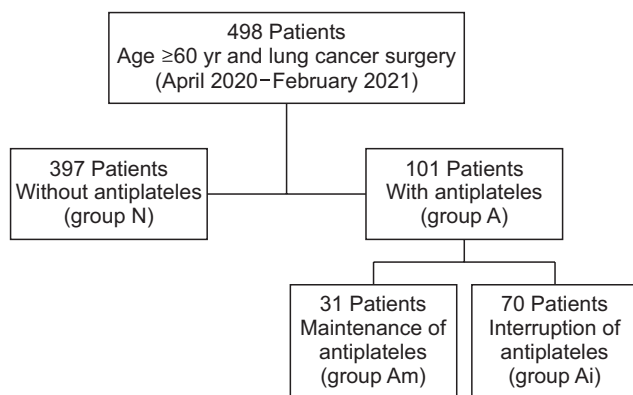


Fig. 1. Flow diagram of the patient selection process.

Table 1. Characteristics of patients who underwent lung cancer surgery

Characteristic	No antiplatelet (group N)	Antiplatelet (group A)	Interruption (group Ai)	Maintenance (group Am)	p-value ^{a)}	p-value ^{b)}
No. of patients	397	101	70	31		
Age (yr)	67 (60–87)	71 (60–83)	71 (60–83)	71 (60–83)	<0.0001	0.55
Sex (male)	214 (53.9)	74 (73.3)	48 (68.6)	26 (83.9)	<0.0001	0.09
Body mass index (kg/m ²)	23.85 (13.9–36.2)	23.62 (15.7–32.5)	23.51 (15.7–32.5)	25.47 (17.5–28.8)	0.94	0.24
FEV ₁ (%)	109 (57–170)	101 (60–152)	102.5 (60–152)	98 (67–125)	0.003	0.15
DLCO (%)	95 (50–164)	93 (42–144)	92 (42–144)	94.5 (52–121)	0.005	0.80
Smoking history						
Non-smoker	214 (53.9)	31 (30.7)	24 (34.3)	7 (22.6)	<0.0001	0.14
Ex-smoker	120 (30.2)	56 (55.5)	35 (50.0)	21 (67.6)		
Current	63 (15.9)	14 (13.9)	11 (15.7)	3 (9.7)		
Previous cancer history	108 (27.2)	9 (8.9)	5 (7.1)	4 (12.9)	0.0006	0.35
Hypertension	141 (35.5)	51 (50.5)	33 (47.1)	18 (58.1)	0.006	0.41
Diabetes mellitus	69 (17.4)	28 (27.7)	20 (28.6)	8 (25.8)	0.03	0.60
Chronic kidney disease	7 (1.8)	4 (4.0)	3 (4.3)	1 (3.2)	0.18	0.80
Pulmonary tuberculosis	37 (9.3)	9 (8.9)	6 (8.6)	3 (9.7)	0.89	0.86
Histology						
Adenocarcinoma	315 (79.3)	60 (59.4)	40 (57.1)	20 (64.5)	<0.0001	0.44
Squamous cell carcinoma	49 (12.3)	24 (23.8)	16 (22.9)	8 (25.8)		
Others	33 (8.3)	17 (16.8)	14 (20.0)	3 (9.7)		
Stage ^{c)}						
I	272 (68.5)	55 (54.5)	37 (52.9)	18 (58.1)	0.02	0.76
II	56 (14.1)	26 (25.7)	18 (25.7)	9 (29.0)		
III	44 (11.1)	15 (14.9)	11 (15.7)	4 (12.9)		
IV	9 (2.3)	2 (2.0)	2 (2.9)	0		
Approach method						
VATS	335 (84.4)	84 (83.2)	56 (80.0)	28 (90.3)	0.08	0.41
RATS	20 (5.0)	1 (1.0)	1 (1.4)	0		
Thoracotomy	42 (10.6)	16 (15.8)	13 (18.6)	3 (9.7)		
Extent of resection						
Wedge resection	47 (11.8)	11 (10.9)	6 (8.6)	4 (12.9)	0.20	0.67
Segmentectomy	51 (12.9)	20 (19.8)	13 (18.6)	7 (22.6)		
Lobectomy	284 (71.5)	63 (62.4)	44 (62.9)	19 (61.3)		
Bilobectomy	6 (1.5)	3 (3.0)	2 (2.9)	1 (3.2)		
Pneumonectomy	8 (2.0)	4 (4.0)	4 (5.7)	0		
Lymph node dissection	359 (90.4)	95 (94.1)	65 (92.9)	30 (96.8)	0.25	0.44
Pleural adhesion					0.26	0.44
None	205 (51.6)	43 (42.6)	28 (40.0)	15 (48.4)		
Focal	142 (35.8)	42 (41.6)	32 (45.7)	10 (32.3)		
Whole	50 (12.6)	16 (15.8)	10 (14.3)	6 (19.4)		

