Should all patients receive extended thromboprophylaxis after resection of primary lung cancer?

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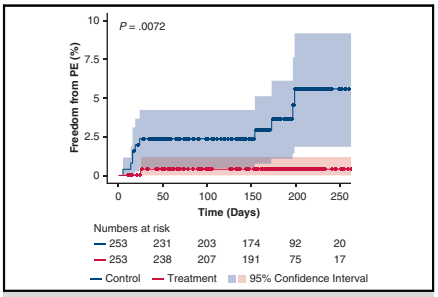
ABSTRACT

Objective: The optimal duration of thromboprophylaxis in patients undergoing resection of primary lung cancer is not known. We investigated the incidence of pulmonary emboli and venous thromboembolism in patients undergoing early-stage lung cancer resection and the impact of change from short duration to extended thromboprophylaxis.

Methods: We reviewed the outcomes of consecutive patients who underwent resection of early-stage primary lung cancer following a change in protocol from inpatient-only to extended thromboprophylaxis to 28 days. Propensity-score matching of control (routine inpatient pharmacologic thromboprophylaxis) and treatment group (extended pharmacologic thromboprophylaxis) was performed. Adjustment for covariates based on the Caprini risk assessment model was undertaken. Thromboembolic outcomes were compared between the 2 groups.

Results: Seven hundred fifty consecutive patients underwent resection of primary lung cancer at Oxford University Hospitals NHS Foundation Trust between January 2013 and December 2018. Six hundred patients were included for analysis and propensity-score matching resulted in 253 matched pairs. Extended prophylaxis was associated with a significant reduction in pulmonary emboli (10 of 253 patients [4%] vs 1 of 253 patients [0.4%], $P = .01$). One patient (0.4%) developed a bleeding complication within the treatment cohort. Multivariable logistic regression model demonstrated that extended thromboprophylaxis was independently associated with a reduction in postoperative pulmonary emboli.

Conclusions: Patients undergoing lung cancer resection surgery are at moderate-to-high risk of postoperative thromboembolic disease. Extended dalteparin for 28 days is safe and is associated with reduced incidence of pulmonary embolus in patients undergoing resection of early-stage primary lung cancer. (J Thorac Cardiovasc Surg 2022;164:1603-11)



Extended thromboprophylaxis was associated with reduced incidence of postoperative PE.

CENTRAL MESSAGE

A change from inpatient only to extended pharmacologic thromboprophylaxis was associated with reduced incidence of pulmonary emboli in patients undergoing resection of primary lung cancer.

PERSPECTIVE

Patients undergoing lung cancer resection surgery are at high risk of postoperative venous thromboembolism. The role and optimal duration of extended thromboprophylaxis in patients undergoing thoracic surgery remain uncertain. We demonstrated that extended thromboprophylaxis with 28 days of dalteparin is safe and is associated with reduced incidence of postoperative pulmonary emboli.

See Commentary on page 1612.

Patients undergoing lung cancer resection surgery are at increased risk of postoperative venous thromboembolic (VTE) events, with a reported incidence ranging from 1.6% to 17.9%, and the majority of these events occur after hospital discharge.[1,2] VTE following lung cancer resection is associated with early morbidity and mortality and

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Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
DVT = deep-vein thrombosis
IU = international units
LMWH = low molecular weight heparin
LRTI = lower respiratory tract infection
OR = odds ratio
PE = pulmonary embolism
RAM = risk assessment model
SMD = standardized mean difference
VTE = venous thromboembolism/ thromboembolic

Scanning this QR code will take you to the table of contents to access supplementary information.

reduced survival at a year.[2] This may be related to hypercoagulability secondary to overexpression of tissue factor by malignant cells but may also be influenced by other risk factors, including prolonged operative time, older age, obesity, and pneumonectomy.[1,3] Currently, most VTE prevention guidelines recommend routine inpatient prophylactic low molecular weight heparin (LMWH) in thoracic surgery patients at moderate-to-high VTE risk, with some guidelines recommending consideration of pharmacologic VTE prophylaxis for 7 days within the postoperative period.[4-6]

In major abdominal or pelvic oncological surgery, the role of extended pharmacologic thromboprophylaxis is well-established in reducing the incidence of postoperative VTE compared with shorter regimens.[7] The National Institute for Health and Care Excellence, American Society of Clinical Oncology, and American College of Chest Physicians currently recommend the use of extended prophylaxis with LMWH for up to 4 weeks in these patients.[4-6] By contrast, the role of extended thromboprophylaxis in patients undergoing thoracic surgery remains uncertain. A tailored approach of pharmacologic VTE prophylaxis via a VTE risk assessment model (RAM), the Caprini RAM, showed a nonsignificant downward trend in VTE events in patients who received extended pharmacologic thromboprophylaxis, suggesting a potential role for extended VTE prophylaxis in a thoracic surgery patient cohort.[8,9] We evaluated the incidence of PE and VTE in patients undergoing lung cancer resection and investigated the safety and efficacy of extended pharmacologic thromboprophylaxis in these patients.

METHODS

Study Design and Patient Characteristics

We retrospectively reviewed the outcomes of consecutive patients who underwent resection of early-stage primary lung cancer at Oxford University Hospitals NHS Foundation Trust, United Kingdom, between January 2013 and December 2018 to evaluate the incidence of PE (primary outcome) and VTE (secondary outcome). In July 2016, a change in protocol from inpatient only to postoperative extended VTE prophylaxis with 28 days of dalteparin was instituted within our thoracic surgery department.

