Venous Thromboembolism in Patients Undergoing Operations for Lung Cancer: A Systematic Review

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Background. The risk of venous thromboembolism is perceived to be high in patients with lung cancer. However, existing studies in patients undergoing operations for lung cancer draw inconsistent conclusions and recommendations in terms of thromboprophylaxis. The aim of this study was to perform a systematic review of the risk of perioperative and postoperative venous thromboembolism for patients undergoing potential curative surgical procedures for primary lung cancer.

Methods. This was a systematic review including studies of patients with primary lung cancer undergoing operations with curative intent.

Results. We included 19 studies with a total of 10,660 patients. All studies, except 1, were observational in design. Marked heterogeneity was found between the studies in terms of methodologic aspects, patient characteristics, and findings. The mean risk of venous thromboembolism (VTE) was estimated at 2.0% (range, 0.2%–19%), with a mean observation period of 16 months (range, 0.1–22), and the risk was nearly identical in studies with 1 month of follow-up and studies with a longer follow-up.

Conclusions. The evidence for using thromboprophylaxis after lung cancer operations is relatively sparse, and the use is based predominantly on clinical consensus. However, the risk of VTE seems to occur predominantly within the initial postoperative period, and subsequently the risk falls. Future research should focus on identifying patients and surgical procedures that increase the risk of VTE. This could be accomplished by large observational studies in addition to randomized controlled trials evaluating different thromboprophylaxis strategies.

The risk of venous thromboembolism (VTE) diagnosed in patients with lung cancer has been estimated in different settings. The overall risk of VTE is approximately 3% within 2 years [1]. The risk may result in part from an increased activation of the coagulation system, in particular an overexpression of tissue factor, which brings the patient into a hypercoagulable state [2]. This activation may contribute to cancer progression, especially in metastatic foci [3].

The factors related to the development of VTE can be patient related (eg, age, obesity), cancer-related (eg, histopathologic type of cancer), treatment related (eg, surgical procedure, chemotherapy), or a combination of these factors [4]. Patients having potentially curative operations for lung cancer (ie, wedge resection, segmentectomy, lobectomy, or pneumonectomy) differ from the rest of the group of patients with lung cancer because surgical intervention is known per se to increase the risk of VTE [5]. However, the aim of surgical intervention is to provide curative treatment. Accordingly, the potential advantages of low-molecular-weight heparin (LMWH) treatment is probably limited, because these patients have had the primary tumor removed and metastasis excluded at the time of operation. Patients who have undergone operation have predominantly early-stage disease and accordingly are not as likely to be in a hypercoagulable state as are patients with more advanced disease [5].

In postoperative patients with lung cancer who were followed up to 1 year, Yang and associates [6] found that the highest incidence of VTE was within 1 month after operation.

Even in patients receiving antithrombotic prophylaxis, there seems to be a substantial risk of VTE [3, 5, 7].

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Dentali and colleagues [8] found an in-hospital risk of VTE of 1.7% despite all patients having antithrombotic prophylaxis with heparin. The results seem broadly analogous, showing that despite thromboprophylaxis, there is a risk of VTE in patients undergoing operations for lung cancer. However, the risk of VTE in patients undergoing operations for lung cancer is reported to be less than in patients undergoing other surgical procedures, eg, orthopaedic or gynecologic operations [3]. Furthermore, it is not known whether a specific surgical procedure has a particular effect on the risk of VTE, specifically an open procedure (thoracotomy) versus a minimally invasive operation (video-assisted thoracic surgery [VATS]). VATS has been shown to facilitate earlier mobilization and reduce length of stay [9], thereby potentially reducing the need for antithrombotic prophylaxis.

Attaran and coworkers [5] performed a randomized controlled trial in which patients undergoing surgical procedures for lung cancer were found not to be in a hypercoagulable state and were comparable to patients undergoing operation for benign diseases. Therefore, does the risk-benefit ratio favor antithrombotic prophylaxis or is there a subset of high-risk patients who should receive antithrombotic prophylaxis? This is important because prophylactic treatment is both expensive and carries an inherent and clinically relevant risk of major bleeding [3, 5, 10].

