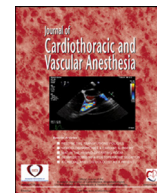


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## Editorial

## How to Mitigate the Risk of Postoperative Thromboembolism in Thoracic Cancer Surgery: Comments on the Joint 2022 European Society of Thoracic Surgery and American Association of Thoracic Surgery Guidelines for the Prevention of Cancer-Associated Venous Thromboembolism in Thoracic Surgery

VENOUS THROMBOEMBOLIC EVENTS (VTE), manifesting as deep venous thrombosis and pulmonary embolism, are important complications in patients after major surgery and are potentially devastating.<sup>1-3</sup> The importance of preventive measures has been recognized for decades, and thromboprophylaxis in the early postoperative period can reduce the risk of VTE by up to 70%.<sup>1,4,5</sup> However, even with prophylactic administration of anticoagulants, VTE after major surgery remains common and might account for up to 25% of all VTE observed in the general population.<sup>6</sup> In addition, the advantage of pharmacologic thromboprophylaxis must be balanced against the increased risk of postoperative bleeding.<sup>1</sup>

Patients undergoing thoracic surgery represent a subset of patients with a high risk of postoperative thromboembolic complications.<sup>7,8</sup> A large percentage of these patients have advanced malignancies, accompanying comorbidities like chronic obstructive pulmonary disease and pulmonary hypertension, extensive surgical resection, prolonged immobilization, and the requirement for longer hospitalization.<sup>7</sup> These risk factors, combined with tumor-associated hypercoagulability, endothelial injury, and venous stasis, summarized as the “Virchow’s triad,” increase the risk of fatal VTE. Timely and adequate preventive measures are advised,<sup>8,9</sup> but the evidence for optimal VTE prophylaxis in thoracic surgery patients is limited and primarily based on clinical consensus.<sup>1,9</sup> Accordingly, institutional practices of VTE prophylaxis vary widely.<sup>7,8</sup>

The recently published guidelines by a Joint Committee of the European Society of Thoracic Surgery (ESTS) and the American Association of Thoracic Surgery (AATS)<sup>10</sup> highlighted some of the ambiguity of this clinically relevant problem. In these guidelines, 3 clinical settings in patients with

cancer-associated thoracic surgery (lobectomy/segmentectomy, pneumonectomy/extended lung resections, and esophagectomy) were evaluated for the following 5 interventions: (1) pharmacologic prophylaxis, (2) mechanical prophylaxis, (3) duration of prophylaxis, (4) pre- versus postoperative administration of prophylaxis, and (5) routine postoperative screening for VTE. An abbreviated summary of the most important recommendations is given in [Table 1](#). Notably, the recommendations in these guidelines are mostly conditional rather than strong and were based on low-to-very low certainty of evidence.

### The Importance of the New Guidelines for the Perioperative Physician and Their Potential Influence on Clinical Practice Patterns

The reported incidence of VTEs after thoracic surgery including lung resection relevantly varies with reported incidences of 0.2%-to-27%, with a mean risk of 2-to-4%.<sup>7,9,11,12</sup> The performed surgery (cancer *v* noncancer, open *v* minimally invasive), implementation of early recovery after surgery programs, and cancer characteristics might relevantly influence postoperative VTE risk.<sup>13,14</sup> For example, pneumonectomy was associated with a 3-times increased VTE risk compared with lobectomy, in a large retrospective database analysis, and open resection had a higher risk than minimally invasive resections.<sup>15</sup> For minimally invasive thoracic surgery, perioperative coagulation activation might be at lowest extent.<sup>13</sup> Further, the different methods of detecting venous thromboembolism (routine screening *v* symptomatic patients only), type of postoperative prophylaxis (pharmacologic/mechanical), and timing of thromboprophylaxis might explain the highly variable VTE incidences.

