Routine venous thromboembolism screening after pneumonectomy: The more you look, the more you see

Siva Raja, MD, PhD,^a Jay J. Idrees, MD,^a Eugene H. Blackstone, MD,^{a,b} Jiayan He, ScD,^b Anish Badjatiya, BS,^a Peter Mazzone, MD, MPH,^c David P. Mason, MD,^a Thomas W. Rice, MD,^a Daniel P. Raymond, MD,^a and Sudish C. Murthy, MD, PhD^a

ABSTRACT

Objectives: Symptomatic venous thromboembolism (VTE) after pneumonectomy is associated with poor prognosis. We describe a new care pathway for patients undergoing pneumonectomy in which asymptomatic lower-extremity VTE screening was performed to determine if it increases VTE detection and potentially decreases sequelae.

Methods: 112 patients underwent pneumonectomy from 2006 to 2013 at Cleveland Clinic and were enrolled in a care pathway that included VTE prophylaxis and routine, pre-discharge, lower-extremity VTE screening. These data were contrasted with a previously published cohort of 336 patients (1990-2001) who underwent pneumonectomy without routine VTE screening.

Results: 10 of 112 patients (8.9%) had VTE detected by screening before discharge. An additional 4 patients (3.6%) with a negative pre-discharge screen developed symptomatic VTE within 30 days. Six patients (5.4%) developed VTE after pneumonectomy beyond the first 30 days. Prevalence of in-hospital VTE in the screened cohort was significantly higher than that of the non-screened cohort (3.0%; $P = .008$). Similarly, VTE within 30 days in the screened cohort (13%) was significantly higher than in the non-screened cohort (5.0%; $P = .007$). In both cohorts, a peak was observed approximately 6 days after pneumonectomy and plateaued after 30 days. The presence of a VTE portended worse long-term survival: 66% at 1 year versus 85% for those not developing a VTE.

Conclusions: Prevalence of VTE after pneumonectomy is higher than previously thought. The risk of developing a VTE peaks at 6 days after pneumonectomy, and remains increased until 30 days, suggesting a need for additional screening or longer prophylaxis. (J Thorac Cardiovasc Surg 2016;152:524-32)

Postpneumonectomy survival in a screened group of patients with/without postoperative VTE.

Central Message

Routine venous thromboembolism screening and prophylaxis are recommended for 30 days after pneumonectomy.

Perspective

The more we looked for venous thromboembolism using routine postpneumonectomy screening, the more we saw, despite standard prophylaxis. Better prophylaxis and additional screening are indicated to limit this potentially lethal complication.

See Editorial Commentary page 533.

A pneumonectomy series from our institution showed a high prevalence of symptomatic venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary

embolism—and worse survival than in those not experiencing a postoperative VTE.^{1,2} Sixty-four percent of these VTEs were diagnosed after hospital discharge. Based on these data, in 2005 we began to routinely screen patients for DVT after pneumonectomy and before discharge as a quality improvement initiative. In this report of that initiative, we (1) present the prevalence of postpneumonectomy VTE when routine screening and prophylaxis were used compared with the prevalence of symptomatic VTE after pneumonectomy in our earlier cohort, (2) assess the risk of developing

From the Departments of ^aThoracic and Cardiovascular Surgery, ^bQuantitative Health Sciences, and ^cPulmonary Medicine, Cleveland Clinic, Cleveland, Ohio.

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S. Raja and J.J. Idrees contributed equally.

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Address for reprints: Siva Raja, MD, PhD, Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, 9500 Euclid Ave, Desk J4-1 Cleveland, OH 44195 (E-mail: rajas@ccf.org).

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Abbreviations and Acronyms

DVT = deep vein thrombosis

VTE = venous thromboembolism

a first postoperative VTE over time in the screened and unscreened population, (3) identify risk factors for developing VTE after pneumonectomy, and (4) present the effect of VTE on survival.

PATIENTS AND METHODS

Patients

From January 1, 2006, to January 1, 2013, 132 patients underwent pneumonectomy for both benign and malignant indications at the Cleveland Clinic. Of these, 112 underwent routine lower-extremity DVT screening, irrespective of symptoms, by noninvasive duplex ultrasonography before hospital discharge as part of a quality initiative; they constitute the group of patients for whom our initiative was evaluated (Table 1 and Table E1). The median number of days from screen to discharge was 1 day. We compare the results with those of our previous study,¹ which included 336 patients who underwent pneumonectomy from January 1990 to January 2001; during that time, imaging for only symptomatic VTE was performed. The clinical characteristics of patients with VTE in the 2 cohorts are presented in Table 2. Postoperative complications are listed in Table E2.