Patients were analyzed according to whether they received inpatient only (control group) or extended pharmacological thromboprophylaxis (treatment group). Our routine inpatient care included an Enhanced Recovery After Surgery protocol where patients were admitted on the day of surgery. A VTE risk assessment was undertaken on admission and subcutaneous prophylactic weight-adjusted dose of dalteparin administered, in accordance with hospital guidelines, providing there were no contraindications.[10] First dose of inpatient thromboprophylaxis was administered in all patients on the evening after their operation. The majority of patients (those weighing between 40 and 120 kg) received 5000 international units (IU) once daily. In patients weighing between 120 and 150 kg, 7500 IU was administered and in those weighing more than 150 kg, 5000 IU twice daily was indicated. All patients donned Thrombo-Embolus Deterrent stockings as mechanical thromboprophylaxis in both preoperative and postoperative settings unless contraindicated; contraindications included skin disease, peripheral vascular disease, or in the absence of appropriate sizing. In addition, patients received intraoperative intermittent pneumatic compression device application.

In the treatment group, dalteparin administration was continued beyond hospital discharge to a total of 28 days from the date of surgery. Before discharge, education on subcutaneous administration of dalteparin was provided to patients by nursing staff or hospital pharmacist. Patients with a prolonged hospital admission exceeding the 28-day prophylaxis period had routine thromboprophylaxis until discharge and were included in the treatment group. Patients who returned to the operating theater for bleeding and patients with previous history of VTE or hypercoagulable conditions were included in the protocol.

Patient demographics and baseline characteristics, including medical comorbidities, smoking history, body mass index, histopathology report, and World Health Organization performance status were included for analysis. Lung cancer was staged using the American Joint Committee on Cancer 8th edition lung cancer staging.[11] Type of surgery was designated as sublobar resection, lobectomy, bilobectomy, extended resection, or pneumonectomy. Surgical approach was video-assisted thoracoscopic surgery or open thoracotomy. Postoperative hemorrhagic complications were recorded and classified according to the Clavien–Dindo grading of surgical complications via review of medical records and electronic patient records.[12]

Caprini RAM scores were retrospectively calculated to assess the risk of VTE. In all patients, duration of surgery exceeded 45 minutes and all patients had lung malignancy. Patients were considered low risk if their Caprini score was <4, moderate risk if score was 5 to 8, and high risk if score was 9 or greater.[13] Lower respiratory tract infections (LRTIs) were defined as postoperative evidence of clinical, biochemical, or radiologic changes consistent with LRTI which warranted treatment with antibiotics.

Patients with a bleeding disorder, patients established on long-term anticoagulation with either a direct oral anticoagulant or warfarin before the operation, and patients commenced on chronic anticoagulation

postoperatively were excluded from our extended thromboprophylaxis protocol. Patients who died from non–VTE-related causes within 6 months of the postoperative period and patients lost to follow-up were excluded from analysis.

Diagnosis of VTE

Diagnosis of VTE, which included both deep vein thrombosis (DVT) and pulmonary embolism (PE), was made on either ultrasound Doppler, computed tomography (CT) pulmonary angiogram performed due to clinical suspicion of PE or follow-up contrast-enhanced CT (chest, abdomen, and pelvis) or CT of the chest at 6 months after surgery as part of our institutional CT follow-up program.[14] To account for logistics of patients and institutional factors on the organization of scans, we analyzed patient scans for up to 9 months postoperatively. Patients who underwent imaging before 28 days due to clinical suspicion of VTE and were found to be VTE negative had results of their repeat imaging after 28 days and up to 9 months reviewed to confirm there was no VTE incidence following the extended period of thromboprophylaxis.

A diagnosis of DVT included acute thrombosis of lower-extremity veins (iliac, femoral, popliteal or calf veins) or upper-extremity veins (axillary, subclavian, brachial or internal jugular veins) and PE was defined as acute thrombosis within the pulmonary vasculature. All detected VTE events were symptomatic unless stated otherwise. When the site of thrombosis correlated with the surgical site, a diagnosis of in situ thrombus was made on a balance of probability by a consultant chest radiologist, based on anatomical location in relation to the site of resection, particularly if the area in question represented an isolated filling defect. Where diagnostic doubt remained and the patient was clinically unwell, CT pulmonary angiogram was performed. In situ thrombi were not considered as VTE events and hence were not treated with anticoagulation. Death from VTE was defined as mortality within 10 days of diagnosis of symptomatic VTE event with no alternative attributable primary cause of death.

Statistical Analysis

Data analysis was undertaken using R statistical software, version 4.0.3 (R Foundation for Statistical Computing).[15] Continuous variables were tested for normality using the Kolmogorov–Smirnov test and expressed as either mean ± standard deviation or median ± interquartile range. Categorical variables were expressed as frequencies and relative percentages.

Propensity-score matching of the control and treatment group was performed by using a logistic regression propensity score. Covariates were determined based on the individual risk factors laid out in the Caprini RAM. One-to-one matching without replacement was performed using nearest-neighbor strategy with caliper width equal to 0.2 sigma.[16] A standardized mean difference (SMD) of <10% between the covariates was deemed to be sufficiently balanced. Sensitivity analysis for unmeasured confounding was performed by calculating the E-value.[17]

Comparative analysis between the 2 groups was performed using the Fisher exact test and χ^2 test for categorical variables and Mann–Whitney *U* test for nonparametric continuous data. Statistical analysis was performed before and after matching. In the matched cohort, we performed a univariable and multivariable logistic regression model using a stepwise approach to evaluate the association of extended thromboprophylaxis with VTE incidence adjusted for each Caprini risk factor. The Hosmer–Lemeshow statistic was used to measure goodness of fit. Cumulative incidence curves of PE and VTE between the 2 matched groups were plotted and compared using the log-rank test.