Values are presented as number, median (range), or number (%).

FEV₁, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for CO; VATS, video-assisted thoracoscopic surgery; RATS, robot-assisted thoracoscopic surgery.

^{a)}Comparison between antiplatelet non-users and antiplatelet users. ^{b)}Comparison between the antiplatelet interruption and maintenance group.

^{c)}Epithelial and neuroendocrine types only.

group Ai than in group Am, the difference was not statistically significant (group Ai: 10.0% versus group Am: 3.23%; $p=0.25$). Prolonged air leak was the second most common postoperative complication, and the incidence rates were similar between group A and group N (6.9% versus 5.3%, $p=0.52$). The prolonged air-leak rates were not significantly

different between group Ai and Am (5.7% versus 9.7%, $p=0.47$). The incidence rates of other complications were not significantly different between groups N and A and between groups Ai and Am (Table 3).

Table 2. Agents and indications for antiplatelet therapy

Characteristic	Total (n=101)	Interruption (n=70)	Maintenance (n=31)	p-value
Antiplatelet agent				
Aspirin	53 (52.5)	35 (50.0)	18 (58.1)	0.07
Clopidogrel	30 (29.7)	25 (35.7)	5 (16.1)	
Aspirin+clopidogrel	9 (8.9)	5 (7.1)	4 (12.9)	
Cilostazol	6 (5.9)	2 (2.9)	4 (12.9)	
Salpogrelate	3 (3.0)	3 (4.3)	0	
Indication for antiplatelet therapy				
Angina	10 (9.9)	6 (8.6)	4 (12.9)	0.50
PCI history	20 (19.8)	14 (20.0)	6 (19.4)	0.87
CABG	3 (3.0)	1 (1.4)	2 (6.5)	0.17
Cerebrovascular disease	32 (31.7)	20 (28.6)	12 (38.7)	0.31
PAOD	3 (3.0)	2 (2.9)	1 (3.2)	0.92
Primary prevention	34 (33.7)	26 (37.1)	8 (25.8)	0.23

Values are presented as number (%).

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PAOD, peripheral artery occlusive disease.