Patient characteristics, including all comorbidities, were extracted from the Society of Thoracic Surgeons database (see http://www.sts.org/sites/default/files/documents/STSAAdultCVDDataSpecificationsV2_81.pdf). Cancer staging, procedural details, complications, and follow-up was performed by J.J.I. and S.R. Collection and use of these data were approved by the Cleveland Clinic Institutional Review Board, with patient consent waived.

Clinical VTE Prophylaxis and Therapy

VTE prophylaxis was given in the operating room 1 hour after placement of the epidural catheter. Postoperative VTE prophylaxis was routinely practiced in both eras and consisted of 5000 units of unfractionated heparin administered subcutaneously twice a day and lower-extremity pneumatic compression devices. Early ambulation strategies were also used. Patients with below-the-knee DVT were observed for progression with serial ultrasonography.^{3,4} Patients with progression of below-the-knee DVT, above-the-knee DVT, or pulmonary embolism, detected with either a helical computed tomography scan or a lung ventilation/perfusion scan, were anticoagulated with warfarin with an unfractionated heparin bridge or low-molecular-weight heparin.

Endpoints

Endpoints were occurrence of VTE after surgery and all-cause mortality. VTE was defined as deep venous thrombosis of lower extremity (below or above knee) or occurrence of pulmonary embolism. Time zero for this analysis was date of pneumonectomy. Vital status was obtained by systematic chart review, augmented by a search of the Social Security Death Master File (for deaths known before April 2011).^{5,6} Common closing date for follow-up was July 1, 2013. Median follow-up was 1.3 years, with 25% of survivors followed more than 2.6 years and 10% more than 4.2 years.

Data Analysis

Time-related occurrence of first VTE and mortality were estimated non-parametrically by the Kaplan-Meier method⁷ and parametrically using a multiphase hazard model⁸ (for additional details, see www.lerner.ccf.org/

TABLE 1. Patient characteristics and procedural details (total N = 112)

Variable	n*	Number (%) or mean $\pm$ SD
Demographics		
Age (y)	112	61 $\pm$ 12
Female	112	29 (26)
Weight loss within 3 mo (kg)	112	2.1 $\pm$ 6.2
Preoperative body mass index (kg m ⁻²)	112	27 $\pm$ 5.0
Comorbidities		
Chronic obstructive pulmonary disease	112	13 (12)
FEV ₁ (% of expected)	109	75 $\pm$ 18
FVC (% of expected)	107	85 $\pm$ 20
DLCO	85	79 $\pm$ 19
Type II diabetes	112	16 (14)
Zubrod score†	112	
0		12 (11)
1		98 (88)
2		2 (1.8)
Hypertension	110	45 (41)
Coronary artery disease	110	15 (14)
Type of pneumonectomy	112	
Standard		34 (30)
Intrapleural		43 (38)
Extrapleural		25 (22)
Completion		10 (8.9)
Cancer characteristics		
Non-small cell lung cancer	112	77 (69)
Clinical cancer stage	73	
1		15 (21)
2		32 (44)
3		26 (36)
Pathologic cancer stage	73	
0		5 (6.8)
1		13 (18)
2		26 (36)
3		29 (40)
Induction chemotherapy	111	47 (42)
Induction radiotherapy	111	27 (24)

SD, Standard deviation; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, spirometry diffusion capacity. *Patients with data available. †0 = asymptomatic; 1 = symptomatic but completely ambulatory; 2 = symptomatic, <50% in bed during the day.

[qhs/software/hazard](#)). Multivariable analysis was performed for VTE in the hazard function domain using the patient and procedure variables listed in Table E1. Variable selection using a bootstrap bagging technique was performed, with a 2-tailed *P* value criterion for retention of variables in the model of .05.^{9,10} For this, 500 bootstrap datasets were used, with risk factors identified using automated forward stepwise selection. Frequencies of occurrence of variables in each model were aggregated, indicating their reliability, and those appearing in 50% or more of the models were incorporated into the final model.

