

Management of venous thromboembolism in patients with lung cancer: a state-of-the-art review

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ABSTRACT

Venous thromboembolism (VTE) is common and life-threatening in patients with lung cancer. Management of VTE is critical for patients with lung cancer. Risk assessment, thromboprophylaxis and treatment of VTE constitute the core issues of VTE management in patients with lung cancer. Although its overall principles should follow recommendations in authoritative guidelines, VTE management in patients with lung cancer may be slightly special in some specific aspects. Despite the extensive validation of Khorana score for patients with all cancer types, its value in VTE risk assessment of patients with lung cancer is controversial. It is important to determine the VTE risk assessment score that can accurately and specifically assess the VTE risk of patients with lung cancer. Clinical practice patterns of thromboprophylaxis may vary by cancer types, since different sites of cancer may have different levels of VTE risk. To understand the thromboprophylaxis specific for lung cancer is of vital importance for patients with lung cancer. Although it is essential to comply with authoritative guidelines, the duration and timing of initiation of thromboprophylaxis in surgical patients with lung cancer may need further study. Taken together, the purpose of this review is to provide an overview of state-of-the-art VTE stewardship specific for patients with lung cancer.

INTRODUCTION

Venous thromboembolism (VTE) is broadly defined as deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis and splanchnic vein thrombosis, whereas narrowly defined as DVT and PE.^{1–3} Epidemiological statistics demonstrated that annual incidence rates of PE range from 39 to 115 per 100 000 population, whereas incidence rates of DVT range from 53 to 162 per 100 000 population. Acute PE is the third most frequent acute cardiovascular diagnosis just behind myocardial infarction and stroke globally.^{2,3}

VTE is a common and life-threatening condition in patients with cancer.^{1,4–6} Among all cancer types, lung cancer is the second most common type with the highest mortality rate globally.^{7,8} Lung cancer is one of the

cancer types that carry the highest risk of VTE and is one of the predisposing factors that predict the risk of VTE recurrence.^{2,3} Patients with lung cancer have an overall VTE incidence of 39.2 per 1000 person-years.⁹ Previous studies demonstrated that prevalence of VTE in patients with lung cancer approximately ranges from 2% to 15%.^{10–15}

VTE is associated with an increased mortality and could be an indicator of mortality in patients with lung cancer.^{9,11,13–16} Patients with lung cancer who develop VTE have an approximately 50% higher risk of mortality than those who do not.⁹ Overall survival (OS) after the diagnosis of VTE in lung cancer patients with VTE which ranges from 14.2 to 23.4 months is significantly shorter than those without VTE that ranges from 24.4 to 45.8 months.^{11,13} The 1-year mortality rate after VTE diagnosis in patients with lung cancer is 60.7%.¹⁵ VTE is an independent predictor of mortality in patients with lung cancer.^{14,16}

The median time interval from diagnosis of lung cancer to diagnosis of VTE approximately ranges from 1.4 months¹⁷ to 2.9 months.¹⁸ With respect to the comparison among different presentations of VTE due to lung cancer, concurrence of DVT and PE indicates the severest status of lung cancer, the earliest occurrence of VTE and the worst survival rate, whereas DVT indicates the mildest status of lung cancer and most stable pattern of VTE.¹⁷

The core issues of VTE management in patients with cancer consist of risk assessment, thromboprophylaxis and VTE treatment.^{1,4–6} Nevertheless, since authoritative guidelines of cancer-associated VTE were written for all cancer types, divergence of VTE management may exist among different cancer types.^{4–6} In other words, although it should follow recommendations of authoritative guidelines in general principles, the management of VTE in patients with lung cancer is special in some details compared with other cancer types.

Accordingly, this review is aimed at the state-of-the-art risk assessment, thromboprophylaxis and treatment of VTE specific for lung cancer.

We searched PubMed from database inception to 1 September 2022, for clinical literature published in English by using diverse combinations of 'lung cancer', 'venous thromboembolism', 'guidelines', 'epidemiology', 'risk assessment', 'prophylaxis', 'treatment' and 'management'. We mainly selected high-quality literature from the past 5 years, whereas considered older publications when the latest evidence was unavailable, or of low quality. Authoritative comprehensive reviews that were published within the past 3 years were also thoroughly read, and their reference lists were reviewed one by one.

ASSESSMENT

Due to the severe morbidity and mortality in patients with lung cancer complicated with VTE, missing a VTE diagnosis or thromboprophylaxis need could be devastating for patients with lung cancer, whereas frequently applying VTE diagnostic tests and/or thromboprophylaxis to all patients with lung cancer definitely increase unnecessary burden. Accordingly, risk assessment of VTE is imperative prior to the diagnostic tests and/or thromboprophylaxis of VTE for patients with lung cancer. Risk assessment of VTE mainly include identifying VTE risk factors and assessing the VTE risk of patients with established VTE risk assessment scores.

Risk factors

A time-dependent association exists between VTE and cancer. The risk factors of VTE occurrence in patients with cancer comprise patient-related, cancer-related, treatment-related factors and a combination of the aforementioned categories. Risk factors for VTE in patients with cancer are mainly cancer sites, metastasis stage, hospitalisation, central venous catheters, surgery, systemic medical anticancer therapies, history of previous VTE, cardiovascular diseases, obesity, immobility, thrombocytosis, leucocytosis and high D-dimer level.⁴ For lung cancer, previous studies showed that risk factors that are associated with the development of VTE mainly comprise but not limited to metastatic disease, adenocarcinoma subtype, chemotherapy administration, emergency admission, weight, performance status (PS), C-reactive protein (CRP), prothrombin time (PT), D-dimer, body mass index (BMI), major vessel infiltration, tyrosine kinase inhibitor (TKI) genetic mutation, surgery, immune checkpoint inhibitor (ICI) therapy and central venous catheter (CVC).^{9 13 17 19–24} Among the aforementioned factors, TKI genetic mutations, surgery and ICI therapy are the most noteworthy ones in recent years.