The literature is relatively sparse, predominantly consisting of small studies with diversity in evidence, and it is difficult to get an overview of the literature and draw clinical conclusions. The present recommendations are based more on clinical consensus and tradition than evidence.

The aim of this article was to perform a systematic review on the risk of perioperative and postoperative VTE for patients undergoing potentially curative operations for primary lung cancer and to identify potential areas for future research.

Material and Methods

**Literature Search**

Publications were identified through searching the Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed (start 1951–May 2013). The search was supplemented by a review of personal files and a manual search of published reviews. The following strategy was used to search the CENTRAL and was adapted appropriately for PubMed: “(Lung Neoplasms/surgery)[Mesh] AND “Anticoagulants”[Mesh] OR (lung cancer) AND anticoagulation* AND (“Heparin, Low-Molecular-Weight”[Mesh] OR (“Thrombosis”[Mesh] AND “Lung Neoplasms/surgery”[Mesh] AND (Humans [Mesh] AND (English[lang] OR Danish[lang] OR Norwegian[lang] OR Swedish[lang]))).” Based on titles and abstracts relevant to the topic, original articles were selected. Additionally, relevant articles were identified by review of references in key publications.

**Data Extraction**

We extracted the following data from all included studies: author and publication year, design (case series, cohort, or randomized controlled trial), country of origin, number of patients included, mean/median age of patients, follow-up time, surgical procedure performed, antithrombotic prophylaxis, type of antithrombotic prophylaxis, and number of cases and incidence of VTE and major bleeding.

**Assessment of Study Eligibility**

The titles (and abstracts when available) identified through the literature search were reviewed. Any article that might meet the eligibility criteria was included. All studies were scanned for additional relevant references. The final assessment of trial quality of each study included was assessed by 2 reviewers (TDC and RW) using predefined criteria [11]. Disagreement was solved using consensus between the 2 reviewers.

**Eligibility Criteria**

Type of studies included case series, cohort studies, or randomized controlled trials assessing the perioperative and postoperative risk of VTE for patients undergoing operations for primary lung cancer. The type of participants included patients > 18 years of age who were diagnosed with primary lung cancer and who had undergone potential curative operations for the indication of primary lung cancer. Types of intervention included wedge resection, segmentectomy, lobectomy (including bilobectomy, sleeve lobectomy), or pneumonectomy performed either through thoracotomy or VATS. Type of outcome measures were (1) death from all causes, (2) major complications in terms of VTE defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE), and (3) major bleeding events. DVT was defined as a new blood clot or thrombus within the venous system confirmed by duplex ultrasonography, venography, or computed tomography. PE was defined as the presence of a blood clot in the pulmonary circulation confirmed by ventilation-perfusion scan, pulmonary arteriography, or computed tomography. However, these investigations were predominantly performed if there was clinical suspicion of a VTE and accordingly were not applied to all patients included in the studies. Major bleeding events were defined as death from bleeding, intracranial bleeding requiring transfusion, and events requiring inpatient treatment.

**Results**

**Data Extraction**

Disagreement was present between the 2 reviewers regarding 18% of the extracted data, but consensus was reached in all cases.

**Description of Studies**

Nineteen trials with a total of 10,660 patients (mean number, 561) were included (Fig 1; Table 1) [5, 6, 8, 12–27].
The mean and median observation period was 16 months and 1 month, respectively (range, 0.1–122 months).

Quality Assessment of Included Studies
All studies were observational in design (predominantly case series), except for 1 randomized controlled trial published by Attaran and colleagues [5]. Therefore, this systematic review was predominantly based on observational studies.

Antithrombotic Prophylaxis
Antithrombotic prophylaxis was used in 5 studies [5, 8, 14, 17, 19], was not used in 2 studies [23, 27], and was not reported in the majority of studies, namely, the remaining 12 studies (Table 1). In the studies in which antithrombotic prophylaxis was used, the mean risk of VTE was 5.8% (range, 1.6%–14%), and in the 2 studies in which no prophylaxis was given, the risk was 1.9% and 19.5%, respectively.

Venous Thromboembolism
A total of 217 VTEs were identified, including 85 DVTs and 132 PEs.

Death from All Causes.
No studies reported directly on death with the exception of fatal PEs.