As our study was an evaluation of our standard of care, ethical approval is not required in our Institution. The study was approved by the audit office of Oxford University Hospitals NHS Foundation Trust, United Kingdom.

RESULTS

Between January 2013 and December 2018, 750 consecutive patients with primary lung cancer underwent resection. In total, 150 patients were excluded from analysis, resulting in 600 patients for analysis, 297 in the control group and 303 in the treatment group (Figure 1). Patient characteristics and demographics are shown in Table 1. Propensity-matched cohorts consisted of 253 patients in each group. Good balance with SMD <10% across matched covariates was achieved, with the exception of surgical access and acute kidney injury (Table 1).

In the unmatched cohort, 15 (2.5%) VTE events were recorded, 11 (3.7%) in the control group and 4 (1.3%) in the treatment group. After matching, 1 VTE event was removed from each group, resulting in a total of 13 (2.6%) VTE events for analysis, 10 (4.0%) in the control group and 3 (1.2%) in the treatment group (Table 2). All 10 VTE events in the control group were PE, 6 within 28 days of the postoperative period, 1 at 5 months, and 3 at 6 months. Three VTE events recorded in the treatment group comprised 1 PE and 2 DVT. The recorded PE occurred within 28 days

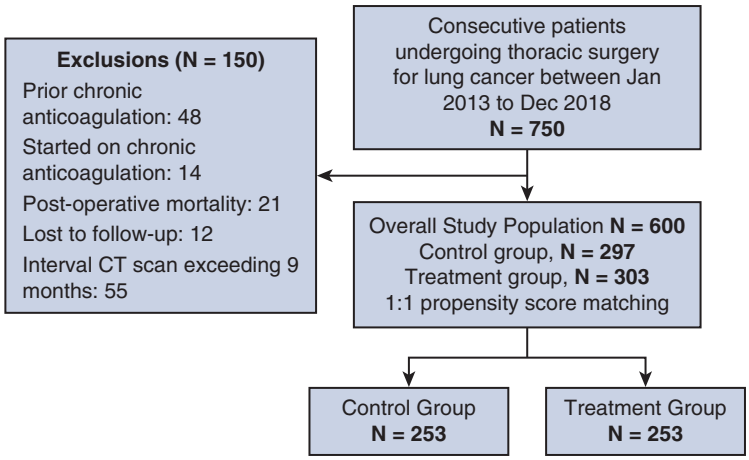

FIGURE 1. Flow diagram of the patient population. *CT*, Computed tomography.

TABLE 1. Summary of patient demographics, baseline characteristics, and postoperative variables before and after propensity score matching