TKI genetic mutations

A multitude of clinical studies explored the relationship between VTE development and TKI genetic mutations in patients with non-small cell lung cancer (NSCLC).

In all types of TKI genetic mutations, the presence of anaplastic lymphoma kinase (ALK) rearrangement is associated with increased incidence of VTE development in patients with NSCLC.^{21 25–33} This could be related to a higher tissue factor (TF) expression in tumour tissues of patients with NSCLC.²⁷ Besides ALK, the presence of c-ros oncogene 1 (ROS1) rearrangement is also associated with increased incidence of VTE development in patients with NSCLC.^{20 31 33–35} NSCLC patients with ROS1 rearrangement have similar or even higher risk of VTE development than those with ALK rearrangement.^{20 31 33} With respect to the association between VTE development and epidermal growth factor receptor (EGFR) mutations in patients with NSCLC, results are inconsistent among previous studies. No significant association between EGFR mutation and VTE development in patients with NSCLC is found in most studies.^{20 27–33} Nevertheless, in one prospective cohort study, EGFR mutation has a negative correlation with the risk of VTE development in Chinese patients with NSCLC.²⁶ In another prospective study, EGFR mutation is an independent risk factor for postoperative VTE development in patients with lung adenocarcinoma.³⁶ The evidence of relationship between VTE development and programmed cell death 1-ligand 1 (PD-L1) in patients with lung cancer is scanty, except one retrospective study revealed that PD-L1 expression may indicate an increased risk of PE in patients with NSCLC.²⁸

Surgery

Postoperative VTE is not uncommon in patients with lung cancer who undergo surgery. Previous studies reported that the incidence of VTE after lung cancer surgery ranges from 4.5% to 13.9%.^{10 12 22 37–40} For patients with lung cancer who undergo thoracic surgery, there are some specific risk factors for postoperative VTE development. Previous studies revealed that immobilisation, bedridden status, central venous catheters, sepsis, use of sedative or anaesthetic drugs, surgical time, mechanical ventilation, D-dimer level, age over 60 years, more extensive surgery than lobectomy and stage IV of lung cancer are associated with the development of VTE for patients with lung cancer who undergo thoracic surgery.^{22 38 39 41} Among the aforementioned risk factors, daily post-thoracic surgery measurement of D-dimer combined with other thrombosis-related risk factors may improve the prediction of VTE in patients with lung cancer.³⁹

ICI therapy

Patients with cancer who undergo ICI therapy are at high risk of VTE.²³ In one retrospective study, the cumulative incidence of VTE in patients with NSCLC who received ICI therapy was 14.8% for an incidence rate of 76.5 thromboses per 1000 person-years. Most thromboses occurred immediately after ICI treatment initiation. Age younger than 65 years old, tumours with PD-L1 ≥ 1 , a delay of less than 12 months from diagnosis to the first ICI treatment and active smoking are associated with more VTE events after 12 months of ICI initiation. Nevertheless, VTE was

not correlated with OS, progression-free survival (PFS) or objective response to ICIs.⁴² However, in another retrospective study, 6-month cumulative incidence of VTE in the ICI cohort (4.5%) was lower than that in the chemotherapy cohort (7.1%). Among ICI-treated patients, the high-risk Khorana score (KS) group was prone to have a lower VTE incidence compared with the low-risk KS group.⁴³

Risk assessment model

Notwithstanding there are diverse risk factors for VTE development in patients with lung cancer, a single risk factor does not reliably identify patients with cancer at high risk of VTE development. In ambulatory patients with cancer treated with systemic therapy, the assessment of VTE development and thromboprophylaxis need is usually performed with validated VTE risk assessment scores.^{4,5} The contemporary VTE risk assessment models (RAMs) for ambulatory patients with cancer in the authoritative guidelines mainly comprise the KS, the Vienna score, the PROTECHT score, the CONKO score, the ONKOTEV score, the COMPASS-CAT score, the Tic-Onco score and the CATS/MICA score. The Vienna score, the PROTECHT score, the CONKO score and the ONKOTEV score are modified KS.^{4,5} Nevertheless, most of the aforementioned VTE risk assessment scores have not been validated specific for patients with lung cancer. In addition, mixed results were produced in the external validation of VTE risk assessment scores recommended by the guidelines^{4,5} for patients with lung cancer. The comparison of performance among authoritative cancer-associated VTE RAMs in guidelines in medical patients with lung cancer is illustrated in [table 1](#).

Khorana score

The KS consists of primary site of cancer, prechemotherapy platelet count of $350 \times 10^9/L$ or more, haemoglobin level $<100 \text{ g/L}$ and/or use of red cell growth factors, leucocyte count $>11 \times 10^9/L$ and body mass index (BMI) of 35 kg/m^2 or more.⁴⁴ As the most extensively validated VTE risk assessment score for patients with cancer,^{4,5} the KS does not perform very well in VTE risk assessment of patients with lung cancer. Several studies consistently confirmed the poor performance of the KS in VTE risk assessment of patients with lung cancer.^{45–51} However, compared with the original KS, a modified one which incorporated D-dimer had a higher predictive value for the risk of VTE occurrence in newly diagnosed patients with lung cancer. Its sensitivity is high enough to fully identify high-risk VTE when the cut-off value is at 2.⁵¹ In addition, the KS is an independent risk factor for mortality in patients with lung adenocarcinoma who receive first-line or adjuvant chemotherapy.⁴⁷