Major Bleeding
Only 5 studies [5, 18, 22, 24, 27] reported on major bleeding events as an outcome measure, and the incidence varied from 0.6% to 4.5%.

Incidence of VTE Events
Based on the data extrapolated from the studies displayed in Table 1, we calculated the incidence/risk of VTE (in percentages). This was done by adding the number of events and dividing it by the number of patients in each study, the nominator being the number of events and the denominator the number of patients.

The overall mean risk of VTE was estimated at 2.0% (range, 0.2%–19%). The risk of VTE was nearly identical in studies with 1 month of follow-up and studies with a follow-up greater than 1 month—2.1% and 2.9%, respectively (Table 2).

Comment
We found that the overall risk of VTE for patients undergoing operations for primary lung cancer was low. Overall, the risk of VTE was 2.0%, but the range was marked (range, 0.2%–19%). The mean and median observation period of the included studies was 16 months and 1 month, respectively (range, 0.1–122 months).

The risk of a VTE developing within the first month postoperatively was nearly the same as it was in studies with a longer follow-up. This could indicate that VTE predominantly occurs within the initial postoperative period, and subsequently the risk falls. In patients undergoing surgical intervention for lung cancer, Yang and associates [6] found that the highest incidence of VTE was within 1 month of operation. Furthermore, in patients undergoing lung cancer operations, Merkow and co-workers [20] found an overall predischarge risk of VTE of 4.2%, with 77% of cases diagnosed before discharge and 23% after discharge. These findings support the previous statement regarding the potential increased risk within the early postoperative period. However, if the results in the studies had been displayed using a time-to-event scale, the risk could have been estimated precisely. The risk of major bleeding was extremely difficult to access because information was very sparse.