Table 1  
Short Summary of Suggestions From the Joint 2022 ESTS/AATS Guidelines

	Lobectomy/segmentectomy	Pneumonectomy	Esophagectomy
Pharmacologic prophylaxis	Use LMWH (or UFH sc) <i>Conditional recommendation, low certainty</i>	Use LMWH (or UFH sc) <i>Conditional recommendation, low certainty</i>	Use LMWH (or UFH sc) <i>Conditional recommendation, low certainty</i>
Mechanical prophylaxis	Use combined mechanical and pharmacological prophylaxis <i>Conditional recommendation, very low certainty</i>	Use combined mechanical and pharmacological prophylaxis <i>Conditional recommendation, very low certainty</i>	Use combined mechanical and pharmacological prophylaxis <i>Conditional recommendation, very low certainty</i>
Duration	Extended prophylaxis (28-35 d) in patients with moderate to high thromboembolic risk <i>Conditional recommendation, low certainty</i>	Extended prophylaxis (28-35 d) <i>Conditional recommendation, low certainty</i>	Extended prophylaxis (28-35 d) <i>Conditional recommendation, low certainty</i>
Pre- v postoperative pharmacologic prophylaxis	No recommendation	No recommendation	No recommendation
Routine postoperative screening for VTE	No routine screening <i>Conditional recommendation, very low certainty</i>	Routine screening suggested <i>Conditional recommendation, very low certainty</i>	Routine screening suggested <i>Conditional recommendation, very low certainty</i>

Abbreviations: AATS, American Association of Thoracic Surgery; ESTS, European Society of Thoracic Surgery; LMWH, low-molecular-weight heparin; sc, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolic events.

As VTEs are a major complication after cancer surgery, perioperative VTE prophylaxis is considered a standard of care in most guidelines.<sup>4,16-18</sup> Accordingly, >85% of European and United States centers performing thoracic cancer surgery had formal institutional VTE prophylaxis protocols based on the presumably best evidence.<sup>8</sup> However, there is a lack of consensus with respect to the timing and dosing of perioperative prophylaxis and, more importantly, to extended VTE prophylaxis after hospital discharge.<sup>7-9,15,19</sup>

Patients undergoing thoracic surgery for cancer deserve special consideration, as hemostatic abnormalities manifesting with hypercoagulability and/or bleeding disorders occur in most cancer patients.<sup>1,20</sup> The pathogenesis of blood coagulation activation in cancer is complex, multifactorial, and still not fully understood.<sup>20</sup> It also might vary with cancer type and stage. However, recently published guidelines from the European Association of Anaesthesiology and Intensive Care, the American College of Chest Physicians, the American Society of Hematology, and the American Society of Clinical Oncology did not specifically consider such factors.<sup>16,18,21,22</sup> The Joint 2022 ESTS/AATS guidelines focused for the first time specifically on patients undergoing different clinical situations of cancer-associated thoracic surgery, and provided evidence for specific conditions regarding perioperative thromboprophylaxis.<sup>10</sup>

In the Joint 2022 ESTS/AATS guidelines, the use of low-molecular-weight heparin (LMWH) was suggested.<sup>10</sup> Subcutaneously administered unfractionated heparin (UFH) could be considered an alternative, but with lower evidence for efficacy.<sup>10</sup> The preference for LMWH might be based on data derived from general surgery patients included in randomized trials and meta-analyses.<sup>23</sup> Most showed a similar or superior efficacy of LMWH compared with UFH. However, there is limited evidence for using LMWH instead of UFH in thoracic surgery patients. A survey among Canadian specialists in the perioperative care of thoracic cancer surgery showed that only

44% of practitioners used LMWH once daily, whereas about 53% of physicians preferred the subcutaneous administration of UFH 2-to-3 times daily.<sup>7</sup>