Table 3. Surgical outcomes of patients who underwent lung cancer surgery

Characteristic	No antiplatelet (group N)	Antiplatelet (group A)	Interruption (group Ai)	Maintenance (group Am)	p-value ^{a)}	p-value ^{b)}
No. of patients	397	101	70	31		
Estimated blood loss (mL)	60 (0–2,700)	100 (10–1,350)	100 (10–1,350)	100 (10–350)	0.76	0.17
No adhesion	50 (0–2,700)	50 (10–300)	50 (10–300)	50 (10–160)	0.58	0.69
Focal adhesion	100 (0–1,300)	100 (10–500)	100 (20–500)	125 (10–300)	0.58	0.27
Whole adhesion	150 (30–1,900)	100 (20–1,350)	200 (20–1,350)	80 (50–350)	0.88	0.28
Intraoperative transfusion (packs)	0 (0–5)	0 (0–2)	0 (0–2)	0 (0–0)	0.61	0.51
Operation time (min)	115 (20–650)	125 (25–375)	125 (35–375)	120 (25–220)	0.56	0.12
Postoperative transfusion (packs)	0 (0–4)	0 (0–1)	0 (0–1)	0 (0–0)	0.24	0.35
Chest tube drainage (mL)	528 (0–20,240)	667 (0–4,405)	633 (0–4,405)	706 (20–4,010)	0.58	0.76
Duration of chest tube (day)	4 (0–39)	4 (2–35)	4 (2–35)	5 (2–17)	0.27	0.61
Length of hospital stay (day)	6 (3–100)	7 (3–71)	8 (3–71)	7 (3–20)	0.05	0.28
Thoracotomy conversion	23 (5.8)	9 (8.9)	7 (10.0)	2 (6.5)	0.23	0.56
Postoperative complication						
Bleeding control	2 (0.5)	1 (1.0)	1 (1.4)	0	0.52	0.49
Cardiovascular	0	1 (1.0) ^{c)}	1 (1.4) ^{c)}	0	0.047	0.50
Atrial fibrillation	4 (1.0)	6 (5.9)	3 (4.3)	3 (9.7)	0.002	0.29
Cerebrovascular	1 (0.3) ^{d)}	1 (1.0) ^{e)}	0	1 (3.2) ^{e)}	0.29	0.14
Pneumonia	21 (5.3)	8 (7.9)	7 (10.0)	1 (3.2)	0.31	0.25
Vocal fold palsy	7 (1.8)	1 (1.0)	1 (1.4)	0	0.58	0.50
Chylothorax	8 (2.0)	0	0	0	0.15	-
Prolonged air-leak	21 (5.3)	7 (6.9)	4 (5.7)	3 (9.7)	0.52	0.47
Acute kidney injury	2 (0.5)	1 (1.0)	1 (1.4)	0	0.57	0.50
Empyema	1 (0.3)	0	0	0	0.61	-

Values are presented as number, median (range), or number (%).

^{a)}Comparison between antiplatelet non-users and antiplatelet users. ^{b)}Comparison between the antiplatelet discontinuation and maintenance groups.

^{c)}ST-elevation myocardial infarction. ^{d)}Transient ischemic attack. ^{e)}Ischemic cerebral stroke preceded by temporary atrial fibrillation.

Discussion

The current study showed that continuation of antiplatelet therapy did not lead to an increase in intraoperative or postoperative bleeding in patients taking antiplatelet medi-

cation. Furthermore, the incidence of bleeding in patients on antiplatelet therapy was not elevated when compared to patients not on such medication. Also, there was no significant difference in cardiovascular or cerebrovascular complications between patients who discontinued their anti-

platelet therapy and those who maintained it.

Lung cancer predominantly affects the elderly population, and a considerable number of these geriatric patients are on antiplatelet therapy. This treatment is often prescribed for atherosclerotic diseases in various organs or as a preventive measure. Our study found that around 20% of elderly patients undergoing lung cancer surgery were taking antiplatelets.

Antiplatelets are a double-edged sword in surgery. Their perioperative use can compromise hemostasis and heighten the risk of bleeding both during and after surgery. Conversely, halting antiplatelet therapy may increase the likelihood of acute thrombotic events, potentially resulting in severe outcomes such as myocardial infarction or stroke. Most guidelines advocate for the continuation of aspirin therapy throughout the perioperative period in patients with a history of cardiovascular disease, assuming the surgeon considers the elevated risk of bleeding to be manageable [10]. The American College of Cardiology/American Heart Association guidelines further recommend sustaining aspirin therapy for the entire perioperative period and, ideally, maintaining dual antiplatelet therapy unless surgical requirements dictate otherwise. If clopidogrel is stopped prior to surgery, it is advised to restart it promptly, ideally within 24 hours postoperatively [11]. Nevertheless, the evaluation of bleeding risk often falls to the surgeon's judgment, leaving thoracic surgeons with the challenging decision of whether to continue or discontinue antiplatelet therapy.