Variables	All patients (n = 600)	Unmatched			Matched		
		Control group (n = 297)	Treatment group (n = 303)	SMD (%)	Control group (n = 253)	Treatment group (n = 253)	SMD (%)
Age, y, mean ± SD	69 ± 9	69 ± 9	69 ± 10	2.0	69 ± 9	69 ± 10	2.2
Female	311 (51.8%)	151 (50.8%)	160 (52.8%)	3.9	132 (52.2%)	129 (51.0%)	–2.4
WHO performance status							
0	443 (73.8%)	224 (75.4%)	219 (72.3%)	–7.0	188 (74.3%)	189 (74.7%)	0.9
1	145 (24.2%)	69 (23.2%)	76 (25.1%)	4.3	61 (24.1%)	61 (24.1%)	0
2	12 (2.0%)	4 (1.3%)	8 (2.6%)	8.1	4 (1.6%)	3 (1.2%)	–2.5
Histopathology							
Adenocarcinoma	393 (65.5%)	191 (64.3%)	202 (66.7%)	5.0	177 (70.0%)	189 (70.3%)	1.7
Squamous cell carcinoma	132 (22.0%)	71 (23.9%)	61 (20.1%)	–9.4	51 (20.2%)	56 (20.8%)	–2.0
Large cell carcinoma	15 (2.5%)	10 (3.4%)	5 (1.7%)	–13.5	6 (2.4%)	4 (1.5%)	–3.1
Small cell carcinoma	6 (1.0%)	5 (1.7%)	1 (0.3%)	–23.6	1 (0.4%)	1 (0.4%)	0
Other or mixed	54 (9.0%)	20 (6.7%)	34 (11.2%)	14.2	18 (7.1%)	19 (7.1%)	1.3
Type of surgery							
Lobectomy	459 (76.5%)	218 (73.4%)	241 (79.5%)	15.2	197 (77.9%)	206 (81.4%)	8.8
Sublobar resection	95 (15.8%)	59 (19.9%)	36 (11.9%)	–24.7	41 (16.2%)	34 (13.4%)	–8.6
Bilobectomy	16 (2.7%)	8 (2.7%)	8 (2.6%)	–0.3	6 (2.4%)	6 (2.4%)	0
Extended resection	13 (2.2%)	8 (2.7%)	5 (1.7%)	–8.1	5 (2.0%)	5 (2.0%)	0
Pneumonectomy	17 (2.8%)	4 (1.3%)	13 (4.3%)	14.5	4 (1.6%)	2 (0.8%)	–3.9
Surgical access							
VATS	414 (69.0%)	190 (64.0%)	224 (73.9%)	22.6	170 (67.2%)	197 (77.9%)	24.1
Open	186 (31.0%)	107 (36.0%)	79 (26.1%)	–	83 (32.8%)	56 (22.1%)	–
Cancer stage*							
Tis	11 (1.8%)	6 (2.0%)	5 (1.7%)	–2.9	6 (2.4%)	5 (2.0%)	–3.1
IA1	63 (10.5%)	28 (9.4%)	35 (11.6%)	6.6	26 (10.3%)	27 (10.7%)	1.2
IA2	142 (23.7%)	75 (25.3%)	67 (22.1%)	–7.6	66 (26.1%)	60 (23.7%)	–5.7
IA3	110 (18.3%)	50 (16.8%)	60 (19.8%)	7.5	47 (18.6%)	49 (19.4%)	2.0
IB	63 (10.5%)	29 (9.8%)	34 (11.2%)	4.6	26 (10.3%)	29 (11.5%)	3.8
IIA	29 (4.8%)	13 (4.4%)	16 (5.3%)	4.0	12 (4.7%)	13 (5.1%)	1.8
IIB	95 (15.8%)	53 (17.8%)	42 (13.9%)	–11.5	41 (16.2%)	37 (14.6%)	–4.6
IIIA	72 (12.0%)	37 (12.5%)	35 (11.6%)	–2.8	25 (9.9%)	26 (10.3%)	1.2
IIIB	12 (2.0%)	4 (1.3%)	8 (2.6%)	8.1	3 (1.2%)	6 (2.4%)	7.4
IVA	3 (0.5%)	2 (0.7%)	1 (0.3%)	–6.0	1 (0.4%)	1 (0.4%)	0
BMI, kg/m^2, median ± IQR†	24.8 ± 7.0	24.6 ± 8.0	24.8 ± 6.6	–	24.7 ± 8.1	24.2 ± 6.2	–
BMI >30 kg/m^2	97	40 (13.5%)	57 (18.8%)	14.6	38 (15.0%)	35 (13.8%)	–3.0
Comorbidities							
COPD	149 (24.9%)	80 (26.9%)	69 (22.8%)	9.6	62 (24.5%)	62 (24.5%)	0
Inflammatory bowel disease	3 (0.5%)	2 (0.7%)	1 (0.3%)	4.9	1 (0.4%)	1 (0.4%)	0
Previous VTE	8 (1.3%)	3 (1.0%)	5 (1.7%)	5.6	2 (0.8%)	2 (0.8%)	0
Cardiovascular disease‡	277 (46.2%)	129 (43.4%)	148 (48.8%)	10.9	113 (44.7%)	124 (49.0%)	8.7
Previous/ongoing other malignancy	136 (22.7%)	65 (21.9%)	71 (23.4%)	3.7	51 (20.2%)	61 (24.1%)	9.5
Estimated smoking pack y, median ± IQR§	30 ± 29	30 ± 37	25 ± 25	15.9	30 ± 41	30 ± 27	0
Perioperative oncologic treatment	10 (1.7%)	3 (1.0%)	7 (2.3%)	10.2	3 (1.2%)	3 (1.2%)	0
Postoperative complications							
LRTI	111 (18.5%)	43 (14.5%)	68 (22.4%)	20.6	41 (16.2%)	45 (17.8%)	3.8
Stroke <1 mo onset	5 (0.8%)	4 (1.3%)	1 (0.3%)	11.2	2 (0.8%)	1 (0.4%)	–6.9
Atrial fibrillation	27 (4.5%)	13 (4.4%)	14 (4.6%)	1.2	11 (4.3%)	14 (5.5%)	5.5
Acute kidney injury	13 (2.2%)	3 (1.0%)	10 (3.3%)	15.8	2 (0.8%)	6 (2.4%)	12.7

(Continued)

TABLE 1. Continued

Variables	All patients (n = 600)	Unmatched: Control group (n = 297)	Unmatched: Treatment group (n = 303)	SMD (%)	Matched: Control group (n = 253)	Matched: Treatment group (n = 253)	SMD (%)
Postoperative LOS, d, median ± IQR	5 ± 5	6 ± 4	5 ± 5	1.0	6 ± 5	4 ± 5	–1.3
Caprini RAM score, median ± IQR	7 ± 2	7 ± 1	7 ± 1	0	7 ± 1	7 ± 2	0
Low (≤4)	2 (0.3%)	2 (0.7%)	0	–	2 (0.8%)	0	–
Medium (5-8)	521 (86.8%)	263 (88.6%)	258 (85.1%)	–	222 (87.7%)	227 (89.7%)	–
High (≥9)	77 (12.8%)	32 (10.8%)	45 (14.9%)	–	29 (11.5%)	26 (10.3%)	–
Time to CT, mo, median ± IQR	5 ± 2	6 ± 2	5 ± 2	–	6 ± 2	6 ± 1	–

Covariates used for matching included age, sex, BMI, WHO performance status, histopathology, type of surgery, cancer stage, perioperative oncological treatment, comorbidities (COPD, inflammatory bowel disease and history of previous VTE), postoperative complications (LRTI and stroke <1 month onset), Caprini RAM score, and postoperative length of stay. *SMD*, Standardized mean difference; *SD*, standard deviation; *WHO*, World Health Organization; *VATS*, video-assisted thoracoscopic surgery; *BMI*, body mass index; *IQR*, interquartile range; *COPD*, chronic obstructive pulmonary disease; *VTE*, venous thromboembolism; *LRTI*, lower respiratory tract infection; *LOS*, length of stay; *RAM*, risk assessment model; *CT*, computed tomography. *Cancer staging was based on the 8th Edition American Joint Commission on Cancer (AJCC) TNM system.[11] †There was no BMI record in 45 patients. For the purpose of propensity score matching, median BMI value was imputed for these patients. ‡Cardiovascular diseases included hypertension, ischemic heart disease, and peripheral vascular disease. §There was no documented smoking data in 14 patients. In total, 28 patients were documented as current smokers and 92 as ex-smokers with no record of estimated pack years.

