Review Article

European perspectives in Thoracic Surgery, the ESTS venous thromboembolism (VTE) working group

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Contributions: (I) Conception and design: Y Shargall; (II) Administrative support: Y Shargall; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Y Shargall; (V) Data analysis and interpretation: Y Shargall; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Venous thromboembolism (VTE), composed of deep vein thrombosis (DVT) and PE is a well-recognized cause for significant perioperative morbidity and mortality. While in orthopedic surgery and general oncology surgery there are well established guidelines regarding VTE prophylaxis, based on carefully conducted high level studies, in thoracic surgery the level of evidence and overall knowledge in the field is still lacking, The European Society of Thoracic Surgeons have established an international working group in 2016, whose task was the define contemporary best practice, coordinate research efforts and eventually define best practice guidelines. This collaboration has matured into a multi-organizational effort, with participation of the American Association for Thoracic Surgery, the International Society on Thrombosis and Haemostasis and Chinese and Japanese thoracic societies. Two major projects (International practice survey and an expert group Delphi process re best practice and VTE risk factors) have been completed so far. For 2018, the working group goals will be to establish VTE prophylaxis guidance in Thoracic Surgery.

Keywords: Venous thromboembolism (VTE); thoracic surgery; deep vein thrombosis (DVT); pulmonary embolus; guidelines

Submitted Mar 26, 2018. Accepted for publication Apr 04, 2018.
doi: 10.21037/jtd.2018.04.70
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.70

Venous thromboembolism (VTE) as a post-operative complication

VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common post-operative complication resulting in significant morbidity, mortality and resource utilization. Without thromboprophylaxis, the incidence of objectively confirmed DVT is 10–40% in general medical and surgical patients and is 40–60% after major orthopedic surgery (1). PE is the third most common cause of cardiovascular death (after myocardial infarction and stroke), the most common preventable cause of hospital death, and is significantly reduced with thromboprophylaxis (1,2). Approximately 20% of all VTE events occur in patients with cancer and more than 20% of cancer patients will be affected by VTE before death (3). In a review of clinical trials of VTE prophylaxis in cancer surgery patients, the average incidence of DVT was 29% in patients who did not receive prophylaxis (4). The American College of Chest Physicians (ACCP) guidelines on peri-operative VTE prevention recommend in-hospital prophylaxis with either low-dose unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (5). For high-risk patients, mechanical prophylaxis with sequential compression devices should be added. Similar recommendations are provided by the British National Institute for Health and Care Excellence (NICE) guidelines (6).

VTE in thoracic surgery

In thoracic surgery, the *de facto* standard-of-care is to administer pharmacological (and mechanical) VTE prophylaxis only until hospital discharge. However, there is limited evidence to support this approach. Moreover, fundamental data regarding the incidence and management of VTE in patients having major thoracic surgery, and especially lung and esophageal resections, are lacking. The only related data involves patients having abdominopelvic cancer surgery, which constitutes a different patient population, due to surgical and anatomic factors, and such data are not necessarily applicable to thoracic surgery patients. The most recent 2012 ACCP guidelines on VTE prevention outline perioperative thromboprophylaxis regimens for a broad spectrum of surgical populations, but reference to thoracic surgery patients is noticeably absent. Thus, for patients having hip or knee replacement, there is grade 1B evidence for short duration (10–14 days) and grade 2B evidence for extended-duration (30–35 days) thromboprophylaxis (7). This latter recommendation is based on large RCTs showing that extended-duration prophylaxis is superior to in-hospital prophylaxis only for the prevention of both asymptomatic (screening venography detected) and symptomatic VTE (1,8-12). The American Society of Clinical Oncology (ASCO) guidelines recommend that all major cancer surgeries receive prophylaxis starting before surgery and continuing for at least 7–10 days, and recommend extended-duration thromboprophylaxis for high-risk abdominopelvic surgery (13). There is no guidance from the ACCP (5) or the ASCO (13) as to a need for extended-duration prophylaxis in thoracic surgery patients. Presently, there is only indirect evidence from the ACCP guidelines to recommend in-hospital VTE prophylaxis with low-dose UFH or LMWH for thoracic cancer surgery (Grade 1B) (5).