VTE has been found to increase 30-day mortality after cancer operations from 1.2% to 8.0% [20]. Because the incidence of death in the included studies was low, and
<table>
<thead>
<tr>
<th>First Author, year [Ref]</th>
<th>Design</th>
<th>Country of Origin</th>
<th>Number of Patients</th>
<th>Mean Age (year)</th>
<th>Follow-Up Time</th>
<th>Type of Operation</th>
<th>Antithrombotic Prophylaxis and Type</th>
<th>VTE (n and incidence [% per year])</th>
<th>Major Bleeding Episodes (n and Incidence [% per year])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amar, 2010 [12]</td>
<td>CS</td>
<td>US</td>
<td>956</td>
<td>65</td>
<td>NR</td>
<td>All thoracotomy; 25% pneumonectomies, 67% lobectomies, 8% wedge resections</td>
<td>NR</td>
<td>PE: n = 12</td>
<td>NR</td>
</tr>
<tr>
<td>Attaran, 2010 [5]</td>
<td>RCT</td>
<td>UK</td>
<td>22</td>
<td>68.6</td>
<td>3 d</td>
<td>All thoracotomy; 9% pneumonectomies, 91% lobectomies</td>
<td>LMWH, 40 mg once or twice daily</td>
<td>0</td>
<td>n = 1</td>
</tr>
<tr>
<td>Bobbio, 2007 [13]</td>
<td>CS</td>
<td>Italy</td>
<td>30</td>
<td>71</td>
<td>30 d</td>
<td>All thoracotomy; 10% pneumonectomies, 63% lobectomies, 7% segmentectomies</td>
<td>NR</td>
<td>PE: n = 1</td>
<td>NR</td>
</tr>
<tr>
<td>Daddi, 2006 [14]</td>
<td>CS</td>
<td>Italy</td>
<td>50</td>
<td>66.5</td>
<td>11 d (mean)</td>
<td>All thoracotomy; 24% pneumonectomies, 72% lobectomies, 4% wedge resections</td>
<td>LMWH 3,000–4,000 IU daily (2 patients had no prophylaxis)</td>
<td>PE: n = 7</td>
<td>NR</td>
</tr>
<tr>
<td>Davini, 2009 [15]</td>
<td>CS</td>
<td>Italy</td>
<td>89</td>
<td>55.5</td>
<td>122 mo (median)</td>
<td>All thoracotomy; 9% pneumonectomies, 72% lobectomies, 4% wedge resections, 8% other</td>
<td>NR</td>
<td>PE: n = 1</td>
<td>NR</td>
</tr>
<tr>
<td>Dentali, 2008 [8]</td>
<td>CS</td>
<td>Canada and Italy</td>
<td>693</td>
<td>66.7</td>
<td>28 d</td>
<td>Pneumonectomy; 13.5% Lobectomy or wedge resections: 86.5% (VATS/open operation: NR)</td>
<td>(1) Postoperatively, UFH 5,000 IU twice daily (67.2%); (2) LMWH 5,000 IU twice daily (22.2%); (3) no prophylaxis (2.3%) (Given until discharge)</td>
<td>VTE: n = 12, PE: n = 9, DVT: n = 3</td>
<td>NR</td>
</tr>
<tr>
<td>Deslauriers, 1989 [16]</td>
<td>CS</td>
<td>Canada</td>
<td>1,076</td>
<td>29–86 (range)</td>
<td>NR</td>
<td>All thoracotomy; 38% pneumonectomies, 57% lobectomies, 8% wedge or segmentectomy resections</td>
<td>NR</td>
<td>PE: n = 2</td>
<td>NR</td>
</tr>
<tr>
<td>Licker, 1999 [18]</td>
<td>CS</td>
<td>Switzerland</td>
<td>621</td>
<td>61</td>
<td>30 d</td>
<td>All thoracotomy; 25% pneumonectomies, 58% lobectomies, 12% segmentectomy with edge resection</td>
<td>NR</td>
<td>PE: n = 1</td>
<td>n = 4</td>
</tr>
<tr>
<td>Kalweit, 1996 [17]</td>
<td>CS</td>
<td>Germany</td>
<td>1,735</td>
<td>62</td>
<td>14 d</td>
<td>All thoracotomy; pneumonectomies, lobectomies, segmentectomy with edge resection (numbers not applied)</td>
<td>Postoperatively D 1: UFH 5 IU/kg continuous infusion, D 2: 7,500/10,000 IU mL every 8 h</td>
<td>PE: N = 27</td>
<td>NR</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>First Author, year [Ref]</th>
<th>Design</th>
<th>Country of Origin</th>
<th>Number of Patients</th>
<th>Mean Age (year)</th>
<th>Follow-Up Time</th>
<th>Type of Operation</th>
<th>Antithrombotic Prophylaxis and Type</th>
<th>VTE (n and incidence [% per year])</th>
<th>Major Bleeding Episodes (n and Incidence [% per year])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason, 2006 [19]</td>
<td>CS</td>
<td>US</td>
<td>336</td>
<td>61</td>
<td>1.6 y (median)</td>
<td>All thoracotomy; 100% pneumonectomies</td>
<td>LMWH 5,000 IU twice daily</td>
<td>VTE: n = 25; PE: n = 8; DVT: n = 17</td>
<td>NR</td>
</tr>
<tr>
<td>Merkow, 2011 [20]</td>
<td>CS</td>
<td>US</td>
<td>952</td>
<td>NR</td>
<td>30 d</td>
<td>NR</td>
<td>NR (patients probably received some sort of prophylaxis)</td>
<td>VTE: n = 26; PE: n = 13; DVT: n = 13</td>
<td>NR</td>
</tr>
<tr>
<td>Muscolino, 1997 [21]</td>
<td>CS</td>
<td>Italy</td>
<td>15</td>
<td>57</td>
<td>NR</td>
<td>Lobectomies: 53%, sublobar resection: 47%</td>
<td>NR</td>
<td>PE: n = 7</td>
<td>NR</td>
</tr>
<tr>
<td>Nagasaki, 1982 [22]</td>
<td>CS</td>
<td>US</td>
<td>961</td>
<td>61</td>
<td>NR (60 d)</td>
<td>All thoracotomy; 8% pneumonectomies, 59% lobectomies, 12% wedge, 5% biopsy procedures</td>
<td>NR</td>
<td>VTE: n = 7; PE: n = 6; DVT: n = 1</td>
<td>n = 11</td>
</tr>
<tr>
<td>Sakuragi, 2003 [23]</td>
<td>CS</td>
<td>Japan</td>
<td>372</td>
<td>NR</td>
<td>NR</td>
<td>All thoracotomy; (type and number NR)</td>
<td>No prophylaxis given</td>
<td>PE: n = 7</td>
<td>NR</td>
</tr>
<tr>
<td>Shapiro, 2010 [24]</td>
<td>CS</td>
<td>US</td>
<td>1,267</td>
<td>61</td>
<td>NR (30 d)</td>
<td>All thoracotomy; 100% pneumonectomies</td>
<td>NR</td>
<td>PE: n = 10; n = 19</td>
<td></td>
</tr>
<tr>
<td>Stamatis, 2002 [25]</td>
<td>CS</td>
<td>Germany</td>
<td>350</td>
<td>NR</td>
<td>NR</td>
<td>All thoracotomy; 35% pneumonectomies, 71% lobectomies, 0.6% segmentectomy, 4% exploration only</td>
<td>NR</td>
<td>PE: n = 2</td>
<td>NR</td>
</tr>
<tr>
<td>Tavecchio 1994 [26]</td>
<td>CS</td>
<td>Italy</td>
<td>57</td>
<td>56</td>
<td>36 months</td>
<td>All thoracotomy; 32% pneumonectomies, 49% lobectomies, 19% exploration only</td>
<td>NR</td>
<td>PE: n = 2</td>
<td>NR</td>
</tr>
<tr>
<td>Yang, 2012 [6]</td>
<td>CS</td>
<td>China</td>
<td>1,001</td>
<td>NR</td>
<td>25.7 mo (median)</td>
<td>NR</td>
<td>Prophylaxis given but not further specified</td>
<td>VTE: n = 53; PE: n = 12; DVT: n = 41</td>
<td></td>
</tr>
<tr>
<td>Ziomek, 1993 [27]</td>
<td>CS</td>
<td>US</td>
<td>77</td>
<td>65</td>
<td>30 d</td>
<td>All thoracotomy; 10% pneumonectomies, 53% lobectomies, 18% segmentectomy, 18% wedge resection</td>
<td>No prophylaxis given</td>
<td>VTE: n = 15; PE: n = 4; DVT: n = 11</td>
<td>n = 1</td>
</tr>
</tbody>
</table>