Further, optimal dosing and perioperative timing of pharmacologic VTE prophylaxis are unclear.<sup>24</sup> A preoperative administration of LMWH for VTE prophylaxis seems common in clinical practice,<sup>7,8</sup> but evidence for its beneficial effects is scarce. Similarly, the optimal dosing remains unclear. A recent study in thoracic surgery patients concluded that the commonly applied LMWH dose (40 mg of enoxaparin) might be insufficient to protect most patients adequately from VTE.<sup>25</sup> This conclusion was based on testing of anti-Xa activity only.<sup>25</sup> In some agreement, a small randomized controlled trial investigating prophylaxis with LMWH (dalteparin, 5000 U once daily) versus no prophylaxis found no differences in coagulation profile between the 2 groups.<sup>26</sup> Evaluation of thromboembolic events rather than changes in coagulation tests might be of more clinical relevance. Unfortunately, the number of included patients was too low for meaningful clinical conclusions.<sup>26</sup> Another randomized controlled trial in 111 patients undergoing esophagectomy compared LMWH (nadroparin) twice a day (intensified prophylaxis) with once a day only (standard of care) starting 6 hours after surgery. Venous thromboembolic event prophylaxis was continued until day 7 after surgery. The authors found significantly less VTE with intensified prophylaxis as compared with standard care (0% v 9%,  $p = 0.03$ ).<sup>27</sup> The Joint 2022 ESTS/AATS did not make specific recommendations on dosage or targets of anticoagulation.<sup>10</sup> Potentially, the individualized VTE prophylaxis based on factors such as the timing (elective or emergency), type, and duration of surgery, the estimated risk of bleeding, and especially the patient's baseline risk of VTE (eg, Caprini score<sup>28,29</sup>), seems more recommendable.<sup>10,11,26,28</sup>

Recently, extended VTE prophylaxis has gained specific attention. In a large retrospective database analysis including

>14,000 patients undergoing lung cancer surgery, 44% of identified VTE occurred after hospital discharge.<sup>15,30</sup> The use of extended out-of-hospital prophylaxis for 4-to-6 weeks after surgery is an established and recommended practice in other surgical specialties such as high-risk orthopedic and major oncologic abdominal surgery.<sup>22</sup> In thoracic surgery, surveys reported no agreement among perioperative chest physicians regarding recommended agents or factors mandating the usage of extended VTE prophylaxis.<sup>7,8</sup> A recent study in patients undergoing lung cancer surgery showed that extended VTE prophylaxis with LMWH (dalteparin) for 28 days was safe and might have reduced the incidence of pulmonary embolism.<sup>19</sup> Alternatively, the use of fondaparinux is recommended by the British National Institute for Health and Clinical Excellence for extended VTE prophylaxis in thoracic cancer surgery.<sup>31</sup> The optimal length of prophylaxis, however, remains unclear. The Joint 2022 ESTS/AATS guidelines suggested extended prophylaxis for 28-to-35 days in patients undergoing lobectomy and/or segmentectomy, and moderate-to-high thromboembolic risk, as well as all patients undergoing pneumonectomy, extended lung surgery, and esophagectomy. At the authors' institution, VTE prophylaxis for up to 6 months is sometimes used in patients at high risk for thromboembolism or pulmonary hypertension after pneumonectomy. The long-term use of LMWH or fondaparinux might be acceptable for most patients. However, oral anticoagulants might be preferred for extended VTE prophylaxis. Notably, the optimal range of anticoagulation level (international normalized ratio) during prophylactic therapy with vitamin K antagonists is unknown, and experience using direct oral anticoagulants is limited. Clinical data and studies with direct oral anticoagulants are limited to nonthoracic surgery,<sup>32,33</sup> and are urgently warranted in thoracic cancer surgery before further recommendations can be made.<sup>10</sup>