COMPASS-CAT score

The COMPASS-CAT score consists of anti-hormonal or anthracycline therapy, time since cancer diagnosis

≤ 6 months, central venous catheter, advanced stage of cancer, cardiovascular risk factors, recent hospitalisation, history of VTE and platelet count $\geq 350 \times 10^9/L$.⁵² In one retrospective study, the efficiency of VTE risk assessment among the Khorana, PROTECHT, CONKO and COMPASS-CAT scores were compared for 118 outpatients with lung cancer. Only the COMPASS-CAT score identified 100% of patients who developed VTE, and best discriminated patients at high from those at low risk of VTE development (C-statistic 0.89).⁴⁶

ONKOTEV score

In a retrospective study that explored which authoritative risk assessment score of cancer-associated VTE was most suitable for the risk assessment of VTE occurrence in 1263 hospitalised medical patients with lung cancer, the ONKOTEV score had the highest adjusted agreement (78.6%) and Youden index (0.68) with respect to the assessment efficiency for VTE occurrence among the Khorana, the PROTECHT, the CONKO, the ONKOTEV, the COMPASS-CAT and the CATS/MICA scores. The ONKOTEV score is an optimal model for the assessment of VTE occurrence in hospitalised medical patients with lung cancer. Despite this, such conclusion may not be applicable to ambulatory or surgical patients with lung cancer.⁵³

RAMs specific for lung cancer

The VTE risk assessment scores recommended by authoritative guidelines are designed for all cancer types, whereas not specific for patients with lung cancer.^{4,5} In recent years, several studies endeavoured to establish VTE risk assessment scores specific for patients with lung cancer. RAMs specific for risk assessment of VTE in patients with lung cancer are demonstrated in [table 2](#).

ROADMAP-CAT score

The ROADMAP-CAT study established a VTE risk assessment score for patients with lung adenocarcinoma. According to the ROADMAP-CAT score, patients with procoagulant phospholipid-dependent clotting time (Procoag-PPL) $<44 \text{ s}$ and mean rate index of thrombin generation (MRI) $<125 \text{ nM/minute}$ are stratified at high-risk VTE group, whereas those with procoag-PPL $>44 \text{ s}$ or MRI $>125 \text{ nM/min}$ are stratified into intermediate or low-risk VTE group. Based on such stratification, the sensitivity and specificity for assessment of VTE development was 88% and 52% in patients with lung adenocarcinoma, respectively. The measurement of aforementioned biomarkers and their incorporation into the COMPASS-CAT score significantly improve the capacity of this model to stratify patients into different VTE risk strata.⁵⁴

Score of Alexander

Alexander *et al* established a VTE risk assessment score which consists of fibrinogen $\geq 4.0 \text{ g/L}$ as well as D-dimer $\geq 0.5 \text{ mg/L}$, D-dimer $\geq 1.5 \text{ mg/L}$ at baseline and D-dimer



Table 1 Comparison of performance among authoritative cancer-associated VTE RAMs in guidelines in medical patients with lung cancer

RAMs	Items	Score	High risk	Be validated in ambulatory patients with lung cancer	Be validated in inpatients with lung cancer
Khorana	Cancer site		Score ≥ 3	No	No
	Very high-risk site (stomach, pancreas)	2			
	High-risk site (lung, lymphoma, gynaecologic, bladder, testicular)	1			
	Platelet count $\geq 350 \times 10^9/L$	1			
	Haemoglobin < 100 g/L and/or use of ESA	1			
	Leucocyte count $> 11 \times 10^9/L$	1			
	BMI ≥ 35 kg/m ²	1			
Vienna	Khorana score		Score ≥ 3	Unknown	Unknown
	D-dimer ≥ 1.44 $\mu\text{g/mL}$	1			
	Soluble P-selectin ≥ 53.1 ng/mL	1			
PROTECHT	Khorana score		Score ≥ 3	No	No
	Gemcitabine chemotherapy	1			
	Platinum-based chemotherapy	1			
CONKO	Khorana score with BMI ≥ 35 kg/m ² being replaced with ECOG PS ≥ 2	1	Score ≥ 3	No	No
ONKOTEV	Khorana score > 2	1	Score ≥ 2	Unknown	Yes
	Metastatic disease	1			
	Previous VTE	1			
	Vascular/lymphatic macroscopic compression	1			
COMPASS-CAT	Anthracycline treatment	6	Score ≥ 7	Yes	No
	Time since cancer diagnosis ≤ 6 months	4			
	CVC	3			
	Advanced stage of cancer	2			
	Cardiovascular risk factors	5			
	Hospitalisation for acute medical illness	2			
	A history of VTE	1			
	Platelet count $\geq 350 \times 10^9/L$	2			
Tic-Onco	BMI > 25 kg/m ²	Not mentioned	\geq point which maximises the Youden index	Unknown	Unknown
	Family history				
	Cancer site				
	HR				
	VHR				
	Cancer stage				
	GRS				
	rs2232698				
	rs6025				
	rs5985				
rs4524					
CATS/MICA	Cancer site	Nomogram	Score ≥ 110	Unknown	No
	D-dimer				

BMI, body mass index; CVC, central venous catheter; ECOG, Eastern Cooperative Oncology Group; ESA, erythropoiesis-stimulating agent; GRS, genetic risk score; HR, high risk; RAMs, risk assessment models; VHR, very high risk; VTE, venous thromboembolism.