Effect of VTE on survival. To estimate the effect of VTE on survival, an initial competing-risks analysis was performed. All patients were initially included as surviving free of VTE and censored at occurrence of VTE, death, or end of follow-up. Patients experiencing VTE were entered into a survival analysis in which time zero was the time of VTE. These patients were then traced for subsequent mortality.

TABLE 2. Characteristics of patients with postoperative venous thromboembolism in the early and current cohorts

Characteristic	Early-era cohort (1990-2001; total N = 25)		Current era cohort (2006-2012; total N = 20)		P
	n*	Number (%) or mean $\pm$ SD	n*	Number (%) or mean $\pm$ SD	
Age (y)	25	61 $\pm$ 13	20	64 $\pm$ 13	.2
Diabetes	25	2 (8.0)	20	2 (10)	.8
Hypertension	25	7 (28)	19	8 (42)	.3
Coronary artery disease	25	4 (16)	19	2 (11)	.6
Induction chemoradiation	21	4 (19)	20	11 (55)	.02
Adjuvant chemoradiotherapy	21	4 (19)	20	5 (25)	.6
FEV ₁ (% of expected)	22	72 $\pm$ 12	19	76 $\pm$ 19	.2
FVC (% of expected)	22	82 $\pm$ 13	18	84 $\pm$ 24	.3
Smoker (pack-years)	24	62 $\pm$ 32	16	34 $\pm$ 24	.003
In-hospital VTE	25	10 (40)	20	10 (50)	.5
VTE within 30 d after surgery	25	17 (68)	20	14 (70)	.9

SD, Standard deviation; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; VTE, venous thromboembolism. *Patients with data available.

RESULTS

Prevalence of VTE After Pneumonectomy With Screening

Ten of 112 patients (8.9%) were found to have postoperative VTE on pre-discharge ultrasonographic screening; 5 (4.5%) were asymptomatic at the time of screening. Seven of these 10 patients were immediately anticoagulated. Three patients had asymptomatic below-the-knee DVT and were managed by serial ultrasonography. Of these, 2 had VTE progression and were therapeutically anticoagulated. Four who had negative screens before discharge subsequently developed symptomatic VTE within 30 days of pneumonectomy, resulting in a 30-day prevalence of 12%. Another 6 patients developed VTE after 30 days. Mean interval from surgery to pre-discharge screen was 5.4 ± 3.0 days. In 17 patients (15%), screening was performed on the day of discharge. Distribution of VTE by type of pneumonectomy was standard (4/34), intrapericardial (7/43), extrapleural (7/25), and completion (2/10).

In contrast, in the previous unscreened cohort, symptomatic VTE developed in 10 of 336 patients (3.0%) before discharge and in an additional 7 patients within 30 days. This resulted in a 30-day prevalence of only 5.0% and a 1-year prevalence of 6.2% ($P[\log \text{rank}] = .001$ for screened vs unscreened groups) (Figure 1).

Risk of First Postoperative VTE

Instantaneous risk of a first VTE resolved into 2 hazard phases, with an early risk peaking on day 6 (0.96 VTE events per 100 patient days) (Figure 2) and a constant late risk of 0.010 VTE events per 100 patient days for the screened cohort. Compared with the screened era, peak incidence for the unscreened cohort in the early phase was about 1 day later (0.52 VTE events per 100 patient days), with a constant late risk of 0.0026 VTE events per 100 patient days.

Risk Factors for VTE

Risk factors for early VTE (Table 3) were older age (Figure E1, A), chronic obstructive pulmonary disease

(Figure E1, B), and extrapleural pneumonectomy (Figure E1, C). Younger age was associated with a higher risk of late VTE (Table 3).

Effect of VTE on Survival

Patients experiencing a VTE had a higher risk of death than those who did not (Figure 3).

DISCUSSION

Principal Findings

Prevalence of VTE in our patients screened after pneumonectomy was higher than we previously reported in unscreened patients. Thus, this quality initiative revealed that the more we looked, the more we saw. We found a near 3-fold increase in in-hospital prevalence when routine pre-discharge screening was initiated and a 2-fold increase in late follow-up. We also found that two-thirds of below-the-knee DVTs progressed, necessitating therapeutic anticoagulation. Risk of VTE was elevated for at least 30 days postoperatively. Older age, chronic obstructive pulmonary disease, and extrapleural pneumonectomy were risk factors for early VTE. Development of VTE postpneumonectomy was associated with worse survival.