VTE in lung resections

The literature describing the clinical burden of postoperative VTE in lung resections is scarce. Older studies reported PE as a common fatal postoperative complication with incidence rates as high as 15.2% of all post-lung cancer resection deaths (14). However, these studies were done when thromboprophylaxis was not routinely used (15). Other studies reported the incidence of PE in this population to be 5% and that of DVT to be 4–14% (14,16,17). A recent systematic review of VTE in patients undergoing lung cancer surgery included 19 studies with a total of 10,660 patients. Apart from one small prospective study (22 patients), all studies were retrospective, observational, predominantly case series and did not systematically collect information on VTE rates. Prophylaxis was used in 5 studies, not used at all in two, and not reported in 12 studies. When VTE was reported over time, the highest risk for developing VTE was within the first month after surgery (18,19). The overall risk for VTE was 2% but the range was wide (0.2–19%) with a low-quality level of evidence (20). Furthermore, the *clinical burden* of postoperative PE in TS patient population is likely underestimated, as some patients with PE might potentially remain clinically undetected with signs and symptoms often attributed to post-thoracotomy/thoracoscopy changes (21). The TS patient population is unique in that several factors increase the thromboembolic risk, including intrinsic pro-coagulant effect of cancer, extensive surgical intervention and dependent limb position in the operating room (15). Local factors related to surgical technique and direct pulmonary vascular injury, including manipulation of the pulmonary arteries and stapling/tying of arterial branches (leading to the resected part) may potentially play an important role in the formation of *in situ* thrombi even without antecedent DVT (21). It is also unclear whether *in situ* thrombi in an arterial stump following resection carry a significant risk to patients, related to propagation and embolization of large clots to other vascular beds, eventually resulting in massive PEs (22-26). VTE appears to be an under-appreciated problem in the TS population, the consequence of which may be that patients are dying, perhaps unnecessarily, due to inadequate thromboprophylaxis. This is particularly concerning given that such patients are having surgery with a curative intent. Indeed, studies of VTE in pneumonectomy patients found that survival was inferior in patients who experienced a VTE after surgery (66%), compared to those who did not experience this event (85%), although the causes of death were not known (19,27). Those studies also found that more than 50% of the events occurred *post discharge*.

VTE and esophagectomy

For esophageal cancer surgery, all guidelines (ACCP, ASCO, NICE) recognize that this patient population is at a high risk for VTE (5,6,13), but specific guidelines for post-esophagectomy thromboprophylaxis are lacking. Instead,

patients having esophagectomy are combined with other thoracic surgery patients or with abdominopelvic surgery populations. Esophageal cancer is one of the deadliest malignancies, with a contemporary 5-year survival rate of 15%. Most patients who will eventually have surgical resection also receive pre-operative chemotherapy or chemo-radiation, which are additional risk factors for VTE (28,29). It is not surprising, therefore, that patients having esophagectomy for cancer are amongst the highest risk populations for perioperative VTE, with rates of symptomatic events of 5–14% (30,31). In-hospital post-esophagectomy mortality increased from 6.9% to 13.6% when VTE occurred (14,32). Reliable estimates as to the incidence of perioperative VTE in esophagectomy patients is limited and only considers symptomatic patients. Uncertainty as to the clinical burden of post-esophagectomy VTE is reflected in a recent survey of U.S. thoracic surgeons regarding practice patterns of prophylaxis. There was substantial variability in post-esophagectomy VTE prophylaxis, with a significant proportion of patients receiving what may be considered as potentially inadequate thromboprophylaxis (33).

Contemporary research activities on VTE in thoracic surgery

Several groups around the world have been actively investigating the field and conducting studies related to risk factors, practice patterns, incidence and extended regimens. The McMaster group had conducted a prospective cohort studies checking the incidence of postoperative VTE in both lung and esophageal resections (34), a Delphi study to analyze practice patterns amongst Canadian surgeons, anesthesiologists and thrombosis experts (35), and is currently completing a pilot randomized control trial comparing 30 days post-hospital discharge administration of low molecular weight heparin with placebo (ClinicalTrials.gov, NCT0311554). The Boston University group has extensively studied risk stratification of thoracic surgery patients with a Caprini scoring system in which moderate and high-risk patients receive prolonged postoperative chemoprophylaxis with LMWH to decrease the risk of VTE (36-39). The group from Beijing Chao-Yang Hospital, Capital Medical University has been studying the incidence of perioperative VTE in thoracic surgery patients not receiving perioperative chemical prophylaxis (Dr. Hui Li, unpublished data, see ESTS 2018 abstracts for more details). The Cleveland clinic group investigated the incidence and clinical manifestations of VTE post pneumonectomy (19). All those groups are represented at the ESTS VTE working group.