of the postoperative period. Both DVTs were incidental, one of which was an incidental central-line associated thrombus detected on CT chest to investigate chest sepsis at day 27 and the other, an incidental asymptomatic right femoral vein DVT detected during surveillance CT (chest, abdomen, and pelvis) at 6 months.

Following VTE diagnosis, patients were anticoagulated according to local guidelines with either direct oral anticoagulants, warfarin, or subcutaneous dalteparin at weight-adjusted therapeutic doses where oral alternatives were contraindicated. No VTE recurrence following treatment was identified. Patients were followed up by the thrombosis service to determine whether long-term anticoagulation was indicated.

Extended chemoprophylaxis was associated with a significant reduction in the primary outcome of pulmonary embolic events compared with inpatient-only treatment (10 of 253 patients [4%] vs 1 of 253 patients [0.4%],

TABLE 2. Comparison of outcomes between control and treatment group

Variables	Unmatched: Control group (N = 297)	Unmatched: Treatment group (N = 303)	*P* value	Matched: Control group (N = 253)	Matched: Treatment group (N = 253)	*P* value
Pulmonary embolism	11 (3.7%)	2 (0.7%)	.01	10 (4.0%)	1 (0.4%)	.01
Deep-vein thrombosis	0	2 (0.7%)	.50	0	2 (0.8%)	.50
Death related to VTE	4 (1.3%)	0	.06	3 (1.2%)	0	.25
Postoperative mortality related to VTE	2 (0.7%)	0	.24	2 (0.8%)	0	.50
VTE within 28 d	6 (2.0%)	2 (0.7%)	.17	6 (2.4%)	2 (0.8%)	.29
PE within 28 d	6 (2.0%)	1 (0.3%)	.07	6 (2.4%)	1 (0.4%)	.12
Bleeding complications	0	1 (0.3%)	1.00	0	1 (0.3%)	1.00
VTE events	11 (3.7%)	4 (1.3%)	.07	10 (4.0%)	3 (1.2%)	.09
PE	11 (100%)	2 (50.0%)	.06	10 (100%)	1 (33.3%)	.04
DVT	0	2 (50.0%)		0	2 (66.7%)	
VTE within 28 d	6 (54.5%)	2 (50.0%)	1.00	6 (60.0%)	2 (66.7%)	1.00
PE within 28 d	6 (54.5%)	1 (50.0%)	.57	6 (60.0%)	1 (33.3%)	.56
DVT within 28 d	0	1 (50.0%)	.27	0	1 (33.3%)	.23
Time to VTE, d, median ± IQR	24 ± 147	45 ± 65	.56	22 ± 152	27 ± 78	.45
Symptomatic VTE	11 (100%)	2 (50.0%)	.06	10 (100%)	1 (33.3%)	.04
Death related to VTE	4 (36.4%)	0	.27	3 (30.0%)	0	.53

Cohorts before and after propensity score matching are included for comparison. VTE subgroups were analyzed. *VTE*, Venous thromboembolic; *PE*, pulmonary embolism; *DVT*, deep vein thrombosis; *IQR*, interquartile range.

$P = .01$), and a nonsignificant reduction in secondary outcome of overall VTE events (10 of 253 patients [4%] vs 3 of 253 patient [1.2%], $P = .09$). No VTE-associated mortality was observed in the treatment group, whereas 3 VTE-related deaths (1.2%) occurred in the control group ($P = .25$) (Table 2). There was no difference in patient characteristics between patients who developed fatal VTE and those who did not (Table E1). One patient (0.3%) in the treatment group developed upper gastrointestinal bleeding during extended chemoprophylaxis 10 days postoperatively. Endoscopic treatment was successfully instigated to a proximal duodenal (D1) ulcer with no further episodes of bleeding (Clavien–Dindo grade 3a complication).[12] Dalteparin was restarted following cessation of bleeding and patient was discharged 4 days later. There were no further recorded bleeding complications in either group.

Multivariable regression model demonstrated that extended thromboprophylaxis significantly reduced the incidence of postoperative PE (odds ratio [OR], 0.06; 95% confidence interval [CI], 0-0.44, $P = .02$) independent of age, sex, type of surgery, surgical access, histopathology, performance status, chronic obstructive pulmonary disease, postoperative length of stay, and postoperative LRTI. Other/mixed histopathology subtypes of lung cancer (OR, 10.3; 95% CI, 1.5-71.4, $P = .01$ compared with adenocarcinoma) and LRTI (OR, 7.0; 95% CI, 1.4-40.2, $P = .02$) were significant risk factors of postoperative PE (Figure 2).

Cumulative incidences of overall VTE and PE were plotted and demonstrated in Figure 3. Extended treatment was associated with a significant reduction in PE risk over time compared with the control group (log rank $P < .01$) and a nonsignificant reduction in VTE risk over time (log rank $P = .055$) (Figures 3 and 4). The majority of VTE events occurred within the first 28 days after surgery. Interestingly, an increased risk of VTE in both groups at approximately 6 months after the initial operation was also observed.