Findings in Context

Patients with lung cancer are at high risk of developing VTE,¹¹ and those undergoing pneumonectomy are at a higher risk than those undergoing lobectomy.¹² Patients undergoing pneumonectomy often have the least pulmonary reserve to withstand the impact of pulmonary embolism.

There are several possible hypotheses for the increased prevalence of VTE after pneumonectomy. One potential mechanism is that removal of an entire lung results in some pulmonary hypertension and altered venous return to the right heart. In addition, attempts to mitigate right heart strain from increased pulmonary hypertension by fluid restriction and diuresis often leave patients intravascularly dry, with potentially increased blood viscosity, leading to

FIGURE 1. Probability of first venous thromboembolism (VTE) after pneumonectomy in 2 eras. Each *symbol* represents an event, *vertical lines* are 68% confidence intervals (± 1 standard error), and *solid lines* are parametric estimates enclosed within a *dashed* 68% confidence band.

a thrombogenic milieu. Given the more extensive resection of lung tissue, patients undergoing pneumonectomy may also be less mobile in the postoperative period than those who have had a lobectomy, leading to a higher prevalence of VTE.

The published prevalence of symptomatic VTE in patients undergoing resection for lung cancer is highly variable (0%-47%), with a mean prevalence of 2.0%.¹² Studies are difficult to compare, however, because prophylaxis regimens and clinical diagnoses vary widely.^{3,13,14} In our previously published unscreened series, many VTEs were detected after discharge.¹ Thus, we are unaware of data on the overall prevalence of VTE (symptomatic or asymptomatic) in the postpneumonectomy population.

The downturn in the prevalence of VTE diagnosed after discharge could represent the effect of decreased scrutiny, because absence of a second screening resulted in only symptomatic VTE being detected. This raises the possibility that the prevalence of VTE might be even higher if a comprehensive serial screening program were initiated.

An interesting observation in this study was detection of VTE in 4 patients during the 30-day postdischarge period who had a negative screen before discharge. This suggests that in addition to the possibility of VTE developing after discharge, the diagnostic sensitivity of our noninvasive lower-extremity ultrasonography may not be high enough to detect subclinical VTE. Our findings also suggest that after pneumonectomy patients carry a high risk of DVT progression even when it is asymptomatic and below the knee at the time of screening; therefore, more aggressive management in such patients is reasonable.

Despite standard prophylaxis, VTE did occur, indicating that our prophylaxis may be inadequate. The ideal agent will require no more than 1 daily dose, be effective yet

FIGURE 2. Instantaneous risk of VTE after pneumonectomy in 2 eras. *Solid lines* represent parametric estimates enclosed within a *dashed* 68% confidence band.

TABLE 3. Incremental risk factors for first venous thromboembolism

Factor	Estimate $\pm$ SE	P	Reliability (%)*
Early risk			
Older age†	1.5 $\pm$ 0.48	.002	74
Chronic obstructive pulmonary disease	1.9 $\pm$ 0.70	.008	50
Extrapleural pneumonectomy	1.7 $\pm$ 0.72	.02	56
Late risk			
Younger age‡	1.9 $\pm$ 0.83	.02	55

SE, Standard error. *Percent of times factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡(50/age), inverse transformation.

FIGURE 3. Survival before (triangles) and after (circles) occurrence of VTE. Format is as for nonparametric estimates in Figure 1. VTE, Venous thromboembolism.

inexpensive, have a low risk of bleeding complications, and have a reversal agent. In addition, postdischarge exercise programs may also help decrease VTE formation in the perioperative period.

Additional screening in the postdischarge period up to 30 days and prolonged prophylaxis with more effective agents would increase detection, although the optimal timing of another screen is uncertain. Our study suggests that an additional screening may be particularly relevant in elderly patients, those with chronic obstructive pulmonary disease, and those undergoing extrapleural pneumonectomy. Additional screening also raises concerns about increasing health care costs in this patient population. Given the variability in insurance coverage in the United States, the financial burden on patients must be considered.