Bleeding is a major concern for thoracic surgeons. Previous studies have produced conflicting results regarding the risk of bleeding associated with the use of preoperative antiplatelet agents. For instance, the Perioperative Ischemic Evaluation-2 (POISE-2) study found an increased risk of major bleeding in the aspirin group compared to the placebo group during non-cardiac surgery, with a hazard ratio of 1.23 (95% confidence interval, 1.01–1.49) [12]. Conversely, a prospective randomized study that included 666 patients on antiplatelet therapy scheduled for non-cardiac surgery did not observe a statistically significant difference in the incidence of significant bleeding requiring transfusion [13]. A meta-analysis also suggested that aspirin use heightened the risk of bleeding, ranging from 2.5% to 20%, but did not increase patient mortality or morbidity rates [14]. The findings of our study further corroborate the safety of perioperative antiplatelet therapy. In our current research, continuing antiplatelet therapy during lung cancer surgery did not lead to an increase in intraoperative or postoperative bleeding, nor did it raise the risk of bleed-

ing-related complications, such as estimated blood loss, total drainage volume, or the necessity for transfusions, compared to discontinuing antiplatelet therapy. Moreover, the bleeding outcomes in the antiplatelet group were not significantly different from those in the group not receiving antiplatelet therapy. Even in patients with extensive pleural adhesion, antiplatelet therapy did not increase the risk of intraoperative bleeding in our study. The amounts of bleeding were comparable between groups A and N, as well as between groups Ai and Am. In conclusion, bleeding during non-cardiac surgery is generally considered a minor complication.

The current standard method for lung cancer surgery is a minimally invasive approach, which may reduce the risk of bleeding, even when antiplatelet agents are used perioperatively. However, there is a concern that antiplatelet use could increase intraoperative bleeding, potentially necessitating a conversion to thoracotomy. Yu and Lee [15] reported that continuing antiplatelet therapy did not result in increased operation time, estimated blood loss, transfusion requirements, postoperative complications, or, notably, thoracotomy conversion rates in patients undergoing thoracoscopic surgery for lung cancer. In our study, approximately 90% of patients underwent minimally invasive surgery, with an overall conversion rate of about 7.8%. There were no significant differences in intraoperative estimated blood loss and conversion rates between the antiplatelet group and the non-antiplatelet group, nor between the maintenance and interruption groups. These findings suggest that perioperative continuation of antiplatelet therapy may not significantly increase the technical challenges of minimally invasive surgery, and that such surgery can be safely performed with perioperative antiplatelet therapy.

The primary purpose of maintaining antiplatelet therapy in the perioperative period is to prevent thrombotic complications related to underlying diseases. Several studies have reported that a short-term interruption of antiplatelet therapy did not increase the risk of thrombotic complications. The POISE-2 study found that discontinuing aspirin during non-cardiac surgery did not increase the risk of stroke or myocardial infarction [12]. Lewis et al. [13] reported no significant difference in mortality rates between patients who continued or discontinued antiplatelet therapy for up to 6 months after surgery. In our study, the incidence rates of thrombotic complications were not different between the maintenance and interruption groups. This finding suggests that interrupting antiplatelet therapy is safe, and maintaining antiplatelet therapy might not be as effective as expected. However, guidelines recommend

maintaining antiplatelet therapy because thrombotic complications are more serious and can result in long-term sequelae or death. A Korean nationwide study showed that interrupting antiplatelet therapy during pulmonary resection increases the risk of major adverse cardiac events (MACE) [16]. Additionally, interruption of antiplatelet therapy within the first month after percutaneous coronary intervention (PCI) is known to be significantly associated with an increased MACE rate [17]. Thrombotic complications in our study also resulted in severe complications. A patient in the interruption group, who had a history of 4 stent insertions due to 2-vessel coronary artery occlusive disease 11 years prior to lung cancer surgery, experienced an STEMI due to occlusion of a previous stent and had to undergo urgent PCI (Clavien-Dindo classification grade 3a). There were no severe thrombotic complications in the maintenance group, except for 1 transient ischemic attack presenting with right hemianopsia (Clavien-Dindo classification grade 2) in a patient who had undergone PCI 14 years ago. Lung cancer is a well-recognized risk factor for ischemic strokes [18]. Previous studies have indicated that the cumulative stroke incidence in lung cancer patients was reported to be 5.1% [19]. Therefore, maintaining antiplatelet therapy during the perioperative period would be a safer strategy in lung cancer surgery.