Table 2 RAMs specific for risk assessment of VTE in patients with lung cancer

RAMs	Items	Score	High risk	AUC in validation
ROADMAP-CAT	Procoag-PPL <44 s, and MRI <125 nM/min	1	Score=1	0.77
Score of Alexander	Baseline fibrinogen ≥4.0 g/L and baseline D-dimer ≥0.5 mg/L	1	Score ≥1	0.67(0.61–0.73)
	Baseline D-dimer ≥1.5 mg/L	1		
	Month-1 D-dimer ≥1.5 mg/L	1		
Score of Li	Male	1	Score ≥6	0.827 (0.782–0.866)
	Age ≥65 years	1		
	Clinical stage in III-IV	1		
	Adenocarcinoma	1		
	History of chemotherapy	1		
	History of surgery	1		
	D-dimer >0.55 mg/L	1		
	History of CVC	2		
Thrombo-NSCLC	FVIII (%) ≥241%	1	Score ≥3	0.93 (0.87–0.98)
	Soluble P-selectin ≥20.4 mADU	3		
Rising-VTE/NEJ037	Female	1	Score ≥5	0.751 (0.692–0.809)
	Adenocarcinoma	1		
	TNM ≥3	1		
	PS score ≥1	1		
	Lymphocyte percentage <18%	1		
	Platelet count <280 000/μL	1		
	Prothrombin fragment 1+2 ≥325 pmol/L	1		
	Diastolic blood pressure ≥70 mmHg	1		
SII	Age	Nomogram	Not mentioned	0.708 (0.643–0.772)
	Metastasis			
	Antitumour treatment			
	Haemoglobin <100 g/L			
	SII >851.51×10 ⁹ /L			
	D-dimer >2-folds			
Nomogram of Li	Age	Nomogram	Score ≥131	0.813 (0.737–0.890)
	BMI			
	Operation time			
	CA15-3			
	CUS			

AUC, area under the curve; BMI, body mass index; CA15-3, carbohydrate antigen 15-3; CUS, compression ultrasonography; CVC, central venous catheter; FVIII, coagulation factor VIII; mADU, milli-arbitrary density units; MRI, mean rate index of thrombin generation; Procoag-PPL, procoagulant phospholipid-dependent clotting time; PS, performance status; RAMs, risk assessment models; SII, systemic immunoinflammatory index; TNM, tumour node metastasis; VTE, venous thromboembolism.

≥1.5 mg/L at month 1 for patients with NSCLC. The sensitivity and specificity of this model for VTE prediction in a prospective NSCLC cohort was 100% and 34%, respectively (C-index 0.67). By this VTE risk assessment score, the VTE incidence was 27% and 0% in the high-risk and low-risk VTE groups, respectively.⁴⁹

Score of Li

Li *et al* established a VTE risk assessment score which consists of male, age ≥65 years, clinical stage in III-IV, adenocarcinoma, history of chemotherapy, history of surgery, D-dimer >0.55 mg/L and history of CVC for patients with lung cancer. This VTE risk assessment score

achieved proper stratification of high and low VTE risk for 496 patients with lung cancer in the model development group and 331 ones in the validation group (C-statistic 0.819 and 0.827, respectively).⁵⁵

Thrombo-NSCLC score

Thrombo-NSCLC VTE risk assessment score is a score that was established specific for patients with NSCLC. It assigns 1 and 3 points to high level of coagulation factor VIII and soluble P-selectin values, respectively. It performed significantly better than the Khorana score in the prediction of VTE development for 90 patients with NSCLC (area under the curve (AUC) 0.93 vs. 0.55, sensitivity 94.4% vs 35.0%, specificity 93.1% vs 60.0%).⁵⁶

Rising-VTE/NEJ037 score

A new risk assessment tool for VTE in advanced lung cancer by using Rising-VTE/NEJ037 study dataset incorporated female sex, adenocarcinoma, performance status, tumour node metastasis (TNM) factor, lymphocyte count, platelet count, prothrombin fragment 1+2 and diastolic blood pressure. Its AUC for VTE risk assessment in patients with lung cancer was 0.751 (0.692–0.809) ($p < 0.001$).⁵⁷

SII score

A recently developed novel prediction nomogram based on Systemic Inflammatory Index (SII) for VTE risk in patients with lung cancer that incorporated age, metastasis, antitumor treatment, haemoglobin < 100 g/L, $SII > 851.51 \times 10^9$ /L and D-dimer > 2 -folds demonstrated better predictive performance than KS (AUC, 0.708 (0.643–0.772) vs 0.600 (0.531–0.699)).⁵⁸

Scores for surgery

Postoperative risk of VTE occurrence is high for patients with lung cancer who undergo lung cancer surgery. Therefore, some studies committed to identify the risk assessment score specific for patients with lung cancer who undergo tumour surgery.

Caprini score

Caprini VTE risk assessment model is a dynamic tool that requires ongoing evaluation of patients during their hospitalisation. It provides a consistent, accurate and efficient approach for VTE risk stratification and selection of thromboprophylaxis. It has been validated among over 250 000 patients in more than 100 clinical trials worldwide.⁵⁹ A retrospective study validated the efficiency of Caprini score in 232 patients who underwent lung cancer resections. The results demonstrated that the postoperative VTE incidence was correlated with an increasing Caprini score. A Caprini score of low, moderate and high VTE risk stratification was associated with a VTE incidence of 0%, 1.7% and 10.3%, respectively. When a Caprini score > 9 was defined as high risk of VTE, the sensitivity, specificity and accuracy were 83.3%, 60.5%, and 61.6% for the prediction of postoperative VTE

development in patients who underwent lung cancer surgery, respectively.⁶⁰

Nomogram of Li

A nomogram model for postoperative VTE risk assessment was established in a retrospective study of 680 consecutive patients who underwent lung cancer surgery. Age, BMI, operation time, serum level of carbohydrate antigen (CA) 15-3 before surgery, and abnormal venous compression ultrasonography (CUS) before surgery were determined to be the variables in this nomogram. It demonstrated a good predictive performance in the derivation group ($n=475$) (AUC 0.792) and the validation group ($n=205$) (AUC 0.813), respectively. This nomogram could provide an individual VTE risk assessment and guide postoperative thromboprophylaxis decisions for patients with lung cancer who undergo tumour surgery.⁶¹