Strengths and Limitations

The strength of this study is the prospective evaluation of a clinical practice change initiated as a quality improvement project involving predischarge VTE screening. Limitations are related to its small size, retrospective analysis, and single-institution experience. Although the screening protocol substantially improved detection of asymptomatic VTE events compared with the older cohort, the total number of events was small, and it was not statistically feasible to investigate any direct relationship between screening and long-term survival. In addition, we did not have preoperative data about the prevalence of VTE, the nature of VTE in the predischarge population (symptomatic vs

asymptomatic), or the prevalence of asymptomatic VTE after discharge. Further, 20 patients did not undergo screening because of choice or logistical reasons. This may have affected the overall prevalence of VTE in our postpneumonectomy population. Lastly, staging in the unscreened cohort was done using an older version of the American Joint Committee on Cancer staging manual (6th edition). Given that the study goes back to 1990, many of the patient data are from paper charts that cannot be reliably located now. For these reasons, we cannot make specific claims about the effect on screening survival.

VTE prophylaxis comprised twice-daily subcutaneous unfractionated heparin (5000 units) and lower-extremity compression devices. We now know from other clinical settings, including trauma and pelvic surgery, that this regimen is less effective than thrice-daily subcutaneous unfractionated heparin (5000 units) or low-molecular-weight heparin. A recently published study from Spain, in which low-molecular-weight heparin was routinely used perioperatively and for 2 weeks postoperatively, demonstrated a VTE prevalence of 1.3%.¹³ As a result of our study, we have changed our VTE prophylaxis to 40 mg of low-molecular-weight heparin daily.

CONCLUSIONS

This quality improvement initiative revealed a substantially higher prevalence of postpneumonectomy VTE than observed in our unscreened population. Despite a single screening, VTE occurred postdischarge. Based on this

increased prevalence and increased risk to at least 30 days, we support postoperative screening and longer and better VTE prophylaxis.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: [http://www.jtcvsonline.org/article/S0022-5223\(16\)30279-3/addons](http://www.jtcvsonline.org/article/S0022-5223(16)30279-3/addons).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: quality improvement, postoperative care, surveillance, prophylaxis

Discussion

tumor that leads to earlier recurrence and lower survival?

after pneumonectomy, the increased pulmonary pressures and the decreased venous return have been theorized to contribute to this. Obviously, higher tumor stage and tumor burden is noted to be associated with increased development of VTE. So I think that it is a multifactorial phenomenon to which I think this data does not lend itself to providing a causal relationship.

things going on, so they are not likely to do as well. But in the patients that you just screened—not the ones where you did a scan 2 weeks after discharge because they showed up in the emergency room not doing well—was there a difference in survival between the patients who had a VTE detected versus not?

Dr Raja. To reiterate the question, are you asking if they were asymptomatic or symptomatic and did that make a difference?

Dr Detterbeck. Yes. The asymptomatic patients who are just being screened, if they had a VTE detected or not, did it make a difference in survival?

Dr Raja. Well, these are patients who underwent a screening independent of whether they were symptomatic or not prior to the day of discharge. We do not have the data available in the medical chart for those patients who underwent a screening, which was everybody out of the 112, which of those DVTs were symptomatic, and which were not. However, all of the other DVTs, the remainder of the 50% of the DVTs that were identified were actually

Dr D. Sugarbaker (Houston, Tex). It's a very nice study. I have 2 questions. One, do you think that the reduced long-term survival of those patients who developed VTE is due to the occurrence of pulmonary emboli or is it more likely due to the production of procoagulants by a hormonally active

Dr Raja. Thank you for the question, Dr Sugarbaker. At the moment, based on our data, we can only conclude that there is a correlation. I think it would be difficult to attribute a specific causality based on the tumor biology. In the setting of a pneumonectomy, a variety of factors do play into effect;

Dr F. Detterbeck (New Haven, Conn). I'm not sure I understand your survival. I would certainly think that the people who are diagnosed with a nonscreened VTE are likely to not do as well because they are not doing well and that prompts you to say, "We better look for a PE." They may have other

people who were symptomatic. The only screening happened once, which was at the time of discharge.

Dr Detterbeck. That sort of answers it. Second, I'm assuming that when you found a DVT that you treated it.

Dr Raja. Yes.

Dr Detterbeck. And yet you still say they didn't do very well and your conclusion is that we better screen for DVT. If you are saying we better screen for DVT, it also means that we have an intervention that is going to make a difference, and yet you are saying you intervened and it didn't make a difference. The logic doesn't quite work out.