Atrial fibrillation is a common early postoperative complication following lung cancer surgery, with an incidence rate of approximately 10% to 20% [20]. This incidence varies depending on the extent of lung resection: rates are lower for wedge resection (2%–4%), intermediate for lobectomy (10%–15%), and higher for pneumonectomy (over 20%) [21]. Known risk factors for postoperative atrial fibrillation include heart failure, hypertension, a history of myocardial infarction, and male gender [22]. In our study, the overall rate of atrial fibrillation was 2.5% (10 out of 398 patients), with a significantly higher incidence in group A compared to group N (5.9% versus 1.0%, $p=0.002$). This disparity is likely due to the greater number of males, the higher prevalence of hypertension, and the substantial number of patients with pre-existing cardiovascular diseases in group A. There was no significant difference in the incidence of atrial fibrillation between groups Am and Ai.

Prolonged air leak was the second most common postoperative complication observed in this study. It occurred more frequently in group A (6.9%) compared to group N (5.3%), and in group Ai (5.7%) compared to group Am (9.7%), although these differences were not statistically significant. Aspirin, a non-steroidal anti-inflammatory drug

(NSAID), is known to reduce protective prostaglandins and inhibit mucosal cyclooxygenase-1 activity, while also interfering with mucosal restitution in animal models [23]. Consequently, the use of NSAIDs is generally discouraged in pleurodesis, as they can inhibit the inflammatory response that is essential for pleural symphysis [24]. Therefore, the higher incidence of prolonged air leak in the maintenance group may be attributed to delayed pleural healing. Further preclinical and large-scale prospective clinical studies are needed to confirm this observation.

There are several limitations in this study. First, the study's retrospective nature and single-institution design may have introduced selection bias in the decision-making process regarding perioperative antiplatelet use. Second, the small sample size of patients in group Ai, coupled with the low incidence of MACEs (only 3 cases), limited the statistical power of the analysis, particularly for subgroup evaluations based on disease severity. Third, the variability in disease severity among participants presents another limitation. Approximately 10% of patients in the antiplatelet group were presumed to have low-risk cardiovascular disease, and around 30% were taking antiplatelets prophylactically without a documented history of atherosclerotic disease. The inclusion of these low-risk individuals in the study group may have skewed the results towards more favorable outcomes. Nevertheless, it is plausible to suggest that the study mirrors the real-world clinical setting, and the findings offer valuable insights, given that such limitations are often unavoidable in everyday practice.

In conclusion, the maintenance of antiplatelet therapy was found to be safe in terms of bleeding and postoperative MACEs in elderly lung cancer surgery patients. Therefore, it is recommended to maintain antiplatelet therapy during lung cancer surgery.