DISCUSSION

The known high incidence of VTE after major thoracic surgery prompted us to change our thromboprophylaxis protocols in our institution.[2,18] This retrospective, propensity-matched study has demonstrated that extended pharmacologic thromboprophylaxis for 28 days following resection of primary lung cancer is associated with a 10-fold reduction in incidence of PE, compared with the shorter postoperative inpatient regimen. The role for extended thromboprophylaxis in thoracic surgery is increasingly recognized and reinforced by the recent international Delphi consensus, but the ideal thromboprophylactic agent and its optimal duration remain uncertain.[19,20]

The majority of VTE events in our cohort occurred within 28 days of the postoperative period in both groups, consistent with findings in other studies.[2,21] This suggests there

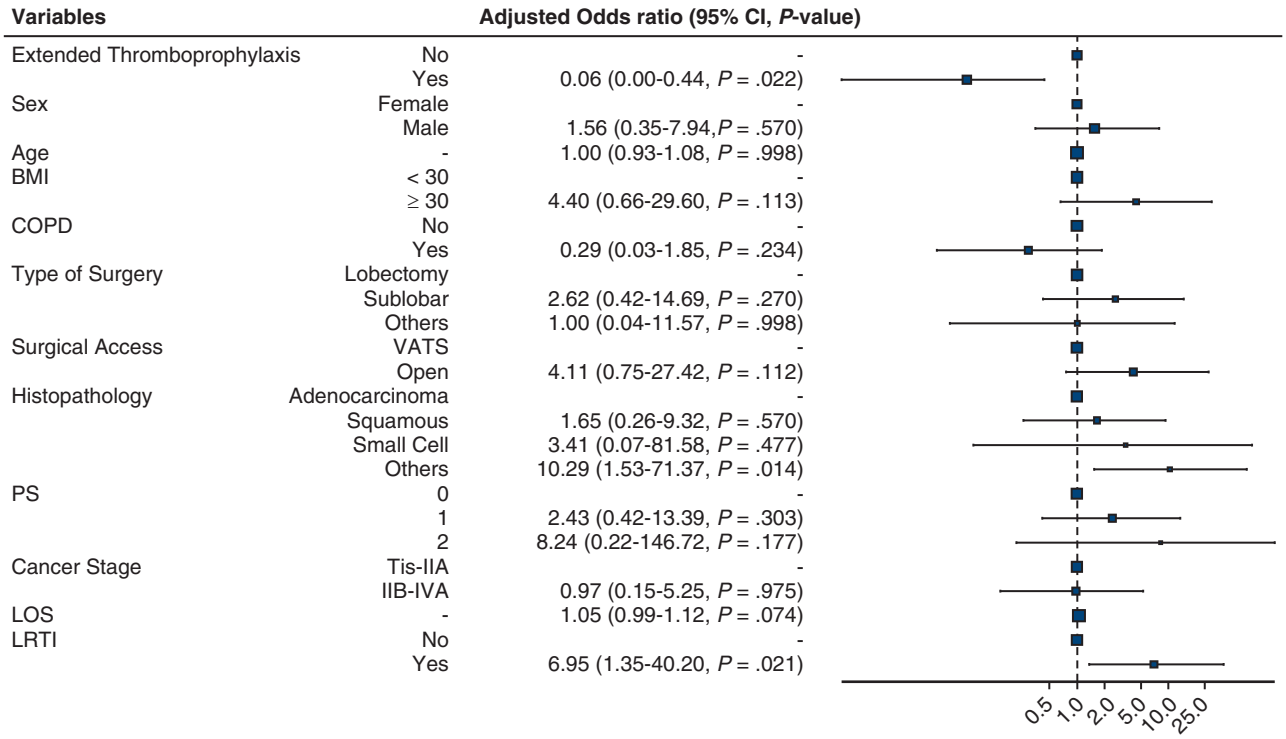

FIGURE 2. Odds ratio plot (and corresponding 95% confidence intervals) to evaluate the association of extended thromboprophylaxis with postoperative PE, adjusted for risk factors in the Caprini RAM. *BMI*, Body mass index; *COPD*, chronic obstructive pulmonary disease; *VATS*, video-assisted thoracoscopic surgery; *PS*, performance status; *LOS*, length of stay; *LRTI*, lower respiratory tract infection.