Dr Raja. Okay. I think I understand your question better at this point. All of the patients who had a DVT weren't treated. There were 3 patients who actually had a below-the-knee DVT who were followed and 2 of them progressed to requiring a therapeutic anticoagulation. So I agree that none of these patients in this study who developed a VTE, and there were 20 DVTs and 4 PEs in 20 patients, none of the mortality in the perioperative period was associated with the DVT or the pulmonary embolism. However, just like in our previous study, the mere diagnosis of having a VTE portends poor long-term survival without any implications as to what the mechanism is. It may just be an indicator that these patients, as Dr Sugarbaker mentioned, are higher-stage patients. Maybe they have higher tumor burden. Maybe there are other endocrine and paracrine factors from the tumor that facilitate these things. We don't know why they have a worse mortality; we just know that they do. So I would say that identifying a patient population at risk is the first step. The second step would be to say that if you were to treat these people with better prophylaxis, do you change the prognosis, and that is where there is some suggestion in the patient population of the screened versus unscreened where more patients were treated and the survival is better, but we do acknowledge that they were not adjusted both for stage as well as the fact that the prophylactic anticoagulation strategies have evolved over the decades and the 2 populations are probably not comparable for that. I would love to do a multicenter study to figure out if anticoagulating these people or prophylaxing longer does change the outcome.

Dr H. Fernando (*Boston, Mass*). It wasn't clear. How did you actually screen for VTEs? Was it with a helical CT and/or duplex? You had some VTE events occurring after discharge. Did you do any screening following discharge, or are you planning to do that in the future, or recommending

that?

Dr Raja. The screen was performed as a lower-extremity ultrasonograph for DVTs, and people were symptomatic or asymptomatic. Every other screen, be it upper extremity ultrasonography or pulmonary embolism scan either by V/Q

scan or by helical CT, was performed based on symptoms only.

Dr V. Rusch (*New York, NY*). I think we are not going to figure out the factors affecting survival, because, as you pointed out, this is a very heterogeneous patient population. It is not necessarily the most important message we should take home from this experience. What I conclude from

your presentation is that this is a high-risk population (especially patients with mesothelioma, who, of course, are especially high risk) and that perhaps we should be either instituting therapeutic treatment or continuing our VTE prophylaxis for a longer period of time than we typically do. As a corollary, our thoracic oncologists will continue or initiate anticoagulation even for patients who have below-knee clots if they are on chemotherapy for non-small-cell or other thoracic malignancies because of the overall risk of progression of VTE in this patient population.

Dr Raja. Thank you for your comment, Dr Rusch. During the conduct of this study as well as the preparation of the manuscript, in my evaluation of the guidelines from NCCN as well as ASCO, for abdominal cancers, they already recommend 4-week anticoagulation in the surgical patient after discharge. Similarly, European cancer organizations have also followed suit for abdominal cancers. Such a guideline does not exist at the moment for thoracic surgery, at least surgery in the chest, and one of the lead-off points for these data would be to suggest that perhaps we need to do the same. I admit that adding the patients with mesothelioma may also increase the risks, but if you refer to Dr Sugarbaker's series of extrapleural pneumonectomies, the incidence of VTE was 6.4% in the original series, which is comparable with the overall rate of about 7.4% that was detected in a previous series. They are all symptomatic VTEs. I think that no matter what kind of thoracic malignancy you have, I think you are at high risk.

Dr E. Savage (*Weston, Fla*). First of all, I have a question about your title. You are really not screening for venous thromboembolism. You are screening for deep venous thrombosis. The second thing is, when you screen everybody, you are going to find some probably not clinically significant

deep venous thromboses and you are treating them. What is the problem with treating some of these? Is there anticoagulation risk and bleeding? The other aspect of this is that what you do by routine screening is you set your hospital up to be called a bad hospital by the government because you have more DVTs than the next guy down the street who doesn't do routine screening.

Dr Raja. Thank you for that comment. Actually, that is something that I encountered in the preparation of this manuscript when I asked for comments from our vascular medicine folks, and they said, “So you’re the reason why our PSI rates are high.” But what I would say is that that is not a reason to not do the right thing. I think that our rates reported in the STS are very low. A 1.2% rate of PE and 1% rate of DVT is just too low in this cancer population. I agree that there is a competing risk of bleeding associated with patients who are being anticoagulated. We have not seen it in this series. However, that is one concern. Below-the-knee DVT in our institution is usually followed by serial ultrasonography within 5 to 7 days, which I believe is different from other institutions, so there are some vagaries associated with that. But the other issue with the anticoagulation that we sort of changed since then is the actual prophylaxis. The original prophylaxis used here, which was standard of care back in 2006, was twice-daily Sub-Q heparin that was given before the induction of anesthesia and they had compression devices and early ambulation strategies. Since then we have gone to using Lovenox afterwards. One of the barriers we noted in our institution, which has subsequently been overcome, is our anesthesia colleagues not wanting to put epidurals in patients who are on Lovenox, even though their own governing bodies and organizations have approved the use of 40 mg of Lovenox. So there is obviously a lag between convincing the people on the ground relative to the people who are making policy from that standpoint.