THROMBOPROPHYLAXIS

Thromboprophylaxis especially pharmacologic anticoagulant thromboprophylaxis is crucial for the prevention of VTE occurrence in patients with cancer who are at high risk of VTE. The guidelines of American Society of Clinical Oncology (ASCO)⁵ and American Society of Hematology (ASH)⁶ also recommend the combination of pharmacologic and mechanical thromboprophylaxis to achieve a better efficacy than mechanical or pharmacologic thromboprophylaxis alone, especially for patients with the highest VTE risk, whereas the guidelines of National Comprehensive Cancer Network (NCCN) and International Initiative on Thrombosis and Cancer (ITAC) suggest that mechanical thromboprophylaxis is only recommended in case of contraindication to anticoagulation.^{4 62} All these three guidelines recommend against using mechanical thromboprophylaxis alone unless there is a contraindication to anticoagulation.^{5 6 62} Inferior vena cava filters are not recommended for routine thromboprophylaxis in patients with cancer either unless there is a contraindication to anticoagulation.⁴⁻⁶

Nevertheless, clinical practice patterns of thromboprophylaxis may vary by cancer types, since different sites of cancer may have different levels of VTE risk.⁴⁻⁶ Accordingly, to understand the thromboprophylaxis specific for lung cancer is of vital importance for patients with lung cancer. In addition, thromboprophylaxis in medical patients with lung cancer differs from that in surgical ones with lung cancer. Of note, the information on indication and contraindication of thromboprophylaxis specific for patients with lung cancer is unavailable in guidelines. Standard operating procedure for a thromboprophylaxis decision in patients with lung cancer should follow the basic principles of thromboprophylaxis for patients with cancer in the guidelines.^{4-6 62} The indication and contraindication of thromboprophylaxis for patients with lung cancer are demonstrated in [table 3](#).

Table 3 The indication and contraindication of thromboprophylaxis for patients with lung cancer

Thromboprophylaxis	Indication	Contraindication
Pharmacologic thromboprophylaxis	Surgical patients with lung cancer Hospitalised medical patients receiving/starting systemic therapy for lung cancer Patients with lung cancer with intermediate or high risk for VTE (Khorana score ≥ 2)	Active bleeding Thrombocytopenia (platelet count $< 50\,000/\mu\text{L}$) Underlying haemorrhagic coagulopathy or known bleeding disorder
Mechanical thromboprophylaxis	The abovementioned situations with (preferred) or without contraindication to anticoagulation	Acute DVT (unless on therapeutic anticoagulation) Severe arterial insufficiency

DVT, deep venous thrombosis; VTE, venous thromboembolism.

Medical thromboprophylaxis

According to previous studies, for most ambulatory outpatients and a few inpatients, administration of low-molecular weight heparin (LMWH) as primary thromboprophylaxis for medical patients with lung cancer is definitely associated with a reduction of VTE incidence.^{63–70} With respect to the survival benefit resulted from thromboprophylaxis, although three meta-analyses suggested that primary thromboprophylaxis was associated with a significant or measurable survival benefit for patients with lung cancer, especially for patients with limited-stage small cell lung cancer (SCLC),^{64 65 67} another three randomised phase III trials and three meta-analyses demonstrated that thromboprophylaxis did not improve OS of patients with lung cancer.^{63 66 68–71} With respect to the bleeding events resulted from thromboprophylaxis, three randomised phase III trials showed that haemorrhagic events were more frequent in the LMWH-treated group than those in the control group,^{63 68 71} whereas five meta-analyses indicated that thromboprophylaxis did not increase the risk of bleeding or thrombocytopenia for patients with lung cancer.^{64–67 70}

Literature is scanty with respect to secondary thromboprophylaxis after 6 months of anticoagulation or thromboprophylaxis with direct oral anticoagulants (DOACs) specific for patients with lung cancer with established VTE in recent years. In the Rising-VTE/NEJ037 study, for 1008 patients with lung cancer who were followed up for 2 years, those with VTE received treatment with edoxaban, whereas those without VTE were observed without anticoagulation. No cases of VTE recurrence were recorded 2 years after treatment initiation with edoxaban, whereas the incidence rate of VTE in the observation group without edoxaban treatment was 4.0%. Nevertheless, major and clinically relevant non-major bleeding events occurred in 4.9% of patients and increased to 22.7% in the edoxaban treatment group. Edoxaban was highly effective in preventing VTE recurrence for patients with lung cancer, along with a high bleeding rate.⁷²