Finally, the clinical burden of postoperative VTE in thoracic surgery is probably underestimated.<sup>15</sup> Perioperative and postoperative VTE can be asymptomatic, which may be the reason for the low incidence of postoperative VTE reported in some studies. It is unclear whether asymptomatic VTE has the same clinical impact as symptomatic VTE. However, evidence suggesting a systematic screening in all thoracic surgery patients does not (yet) exist. The Joint 2022 ESTS/AATS guidelines specifically suggested a VTE screening in patients after a pneumonectomy, extended lung surgery, and esophagectomy.<sup>10</sup> The optimal diagnostic test (eg, computed tomography with pulmonary angiogram/ultrasound) remains to be defined. Of note, the sensitivity of modern computed tomography devices bears the risk of overtreatment with anticoagulants in patients with clinically irrelevant emboli. It remains unclear whether the increased bleeding risk outweighs the beneficial effect of antithrombotic therapy.

### How the New Guidelines Differ From Former Guidelines

Recently, guidelines regarding postoperative thromboembolism prophylaxis from 4 important societies were published. The American College of Chest Physicians guidelines recommended using in-hospital routine VTE prophylaxis with either low-dose UFH or LMWH for the postoperative thoracic

surgery population (grade 1B evidence).<sup>17</sup> In the updated American College of Chest Physicians guidelines, no further specific recommendation regarding thromboembolic prophylaxis in thoracic surgery was given.<sup>4</sup>

The European Society of Anesthesiology and Intensive Care (ESAIC) guidelines from 2019 suggested using a combined pharmacologic and mechanical VTE prophylaxis (grade 2B recommendation), given that most patients undergoing thoracic surgery should be considered to belong to the high-risk population for VTE.<sup>16</sup> In agreement with the Joint 2022 ESTS/AATS guidelines, mechanical prophylaxis without pharmacologic prophylaxis should be used only in patients with contraindications for pharmacologic VTE prophylaxis (recommendation 1B).<sup>16</sup> Of note, the ESAIC guidelines suggested not differentiating between patients undergoing open or thoracoscopic cancer-associated thoracic surgery with respect to risk stratification.<sup>16</sup> Finally, the ESAIC guidelines supported early ambulation as part of the early recovery after surgery program to potentially reduce the VTE risk in thoracic surgery.<sup>14</sup>

The 2019 American Society of Hematology guidelines for managing VTE did not specifically comment on perioperative VTE prevention in thoracic surgery. In partial agreement with the ESTS/AATS and the ESAIC guidelines, the American Society of Hematology guidelines suggested a combined pharmacologic and mechanical prophylaxis over pharmacologic alone, and an extended (considered as >3 weeks) prophylaxis in major surgery. However, both recommendations were conditional with low certainty.<sup>18</sup>

Finally, the American Society of Clinical Oncology recommended in their 2019 guidelines that all patients with malignant diseases undergoing major surgery (including thoracic) should receive pharmacologic thromboprophylaxis with LMWH or UFH unless contraindicated by active bleeding or high bleeding risk (strong recommendation). Again, these guidelines recommended the combined pharmacologic and mechanical approach to potentially improve efficacy, especially in the highest-risk population (strong recommendation). Extended prophylaxis for up to 4 weeks has specifically been recommended for abdominal and pelvic cancer surgery but not for thoracic cancer surgery.<sup>22</sup>

### Conclusion

The Joint 2022 ESTS/AATS guidelines provided valuable evidence-based recommendations for patients undergoing thoracic surgery for lung and esophageal cancer. This population at high risk for VTE has not been considered adequately in most former guidelines that issued recommendations on VTE prevention in major surgery and patients with cancer undergoing surgery. However, their evidence was limited, partially controversial, and based on experts' opinions. An individual and adapted VTE prophylaxis might be considered in many patients undergoing lung cancer surgery based on hemostatic history, lung, and pulmonary vascular morbidity, resection type, and general physical condition. Potentially, application risk scores, such as the Caprini score, could help select patients who might qualify for postoperative VTE screening and intensified

and/or extended prophylaxis.<sup>28,29</sup> Further clinical trials are vital to further support the evidence behind our medical decisions.

### Conflict of Interest

None.

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