Dr T. Grodzki (*Szczecin, Poland*). I would like to congratulate you on an important paper; however, the conclusion seems a little bit paradoxical to me. You indicated that patients who were not screened almost all died. We are not screening and our patients are not dying because we are reacting quickly, and it seems to me that that is more important than screening. However, my question is how the results of your study changed your approach to prophylaxis, early detection, and early reaction to DVT or VTE.

Dr Raja. Thank you for your comment. Let me first clarify the last graph. I think that it is not that our patients are dying. It is just that that graph only represents the patients who develop a VTE. And that is long-term data. It is not in the first 30 days. There were no deaths in the first 30 days that were related directly to the VTE itself, either DVT or pulmonary embolism. So it seems to be a marker of poor prognosis, at least in this population, rather than a direct causal relationship. That being said, I think that, as in other malignancies, using once-a-day Lovenox does seem to decrease the rate of DVT, and that has been the case. We have instituted the use of Lovenox in our institution since 2012, since the completion of this study, and

we find that our rate is obviously less. Now, it is not as low as 1%, but it is much lower than the 8.9% in the pre-discharge rate that we saw. From that standpoint, I think that that is the better prophylaxis we’re looking for.

There are 2 additional questions that these data bring up. One is what is the incidence of DVT or VTE in this population before surgery? That information is not available. We are screening patients on the day of surgery to know what our incidence going into this is. That will allow us to estimate the risk of DVT formation following surgery that you can attribute to the surgical procedure. In an ideal world, given these data, you would screen them once more between the day of discharge and 30 days. It’s just something I’m saying. You already have a certain finite rate of VTE. If you increase your scrutiny with a screen, are you going to notice more? What we do about it and what the overall result of our intervention is, only time will tell once you make the intervention, but I think those are what one can take home from this. Whether it actually works to decrease long-term mortality, only when the intervention is completed and evaluated long-term can you tell, but I think those are what I would take home from this.

Dr D. Odell (*Pittsburgh, Pa*). This is a very short, pragmatic question. Given that 50% of the incidence of DVT in your study was seen after that day of discharge screen, what do you think the actual appropriate and functionally feasible time to screen should be? Second, rather than screening as a mechanism for the institution of anticoagulation, whether it be prophylactic or therapeutic, should we change our thinking such that it is our trigger to discontinue anticoagulation rather than to stop it in a prophylactic way?

Dr Raja. Just so that I can clarify, I didn’t get the last part of the question. Are you saying that instead of discontinuing when we do, should we just keep going? Is that the question?

Dr Odell. Should we continue our prophylactic anticoagulation until we have that 30-day screen and have that be our linchpin for discontinuation?

Dr Raja. All the other cancers have done that already. We are the only ones not doing it. I think it is a reasonable statement. But, once again, that brings up additional questions that one needs to ask, which is, who is going to pay for it? We are having a hard time getting even therapeutic Lovenox in the setting of VTE detection being paid for. I think it needs to be a consensus from an organization such as the AATS or the STS, ESTS. When you have a large number of these consensus organizations saying that that is the right thing to do, then I think that those logistical things can be overcome. I think it is reasonable to prophylax these folks. We have not seen an increase in postoperative bleeding with the use of Lovenox since we changed 3 years ago, and so I don’t think that that is necessarily going to be the case.

There is always going to be some bleeding, but I don't think it is any more elevated because of the use of once-a-day Lovenox. The other issue also is that the utilization of postdischarge exercise programs may also help mobilize the patient and facilitate decreasing VTE. Once all these measures are done, then it will be feasible to understand where we are with maximum therapy that we can do. Now, to borrow the phrase from a previous discussion today, we want to be aggressively aggressive, but not too aggressive. That's my adaptation to the quote from this morning.