Surgical thromboprophylaxis

Several studies specifically investigated thromboprophylaxis of VTE in patients who underwent surgery due to

lung cancer. In a modified Delphi survey on Canadian clinicians with respect to the practice patterns in VTE thromboprophylaxis of patients who underwent thoracic surgery, once daily LMWH administration was the only variable that demonstrated agreement as a common practice pattern. There is no agreement on the timing of initiation of thromboprophylaxis, the role of mechanical thromboprophylaxis or factors mandating usage of extended thromboprophylaxis.⁷³ A retrospective observational study of 358 patients who underwent lobectomies demonstrated that the use of thromboprophylaxis and timing of its initiation were not associated with the postoperative thrombotic or haemorrhagic events. Compliance with VTE prophylaxis guidelines is essential.⁷⁴ In a pilot randomised control trial (RCT) of 103 patients who underwent oncological lung resections, 30-day VTE incidence and 90-day survival rate were compared between the intervention group (n=52) which received post-discharge LMWH and placebo group (n=51) which received post-discharge placebo, once daily for 30 days. Three segmental PE (5.8%) were detected in the intervention group, whereas two segmental PE and one DVT (5.9%) were detected in the placebo group. No deaths were found in both groups.⁷⁵ In another RCT, 212 patients prepared to undergo minimally invasive lung cancer surgery were randomly divided into the preoperative LMWH-administration group and the postoperative LMWH-administration group both of which received 4000 IU/day, until discharge. The trial revealed that preoperative start of LMWH was safe and feasible compared with postoperative start of LMWH for minimally invasive lung cancer surgery patients.⁷⁶

TREATMENT

Studies specific for VTE treatment of patients with lung cancer are scarce in recent years. In the recent RCTs with respect to VTE treatment in patients with various types of cancer, DOACs which are oral factor Xa inhibitors played a pivotal role in VTE treatment. In the Hokusai VTE Cancer trial which included 77 (14.8%) patients with lung cancer in the edoxaban group and 75 (14.3%) ones in the dalteparin group, oral edoxaban was non-inferior to subcutaneous dalteparin with respect to the composite

outcome of recurrent VTE or major bleeding.⁷⁷ In the Caravaggio trial which included 105 (18.2%) patients with lung cancer in the apixaban group and 95 (16.4%) ones in the dalteparin group, oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of cancer-associated VTE without an increased risk of major bleeding.⁷⁸

Likewise, in a retrospective study of patients with lung cancer with established VTE, between 131 patients who were prescribed rivaroxaban and 73 ones who were prescribed dalteparin, no statistical difference was found for the long-term incidence of VTE recurrence (5.3% in the rivaroxaban group vs 2.7% in the dalteparin group, $p=0.495$) and major or non-major bleeding rates (23.7% in the rivaroxaban group vs 13.7% in the dalteparin group, $p=0.089$). No between-group difference was found for the all-cause mortality rates ($p=0.337$). Rivaroxaban has similar efficacy and safety with dalteparin.⁷⁹ Besides efficacy and safety, with respect to economic burden, a 76% decrease of mean cost due to VTE management of patients with lung cancer can be expected with the use of DOACs, compared with the use of LMWH.⁸⁰

GUIDELINES

The authoritative guidelines for management of cancer-associated VTE mainly include the guidelines of ITAC,⁴ ASCO,⁵ ASH⁶ and NCCN.^{1 62} The NCCN guidelines of cancer-associated VTE do not mention any specific issues with respect to lung cancer,^{1 62} whereas such issues are concerned in the other three guidelines.^{1 4-6} Comparison of VTE management specific for patients with lung cancer among the latest ITAC,⁴ ASCO⁵ and ASH⁶ guidelines of cancer-associated VTE is illustrated in [table 4](#).

Assessment

The latest ITAC guidelines do not mention any issues of VTE risk assessment score specific for lung cancer. In the ITAC guidelines, the Khorana risk scoring model is recommended for patients with all cancer types.⁴ Similarly, the KS is also recommended for all types of cancers in the latest ASCO guidelines.⁵ Nevertheless, the latest ASCO guidelines indicate that the KS produced mixed results in the studies of individual cancer type, since no significant association between the KS and VTE risk was reported in three studies of lung cancer.^{45 46 48} The latest ASCO guidelines also suggest that the COMPASS-CAT score best distinguished patients with lung cancer at low from high risk of VTE. The guidelines also mention that the Caprini risk assessment score could be helpful to select surgical patients with lung cancer who would benefit from extended thromboprophylaxis.⁵ In the ASH guidelines, no VTE risk assessment score related to lung cancer is mentioned, whereas the KS is the only mentioned VTE risk assessment score for patients with all cancer types.⁶

Thromboprophylaxis

The latest ITAC guidelines indicate that thromboprophylaxis of LMWH confers a relative VTE risk reduction. However, thromboprophylaxis demonstrates no benefit for OS in patients with lung cancer. At a guidance level which only represents best clinical practice, primary thromboprophylaxis of LMWH is not recommended outside of a clinical trial for patients with locally advanced or metastatic lung cancer who undergo systemic anti-cancer therapy, even if patients have a low risk of bleeding.⁴ The latest ASCO guidelines also indicate that

Table 4 Comparison of VTE management specific for patients with lung cancer among the latest ITAC,⁴ ASCO⁵ and ASH⁶ guidelines of cancer-associated VTE

	ITAC	ASCO	ASH
Assessment	No mention of VTE risk assessment score specific for lung cancer. The Khorana score is recommended for pan-cancer patients.	The COMPASS-CAT score performs better, compared with the Khorana score, for lung patients with cancer, although the latter is recommended for pan-cancer patients.	No mention of VTE risk assessment score specific for lung cancer. The Khorana score is recommended for pan-cancer patients.
Thromboprophylaxis	Thromboprophylaxis reduces VTE incidence without improving OS for patients lung cancer. Primary thromboprophylaxis is not routinely recommended for patients with lung cancer.	Thromboprophylaxis reduces VTE incidence without improving OS for patients with lung cancer.	Thromboprophylaxis reduces VTE incidence and improves OS without increasing the bleeding risk or thrombocytopenia for patients with lung cancer.
Treatment	No mention of VTE treatment specific for lung cancer. VTE treatment for patients with lung cancer follows the guidelines.	No mention of VTE treatment specific for lung cancer. VTE treatment for patients with lung cancer follows the guidelines.	No mention of VTE treatment specific for lung cancer. VTE treatment for patients with lung cancer follows the guidelines.

ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; ITAC, International Initiative on Thrombosis and Cancer; OS, overall survival; VTE, venous thromboembolism.

prophylactic LMWH reduces the risk of VTE by roughly half. The guidelines definitely suggest that prophylactic anticoagulation does not improve OS in patients with cancer without established VTE.⁵ Although one study⁶⁴ cited by the guidelines indicated that thromboprophylaxis improved the OS of patients with lung cancer, the other studies^{66–68} cited by the guidelines consistently reported the ineffectiveness of thromboprophylaxis for OS improvement.⁵ In the latest ASH guidelines, the cited study⁶⁷ with respect to lung cancer indicated that LMWH reduced the incidence of VTE and improved the OS of patients with lung cancer who underwent chemotherapy without increasing the incidence of major bleeding events or thrombocytopenia.⁶

Treatment

With respect to treatment, none of the ITAC, ASCO and ASH guidelines specifically address VTE treatment in patients with lung cancer who are diagnosed with established VTE. Treatment of established VTE in patients with lung cancer follows the general VTE treatment principles of patients with all cancer types in authoritative guidelines.^{1–4,6}

CONCLUSIONS

VTE is common and life-threatening in patients with cancer especially lung cancer. Management of VTE is of great importance for patients with lung cancer. Although its overall principles should follow recommendations in authoritative guidelines, VTE stewardship in patients with lung cancer is special in some specific situations. Despite the KS is highly recommended for patients with all cancer types by authoritative guidelines, its value in VTE risk assessment of patients with lung cancer is debatable due to the divergent results of several previous studies specific for patient with lung cancer. Among the VTE risk assessment scores recommended by authoritative guidelines, the COMPASS-CAT score performed best for the VTE risk assessment in ambulatory patients with lung cancer, whereas the ONKOTEV score is optimal for the assessment of VTE occurrence in hospitalised medical patients with lung cancer by far. Despite several VTE risk assessment scores specific for lung cancer were established, the further external validation of their efficiency is warranted in the future. For surgical patients with lung cancer, the Caprini VTE risk assessment score could be helpful to identify who would benefit from extended thromboprophylaxis. Primary thromboprophylaxis with LMWH reduces VTE incidence with an increased risk of bleeding without improving OS for patients with lung cancer. Different from some cancer types such as pancreatic or gastric cancer which may need routine thromboprophylaxis due to their highest VTE risk among all cancer types, pharmacologic thromboprophylaxis should only be considered for those are at high VTE and low bleeding risks in medical patients with lung cancer. Compliance with authoritative guidelines is

essential for the thromboprophylaxis of surgical patients with lung cancer. Nevertheless, the duration and timing of initiation of thromboprophylaxis in surgical patients with lung cancer may need further study. Treatment of established VTE in patients with lung cancer could follow the authoritative guidelines. DOACs are favoured in the VTE treatment of patients with lung cancer in recent years. Future studies should focus on exploring and validating VTE risk assessment score specific for lung cancer, determining thromboprophylaxis pattern specific for lung cancer and application of newly developed anticoagulant to the treatment of established VTE in patients with lung cancer.

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REFERENCES

- 1 Streiff MB, Holmstrom B, Angelini D, *et al*. NCCN guidelines insights: cancer-associated venous thromboembolic disease, version 2.2018. *J Natl Compr Canc Netw* 2018;16:1289–303.
- 2 Konstantinides SV, Meyer G, Becattini C, *et al*. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J* 2019;54:1901647.
- 3 Konstantinides SV, Meyer G, Becattini C, *et al*. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41:543–603.
- 4 Farge D, Frere C, Connors JM, *et al*. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol* 2019;20:e566–81.
- 5 Key NS, Khorana AA, Kuderer NM, *et al*. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol* 2020;38:496–520.
- 6 Lyman GH, Carrier M, Ay C, *et al*. American Society of hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv* 2021;5:927–74.
- 7 Bade BC, Dela Cruz CS. Lung cancer 2020: epidemiology, etiology, and prevention. *Clin Chest Med* 2020;41:1–24.
- 8 Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2021. *CA Cancer J Clin* 2021;71:7–33.
- 9 Walker AJ, Baldwin DR, Card TR, *et al*. Risk of venous thromboembolism in people with lung cancer: a cohort study using linked UK healthcare data. *Br J Cancer* 2016;115:115–21.