CS = case series; DVT = deep vein thrombosis; IU = international units; LMWH = low-molecular-weight heparin; NR = not reported; PE = pulmonary embolism; RCT = randomized controlled trial; UFH = unfractionated heparin; VATS = video-assisted thoracoscopic surgery; VTE = venous thromboembolism.
potentially underreported, we cannot give an estimate of this factor. The only conclusion we can draw is that PE is associated with increased mortality.

The American guidelines [28] recommend that all patients undergoing surgical procedures for cancer should receive prophylactic anticoagulation therapy, either preoperatively or as early as possible after the operation, preferably as LMWH. Postoperatively, it should be given for at least for 7 to 10 days. It can be extended to 4 weeks for high-risk patients with postoperative residual lesions, obesity, previous history of VTE, or a combination of these factors [6].

Regarding the impact of the use of antithrombotic prophylaxis, based on our study it is not possible to draw any firm conclusions, because the treatment given was diverse in both type and dose. Only 2 studies specifically did not give prophylactic treatment, whereas in the majority of trials the use of VTE prophylaxis was unreported. We also cannot make any conclusions regarding open procedures versus VATS, because only a very limited number of patients had minimally invasive procedures.

Chew and associates [1] found that patients operated on for lung cancer had a lower risk of VTE compared with those who did not undergo operation (hazard ratio, 0.7). This underlines the assumption that there is a substantial difference between the 2 groups (operated versus non-operated), and that these 2 groups are not comparable regarding the need for antithrombotic prophylaxis.

Only a few studies have evaluated the impact of laboratory test results on the risk of VTE. Merkow and associates [20] found that an elevated platelet count preoperatively substantially increased the overall risk of VTE. However, this is a very limited method of evaluating the coagulation system. Using thromboelastometry (ROTEM [Tem International GmbH, Munich Germany] or TEG [Haemonetics Corp, Braintree, MA]), thrombin generation, and analysis of platelet function, the total coagulation profile can be characterized. This is because both platelet function and the overall hemostatic capacity are evaluated. Thereby, both global and dynamic parameters are investigated [29, 30]. These new methods correlate well with the clinical outcome and may possibly be used as predictors for VTE or bleeding events, or both [31].