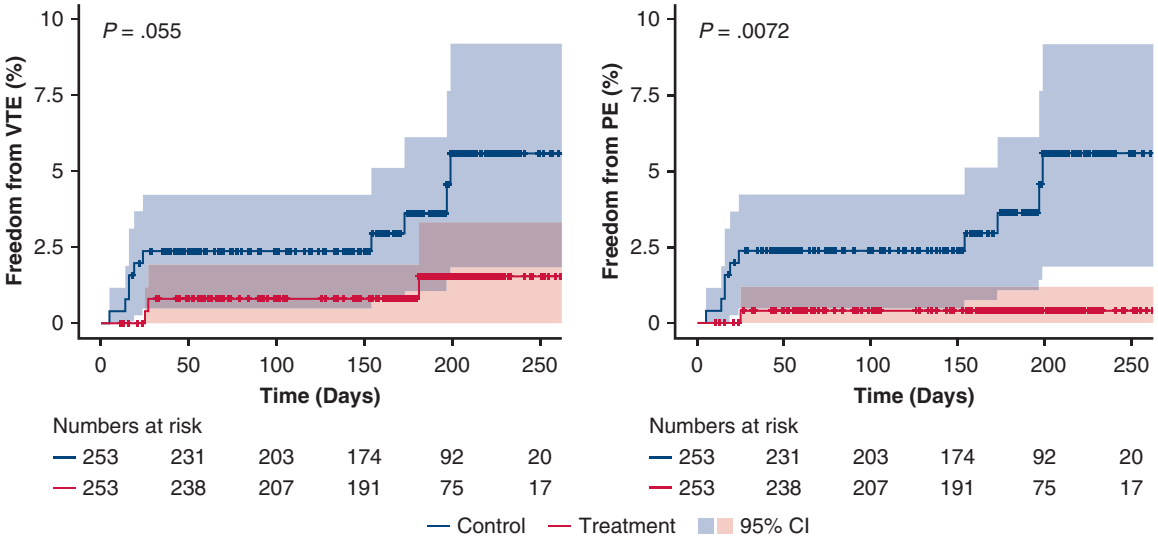

FIGURE 3. Cumulative incidences of VTE (*left*) and PE (*right*) between control and treatment groups with corresponding 95% CIs. *VTE*, Venous thromboembolism; *PE*, pulmonary embolism; *CI*, confidence interval.

may be a critical role for extended thromboprophylaxis. By using rotational thromboelastometry, Mulder and colleagues[22] studied hypercoagulability during the perioperative period in patients with resectable stages of lung cancer. They demonstrated hypercoagulability that persisted for at least 2 weeks following surgical resection. In advanced stages of lung cancer, the risk of VTE increases further.[22] The ambiguity surrounding the optimal duration of extended thromboprophylaxis clearly warrants further research but extended thromboprophylaxis for at least 4 weeks after surgery appears justified.

We observed a second peak in VTE incidence at approximately 6 months following surgery. This may be influenced by factors such as chronic obstructive pulmonary disease, smoking, and the intrinsic procoagulant effects of cancer in the case of patients who develop recurrence.[23] VTE risk appears to be elevated for up to 12 months after surgery, and this is particularly true following cancer-related operations and in cases of incomplete resection.[24] The reasons for a reduced incidence of VTE events beyond 28 days for the duration of the study in the intervention group are not known and it is possible that despite propensity matching, unmeasured differences persist between the groups. A further possible reason is that postdischarge thromboprophylaxis administered either by patients or their relatives has caused an enhanced awareness in this group of patients to the risk of VTE, and there has been additional behavioral change in this group, resulting in a lower incidence of VTE.

Bleeding is a recognized complication associated with anticoagulation and where extended thromboprophylaxis protocols are considered, this will be a concern. We recorded a single bleeding event within our cohort and following cessation of bleeding, LMWH was safely reinstated. While our study design did not screen for bleeding events, a similar safety profile has been demonstrated in other thoracic surgery cohorts and in guidelines involving major abdominal or pelvic surgery where prolonged thromboprophylaxis with LMWH is well-established and routinely used; the benefits of reduced VTE risk were not associated with increasing bleeding complications or mortality.[7-9] Bleeding assessment tools in surgical and oncological patients may be useful in clinical practice and this may be weighed against their postoperative VTE risk,[25]

The role of the Caprini RAM in lung cancer resection surgery may be limited since most patients (up to 99%) have moderate (5-8) to high (≥9) Caprini scores. While a tailored approach of VTE chemoprophylaxis based on the patient's Caprini score has been shown to be effective, there are risk factors specific to lung cancer patients that are not accounted for within the Caprini model.[8,9,13] We identified other/mixed histopathology subtypes as an independent risk factor for postoperative VTE, whereas in other studies, hematologic parameters such as platelet count and operative factors such as pneumonectomy and open approach may also serve predictive roles.[1,3,26] Further research into a specific risk stratification model tailored to thoracic surgery patients may, therefore, be of use to identify patients at greatest risk of VTE and at most benefit from extended thromboprophylaxis.

Our study is subject to the attendant biases of retrospective design. While the postoperative VTE event rate in the study is low, the association of these events with postoperative morbidity and mortality is clinically important. No