Dr E. Vallières (*Seattle, Wash*). You are looking at day 7 which is when I want to send my pneumonectomy patient home. Have you looked earlier, say at day 5 or day 4, so that when we are ready to get him/her home at day 7, we don't have to delay for another 48 hours?

Dr Raja. It was done on the day of discharge. At the time of this study, the median length of stay was day 5. It was done on day 4. That's median. That's why you have the peak that is a little wider around that point.

Dr J. Deslauriers (*Quebec City, Quebec, Canada*). This is an interesting observation. Do you think that, at least in some patients, the deep vein thrombosis could have been there before surgery as a paraneoplastic syndrome, which is generally associated with tumors having a poorer prognosis? This may explain the worse survival in this group of patients.

Dr Raja. The NCCN guidelines on VTE prophylaxis in cancer published in JCO in 2009 goes over the relative risk. There is anywhere from a 2- to 9-fold increased risk of VTE in patients with cancer. We don't really know what the baseline incidence is, but there are indications, such as a lower crit, higher white count, increased nodal

disease, increased tumor burden, that are associated with it. So a lot of times people do get prophylaxis when they undergo chemotherapy. There is a finite rate of VTE in the cancer population, lung cancer population. I just don't know. I can't find a study that gives me a good answer as to what that is.

Dr Sugarbaker. Is Dr Naunheim in the audience?

Dr Naunheim. Yes.

Dr Sugarbaker. Can you give us the short version? We are running over, but we would like to hear from you.

Dr K. Naunheim (*St. Louis, Mo*). The short version is, while it is interesting, most of the points I would have made have been made here. We don't know the preoperative incidence. We don't know the postoperative incidence. We don't even know when we should screen them. I don't think there is any

question that VTE is a problem in the postoperative period, especially for pneumonectomies versus lobectomies. However, from the health policy standpoint, VTE screening might prove phenomenally wasteful. We could spend a phenomenal amount of money trying to routinely screen people and then treat them for an occult DVT that may or may not be injurious to them in terms of possible embolization. We are being called upon to be cost-effective and at the same time ideally provide personalized medicine. So if there is any charge I would ask the authors to undertake, it is to identify, using the risk factors, what the risk is and who would be appropriate to test aggressively and who would not be appropriate, because otherwise we are going to be spending a hell of a lot of money trying to prevent a complication that may have been there before and may not actually hurt the patient anyway. Don't misunderstand me, I still think it was a worthwhile, great paper, very interesting. It brings up one of the interesting topics we need to know about when caring for our patients in the perioperative period.

FIGURE E1. Freedom from first venous thromboembolism (VTE). A, According to age of patient with no chronic obstructive pulmonary disease, stratified by pneumonectomy type. Format is as in Figure 2. B, Stratified by chronic obstructive pulmonary disease. Kaplan-Meier estimates with a symbol at each VTE. Vertical bars represent 68% confidence limits. C, Stratified by pneumonectomy type. Kaplan-Meier estimates with a symbol at each VTE. Vertical bars represent 68% confidence limits. COPD, Chronic obstructive pulmonary disease.

TABLE E1. Variables considered in multivariable analyses

Patient and procedure	
Demographics	Age (y), sex, race, height (cm), weight (kg), body surface area (m ²), body mass index (kg m ⁻²), weight loss within 3 mo
Comorbidities	Hypertension, coronary artery disease, cardiovascular disease, chronic obstructive pulmonary disease, diabetes, Zubrod score, induction chemotherapy, radiation therapy, forced expiratory volume in 1 s (% of predicted), forced vital capacity (% of predicted)], spirometry diffusion capacity (DLCO)
Cancer stage	Cancer type (non-small cell vs other), clinical cancer stage (1, 2, 3), pathologic cancer stage (0, 1, 2, 3)
Procedural	Type of pneumonectomy (standard, intrapericardial, extrapleural, completion), operation side (left or right), flap (fat, muscle, pericardial, pleural)
Interval	Date of operation (interval, days from 1/1/2006 to pneumonectomy)
Time-varying covariables	Venous thromboembolism, time of venous thromboembolism

DLCO, Spirometry diffusion capacity.

TABLE E2. Outcomes after pneumonectomy in screened population

Outcomes	n*	Number (%)
Operative mortality	112	4 (3.6)
Empyema	112	7 (6.3)
Tracheostomy	112	4 (3.6)
Re-operation for bleeding	112	3 (2.7)
Bronchopleural fistula	112	4 (3.6)

*Total number of patients.