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Conflict of interest

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References

1. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. *Contemp Oncol (Pozn)* 2021;25:45-52. <https://doi.org/10.5114/wo.2021.103829>
2. Venuta F, Diso D, Onorati I, Anile M, Mantovani S, Rendina EA. Lung cancer in elderly patients. *J Thorac Dis* 2016;8(Suppl 11):S908-14. <https://doi.org/10.21037/jtd.2016.05.20>
3. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res* 2012;111:245-59. <https://doi.org/10.1161/circresaha.111.261388>
4. Jonsson F, Yin L, Lundholm C, Smedby KE, Czene K, Pawitan Y. Low-dose aspirin use and cancer characteristics: a population-based cohort study. *Br J Cancer* 2013;109:1921-5. <https://doi.org/10.1038/bjc.2013.411>
5. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e89S-e119S. <https://doi.org/10.1378/chest.11-2293>
6. Kim DH, Daskalakis C, Silvestry SC, et al. Aspirin and clopidogrel use in the early postoperative period following on-pump and off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2009;138:1377-84. <https://doi.org/10.1016/j.jtcvs.2009.07.027>
7. Ferraris VA, Saha SP, Oestreich JH, et al. 2012 Update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012;94:1761-81. <https://doi.org/10.1016/j.athoracsur.2012.07.086>
8. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007;99:316-28. <https://doi.org/10.1093/bja/aem209>
9. Cassiano F, Menna C, Andreotti C, Ibrahim M. Major thoracic surgery in patients under antiplatelet therapy. *Transl Cancer Res* 2016;5(Suppl 7):S1473-5. <https://doi.org/10.21037/tcr.2016.12.64>
10. Gerstein NS, Albrechtsen CL, Mercado N, Cigarroa JE, Schulman PM. A comprehensive update on aspirin management during noncardiac surgery. *Anesth Analg* 2020;131:1111-23. <https://doi.org/10.1213/ane.0000000000005064>
11. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 2016;134:e123-55. <https://doi.org/10.1161/cir.0000000000000404>
12. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014;370:1494-503. <https://doi.org/10.1056/nejmoa1401105>
13. Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev* 2018;7:CD012584. <https://doi.org/10.1002/14651858.cd012584.pub2>
14. Burger W, Chemnitz JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention: cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation. Review and meta-analysis. *J Intern Med* 2005;257:399-414. <https://doi.org/10.1111/j.1365-2796.2005.01477.x>
15. Yu WS, Lee CY. Safety of perioperative low dose aspirin therapy in major lung resection. *J Thorac Dis* 2019;11(Suppl 15):S1897-9. <https://doi.org/10.21037/jtd.2019.08.43>
16. Yoon DW, Shin DW, Cho JH, et al. Impact of previous percutaneous coronary intervention on cardiovascular outcomes and mortality after lung cancer surgery: a nationwide study in Korea. *Thorac Cancer* 2020;11:2517-28. <https://doi.org/10.1111/1759-7714.13563>
17. Egholm G, Thim T, Olesen KK, et al. Dual anti-platelet therapy after coronary drug-eluting stent implantation and surgery-associated major adverse events. *Thromb Haemost* 2016;116:172-80. <https://doi.org/10.1160/th15-12-0954>
18. Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol* 2017;70:926-38. <https://doi.org/10.1016/j.jacc.2017.06.047>

19. Navi BB, Reiner AS, Kamel H, et al. Association between incident cancer and subsequent stroke. *Ann Neurol* 2015;77:291-300. <https://doi.org/10.1002/ana.24325>
20. Dobrev D, Aguilar M, Heijman J, Guichard JB, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol* 2019;16:417-36. <https://doi.org/10.1038/s41569-019-0166-5>
21. Semeraro GC, Meroni CA, Cipolla CM, Cardinale DM. Atrial fibrillation after lung cancer surgery: prediction, prevention and anticoagulation management. *Cancers (Basel)* 2021;13:4012. <https://doi.org/10.3390/cancers13164012>
22. Yamashita K, Hu N, Ranjan R, Selzman CH, Dossdall DJ. Clinical risk factors for postoperative atrial fibrillation among patients after cardiac surgery. *Thorac Cardiovasc Surg* 2019;67:107-16. <https://doi.org/10.1055/s-0038-1667065>
23. Freeman LC, Narvaez DF, McCoy A, et al. Depolarization and decreased surface expression of K⁺ channels contribute to NSAID-inhibition of intestinal restitution. *Biochem Pharmacol* 2007;74:74-85. <https://doi.org/10.1016/j.bcp.2007.03.030>
24. Lardinois D, Vogt P, Yang L, Hegyi I, Baslam M, Weder W. Non-steroidal anti-inflammatory drugs decrease the quality of pleurodesis after mechanical pleural abrasion. *Eur J Cardiothorac Surg* 2004;25:865-71. <https://doi.org/10.1016/j.ejcts.2004.01.028>