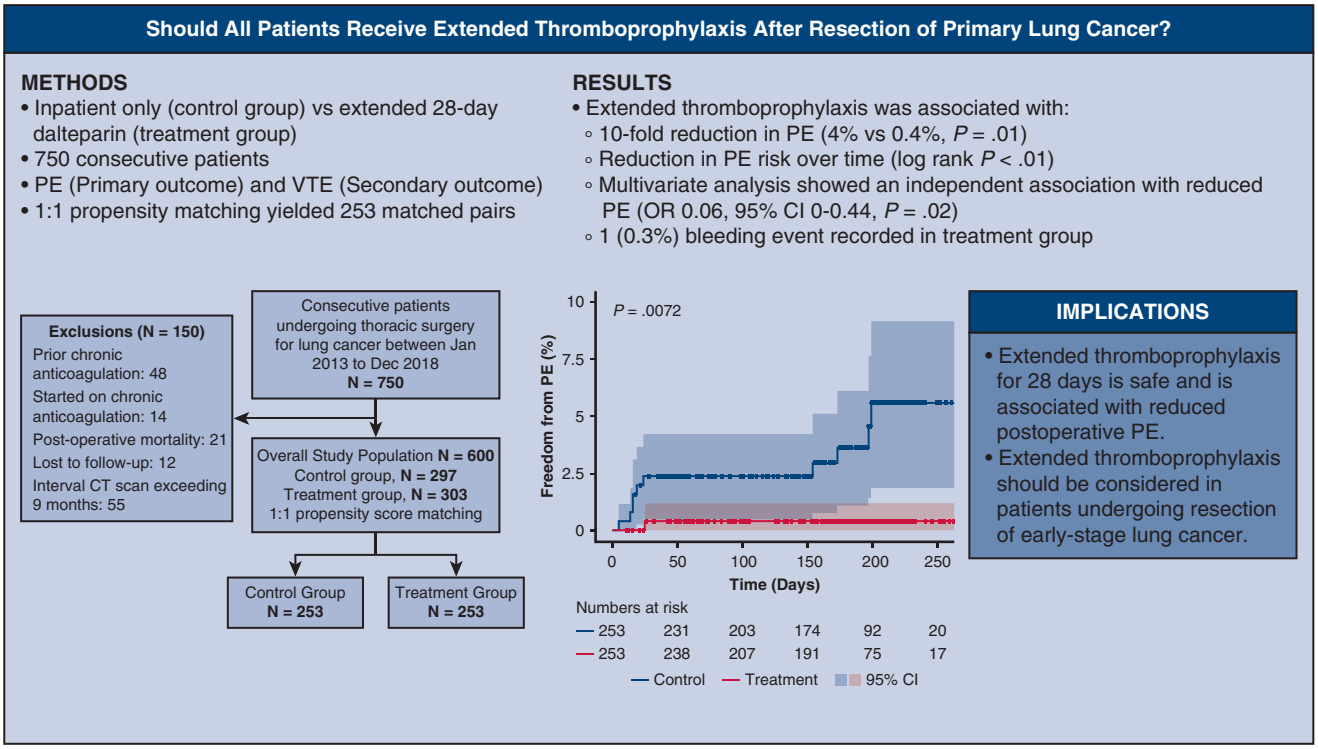

FIGURE 4. Thromboembolic outcomes according to short duration or extended duration thromboprophylaxis in patients who underwent resection of primary lung cancer. *PE*, Pulmonary embolism; *VTE*, venous thromboembolism; *OR*, odds ratio; *CI*, confidence interval; *CT*, computed tomography.

data are available regarding patient compliance with extended thromboprophylaxis however, lack of compliance would serve to underestimate benefit in the extended group. Furthermore, compliance with extended pharmacologic thromboprophylaxis has been shown to be high in other studies.[8] It is possible that subclinical VTE events were not identified but arguably, symptomatic VTEs are of most concern. If this intervention were to be implemented on a larger scale, cost-effectiveness should be considered. Whilst the Caprini RAM and propensity matching process aimed to account for differences between the 2 groups, it remains possible that unaccounted for differences between the groups are an explanation for the greater rate of thromboembolic events beyond the 28 days of extended prophylaxis, in particular SMD of surgical access (video-assisted thoracoscopic surgery vs open) was 24.1%. However, sensitivity analysis for unmeasured confounding with E-value found that moderate confounding would be needed to change our primary outcome result (E-value 19.5, upper confidence limit 1.9).[17] Although variation in ethnicity may account for differences in VTE between groups, ethnicity was White in 97% in a similar institutional surgical cohort.[27] Finally, cancer recurrence rates were not analyzed in our cohort, which may be a contributing factor to VTE events observed several months following resection.

CONCLUSIONS

Patients undergoing lung cancer resection are at moderate-to-high risk of postoperative VTE, with the greatest risk period within the first 28 days following operation. We have demonstrated that extended dalteparin for 28 days is safe and is associated with a significant 10-fold reduction in incidence of PE in patients undergoing resection of early-stage primary lung cancer. We recommend consideration of extended VTE thromboprophylaxis in patients undergoing resection of early-stage lung cancer to reduce important thromboembolic events.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: lung cancer, surgery, thromboprophylaxis, venous thromboembolism

TABLE E1. Fatal VTE versus nonfatal VTE in the matched cohort

Variables	Nonfatal VTE (%)	Fatal VTE (%)
N	10	3
Age, y, median ± IQR	70 ± 13	71 ± 8
Female	5 (50.0)	1 (33.3)
Male	5 (50.0)	2 (66.7)
WHO performance status		
0	5 (50.0)	1 (33.3)
1	5 (50.0)	1 (33.3)
2	0	1 (33.3)
Histopathology		
Adenocarcinoma	3 (30.0)	1 (33.3)
Squamous cell carcinoma	4 (40.0)	1 (33.3)
Small cell carcinoma	1 (10.0)	0
Other or mixed	2 (20.0)	1 (33.3)
Type of surgery		
Lobectomy	5 (50.0)	3 (100)
Sublobar resection	3 (30.0)	0
Others	2 (20.0)	0
Surgical access		
VATS	3 (30.0)	2 (66.7)
Open	7 (70.0)	1 (33.3)
Cancer stage		
Tis-IIA	6 (60.0)	2 (66.7)
IIB-IVA	4 (40.0)	1 (33.3)
Postoperative LOS, median ± IQR	12 ± 16	11 ± 18
BMI > 30 kg/m^2	3 (30.0)	1 (33.3)
COPD	3 (30.0)	1 (33.3)
Previous VTE	1 (10.0)	0
LRTI	7 (70.0)	1 (33.3)

VTE, Venous thromboembolism; *IQR*, interquartile range; *WHO*, World Health Organization; *VATS*, video-assisted thoracoscopic surgery; *LOS*, length of stay; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *LRTI*, lower respiratory tract infection.