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

Thomas D. Christensen, MD, PhD, Henrik Vad, MD, Søren Pedersen, MD, Anne-Mette Hvas, MD, PhD, Robin Wotton, MBChB, Babu Naidu, MD, and Torben B. Larsen, MD, PhD

Department of Cardiothoracic and Vascular Surgery and Institute of Clinical Medicine, Department of Anesthesiology and Intensive Care and Institute of Clinical Medicine, Department of Clinical Biochemistry and Institute of Clinical Medicine, Aarhus University Hospital, Aarhus N, Denmark; Department of Thoracic Surgery, Heart of England NHS Foundation Trust, Birmingham, United Kingdom; University of Birmingham, Birmingham, United Kingdom; Department of Cardiology and Aalborg Thrombosis Research Centre, Aalborg University, Aalborg, Denmark

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.**

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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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Address correspondence to Dr Christensen, Department of Cardiothoracic and Vascular Surgery and Institute of Clinical Medicine, Aarhus University Hospital, DK - 8200 Aarhus N, Denmark; e-mail: tdc@ki.au.dk.

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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 that 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].