Attaran and colleagues [5] used thromboelastography (TEG) and found that patients with lung cancer undergoing surgical procedures were not in a hypercoagulable state. They showed that administration of once or twice daily LMWH might not provide sufficient thromboprophylaxis in specific high-risk patients and advocated screening patients using TEG and ensuring adequate thromboprophylaxis in hypercoagulable patients. However, this has never been tested in a clinical setting.

Our study has several limitations, because the included studies had a substantial interstudy variability, eg, regarding follow-up time, number of patients, comorbidities, and clinical settings. There is also sparse information on surgical technique (open versus VATS), dose of antithrombotic prophylaxis, degree of patient mobilization, and the use of VTE prevention stockings. We advocate early and increased mobilization of patients, relevant daily clinical examination, and identification of patients who have an increased risk of VTE.

Two studies [25, 26] included exclusively patients who underwent neoadjuvant chemotherapy, and there was not an increased risk of VTE compared with those studies in which patients did not receive neoadjuvant chemotherapy. However, because of the limited number of studies (n = 2) in which patients received neoadjuvant chemotherapy, no firm conclusions can be drawn.

The overall incidence of VTE was found to be relatively low. However, this estimate must be taken with caution because of the diversity of the included trials and the methodologic drawback of the studies (ie, predominantly case-series studies including only a small number of patients). Based on these observational studies, there is a risk of VTE in patients undergoing operations for lung cancer, but it appears smaller than in patients not undergoing operations. Recommendations are primarily based on extrapolation from other patient groups, eg, patients undergoing abdominal operations.

In conclusion, the evidence for using thromboprophylaxis after operations for lung cancer is relatively sparse, and its use is based predominantly on clinical consensus. However, the risk of VTE seems to occur predominantly within the initial postoperative period, and subsequently the risk falls. Future research should focus on identifying patients and surgical procedures that increase the risk of VTE. This could be accomplished by large observational studies in addition to randomized controlled trials evaluating different thromboprophylaxis strategies.

Table 2. Incidence of Venous Thromboembolism, Pulmonary Embolism, and Deep Vein Thrombosis Events in Patients Undergoing Operations for Primary Lung Cancer

<table>
<thead>
<tr>
<th>Incidence</th>
<th>VTE Mean and Range Incidence in %</th>
<th>PE Mean and Range Incidence in %</th>
<th>DVT Mean and Range Incidence in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2.0 (0–47)</td>
<td>1.2 (0–47)</td>
<td>0.8 (0–13)</td>
</tr>
<tr>
<td>Within the first postoperative months</td>
<td>2.1 (0–20)</td>
<td>1.3 (0–14)</td>
<td>0.8 (0–14)</td>
</tr>
<tr>
<td>Studies with more than 1 mo of observation</td>
<td>2.9 (0.7–6.5)</td>
<td>1.1 (0.7–3.5)</td>
<td>1.8 (0–5.1)</td>
</tr>
</tbody>
</table>

The studies that did not report the observation period were excluded from the analysis regarding the division of observation time (5 studies).

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
The study was financially supported by Arvid Nilssons fond and Snedkermester Sophus Jacobsen og hustru Astrid Jacobsens Fond. The work was independent of the funders.

References

INVITED COMMENTARY
Christensen and colleagues [1] have reported their review of the literature on venous thromboembolism (VTE) in patients undergoing surgical resection for lung cancer. Their stated aims are to identify the risk of VTE after curative-intent lung cancer resection and to point out areas that require future research. The study is almost entirely descriptive because of the heterogeneous nature of the supporting literature. Additionally, because all but 1 of the studies is retrospective, it is virtually impossible to draw meaningful conclusions that can direct us in our clinical care. Therefore, the most important questions cannot be answered: (1) What is the prevalence of VTE among lung cancer patients who might be surgical candidates; (2) what is the incidence of development of VTE...