The ESTS working group on VTE in Thoracic Surgery

Recognizing the aforementioned lack of high-level evidence for VTE prophylaxis best practice in Thoracic Surgery, as well as the very noticeable wide variety of practice patterns with very little consensus in the field (35), in 2016, the ESTS formed a working group composed of thoracic surgeons, hematology and thrombosis experts and respirologists with the task of better defining the field of VTE prophylaxis in thoracic surgery. This working group has also composed a unique collaboration with the American Association of Thoracic Surgeons (AATS) and the International Society for Thrombosis and Haemostasis (ISTH), with senior experts from both organizations represented at the working group. The working group defined several mandates related to its work: (I) establishing current practice of VTE prophylaxis within the ESTS and AATS communities, and exploring prophylaxis patterns in countries and organizations beyond the those of ESTS/AATS; (II) to establish current expert opinion re VTE prophylaxis in Thoracic Surgery; (III) to oversee VTE related research initiatives and collaborations between centres and organizations, and ultimately; (IV) to establish contemporary guidelines or guidance for VTE prophylaxis in Thoracic Surgery, pending availability of high level evidence or expert opinion agreement paper if the formers are lacking. The expert group met during the 2017 ESTS meeting in Innsbruck, Austria and an additional meeting of part of the group took place in Boston 2017. A third meeting is planned during the 2018 ESTS annual meeting.

Current and future projects of the ESTS VTE working group

So far, two projects have been completed and are now in final stage before publications, pending a review process:

An international survey to evaluate the contemporary practice patterns of VTE prophylaxis amongst Thoracic Surgeons worldwide: Between 2016 and 2017, the ESTS has approached AATS, the Chinese Society of Thoracic Surgeons and the Japanese Association of Thoracic Surgeons (JATS) to create the most comprehensive survey to date, the results of which were presented during the 2017

meeting. A total of 1,609 thoracic surgeons (ESTS: 193; AATS: 139; China: 1,151; Japan: 126) responded to series of questions related to surgical volumes, current practices and institutional VTE prophylaxis details. Most responders practice in academic centres and were the individuals who decided prophylaxis regimens. There was wide variety regarding agents used, though most surgeons preferred LMWH. Prophylaxis starting time varied widely: In Asia most surgeons indicated they start in the first postoperative day whereas ESTS and AATS members most commonly started within 2–6 hours of incision time (before or after surgery). Most ESTS and Japanese surgeons prescribed extended VTE prophylaxis following esophagectomy whereas most AATS and Chinese surgeons did not. Finally, the vast majority (>90%) of participants indicated they are likely or very likely to use new thoracic surgery specific VTE prophylaxis guidelines if and when they are available (40).

The expert group, composed of 20 members from eight countries (15 thoracic surgeons, 4 international thrombosis experts and 1 oncology-respirologist with vast experience in VTE research) performed a modified Delphi exercise (41) to try and reach a consensus on VTE prophylaxis methods in Thoracic Surgery. The protocol consisted of 20 structured questions, which the responders were asked to rank (on a scale from 1–10) their agreement regarding chemical and mechanical methods used for prophylaxis, risk factors for VTE, timing and duration of prophylaxis and the role of extended prophylaxis. The process included 3 rounds, the first and last done on-line and the second during the 2017 ESTS meeting. After each round, statistical analysis was performed, in order to identify areas of consensus. If a consensus was reached, the specific question was removed from the next round. The participants were also asked to provide a narrative feedback regarding what they considered the most important points related to VTE prophylaxis. After the last round, a consensus (defined as coefficient of variant of ≤0.3) was obtained for only a single question. The narrative comments identified several points which will form the basis for an expert opinion guidance, currently under development.

The group is going to meet again during the 2018 ESTS. Potential projects to discuss will include: (I) writing thoracic-specific best practice guidelines, which, for the current time, will be based on a limited evidence but mostly on the results of the aforementioned projects and the opinions of the expert group; (II) potential future role for NOACs/DOACs (stands for Non vitamin-K Oral Anti Coagulants or Direct Oral Anti Coagulants) usage for extended VTE prophylaxis in thoracic surgery, given emerging evidence for its safety and non-inferiority for both surgical and cancer patients (42); (III) development of Thoracic Surgery specific risk assessment model to predict the likelihood of perioperative VTE and accordingly to guide prophylaxis for specific risk groups.

Summary

VTE is a significant cause for morbidity and mortality after thoracic surgery. At the current time, there are no thoracic surgery specific guidelines, nor high level evidence to direct them. However, several groups of researchers worldwide are currently making promising progress in the field. The ESTS working group has been instrumental in gathering together thoracic oncology and thrombosis experts and in establishing collaborations with more organizations such as the AATS, ISTH, JATS and the Chinese association of Thoracic Surgeons. It is our hope that over the next few years we will be able to develop the first thoracic surgery VTE prophylaxis guidelines.

Acknowledgements

The authors would like to thank the members of the VTE working group for their support in this work: Drs. Sudish Murthy, Luca Bertolaccini, Lori-Ann Linkins, Alessandro Brunelli and John Agzarian.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Shargall Y, Litle VR. European perspectives in Thoracic Surgery, the ESTS venous thromboembolism (VTE) working group. J Thorac Dis 2018;10(Suppl 8):S963-S968. doi: 10.21037/jtd.2018.04.70