- 10 Connolly GC, Dalal M, Lin J, *et al.* Incidence and predictors of venous thromboembolism (VTE) among ambulatory patients with lung cancer. *Lung Cancer* 2012;78:253–8.
- 11 Connolly GC, Menapace L, Safadjou S, *et al.* Prevalence and clinical significance of incidental and clinically suspected venous thromboembolism in lung cancer patients. *Clin Lung Cancer* 2013;14:713–8.
- 12 Zhang Y, Yang Y, Chen W, *et al.* Prevalence and associations of VTE in patients with newly diagnosed lung cancer. *Chest* 2014;146:650–8.
- 13 Shen Q, Dong X, Tang X, *et al.* Risk factors and prognosis value of venous thromboembolism in patients with advanced non-small cell lung cancer: a case-control study. *J Thorac Dis* 2017;9:5068–74.
- 14 Howlett J, Benzenine E, Cottenet J, *et al.* Could venous thromboembolism and major bleeding be indicators of lung cancer mortality? A nationwide database study. *BMC Cancer* 2020;20:461.
- 15 Suzuki T, Fujino S, Inaba S, *et al.* Venous thromboembolism in patents with lung cancer. *Clin Appl Thromb Hemost* 2020;26:1076029620977910.
- 16 Cha S-I, Shin K-M, Lim J-K, *et al.* Pulmonary embolism concurrent with lung cancer and central emboli predict mortality in patients with lung cancer and pulmonary embolism. *J Thorac Dis* 2018;10:262–72.
- 17 Guo J, Deng Q-F, Xiong W, *et al.* Comparison among different presentations of venous thromboembolism because of lung cancer. *Clin Respir J* 2019;13:574–82.
- 18 Maia R, Neves I, Morais A, *et al.* Venous and lung thromboembolism in the context of lung cancer: clinical manifestations, risk factors and prognosis. *Acta Med Port* 2019;32:647–53.
- 19 Dimakakos E, Livanios K, Vathiotis I, *et al.* Risk factors for venous thromboembolism in patients with small cell lung cancer. *Anticancer Res* 2021;41:1523–8.
- 20 Ng TL, Smith DE, Mushtaq R, *et al.* ROS1 gene rearrangements are associated with an elevated risk of peridiagnosis thromboembolic events. *J Thorac Oncol* 2019;14:596–605.
- 21 Al-Samkari H, Leiva O, Dagogo-Jack I, *et al.* Impact of ALK rearrangement on venous and arterial thrombotic risk in NSCLC. *J Thorac Oncol* 2020;15:1497–506.
- 22 Li H, Jiang G, Bölükbas S, *et al.* The Society for translational medicine: the assessment and prevention of venous thromboembolism after lung cancer surgery. *J Thorac Dis* 2018;10:3039–53.
- 23 Moik F, Chan W-SE, Wiedemann S, *et al.* Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. *Blood* 2021;137:1669–78.
- 24 Kang JR, Long LH, Yan SW, *et al.* Peripherally inserted central catheter-related vein thrombosis in patients with lung cancer. *Clin Appl Thromb Hemost* 2017;23:181–6.
- 25 Zer A, Moskovitz M, Hwang DM, *et al.* ALK-rearranged non-small-cell lung cancer is associated with a high rate of venous thromboembolism. *Clin Lung Cancer* 2017;18:156–61.
- 26 Dou F, Zhang Y, Yi J, *et al.* Association of alk rearrangement and risk of venous thromboembolism in patients with non-small cell lung cancer: a prospective cohort study. *Thromb Res* 2020;186:36–41.
- 27 Yang S, Yang L, Wu Y, *et al.* Anaplastic lymphoma kinase rearrangement may increase the incidence of venous thromboembolism by increasing tissue factor expression in advanced lung adenocarcinoma. *Ann Transl Med* 2020;8:1307.
- 28 Xiong W, Du H, Ding W, *et al.* The association between pulmonary embolism and the cancer-related genomic alterations in patients with NSCLC. *Respir Res* 2020;21.
- 29 Su Y, Huo M, Hua L, *et al.* Association of venous thromboembolism and early mortality in patients with newly diagnosed metastatic non-small cell lung cancer. *CMAR* 2021;Volume 13:4031–40.
- 30 Qian X, Fu M, Zheng J, *et al.* Driver genes associated with the incidence of venous thromboembolism in patients with non-small-cell lung cancer: a systematic review and meta-analysis. *Front Oncol* 2021;11:680191.
- 31 Liu Y, Wang W, Wu F, *et al.* High discrepancy in thrombotic events in non-small cell lung cancer patients with different genomic alterations. *Transl Lung Cancer Res* 2021;10:1512–24.
- 32 Roopkumar J, Poudel SK, Gervaso L, *et al.* Risk of thromboembolism in patients with ALK- and EGFR-mutant lung cancer: a cohort study. *J Thromb Haemost* 2021;19:822–9.
- 33 Zhu VW, Zhao JJ, Gao Y, *et al.* Thromboembolism in ALK+ AND ROS1+ NSCLC patients: a systematic review and meta-analysis. *Lung Cancer* 2021;157:147.
- 34 Chiari R, Ricciuti B, Landi L, *et al.* Ros1-Rearranged non-small-cell lung cancer is associated with a high rate of venous thromboembolism: analysis from a phase II, prospective, multicenter, two-arms trial (METROS). *Clinical Lung Cancer* 2020;21:15–20.
- 35 Muñoz-Unceta N, Zugazagoitia J, Manzano A, *et al.* High risk of thrombosis in patients with advanced lung cancer harboring rearrangements in ROS1. *Eur J Cancer* 2020;141:193–8.
- 36 Wang J, Hu B, Li T, *et al.* The egfr-rearranged adenocarcinoma is associated with a high rate of venous thromboembolism. *Ann Transl Med* 2019;7:724.
- 37 Song C, Shargall Y, Li H, *et al.* Prevalence of venous thromboembolism after lung surgery in China: a single-centre, prospective cohort study involving patients undergoing lung resections without perioperative venous thromboembolism prophylaxis†. *Eur J Cardiothorac Surg* 2019;55:455–60.
- 38 Ke L, Cui S, Chen S, *et al.* Dynamics of D-dimer in non-small cell lung cancer patients receiving radical surgery and its association with postoperative venous thromboembolism. *Thorac Cancer* 2020;11:2483–92.
- 39 Wang P, Zhao H, Zhao Q, *et al.* Risk factors and clinical significance of D-dimer in the development of postoperative venous thrombosis in patients with lung tumor. *Cancer Manag Res* 2020;12:5169–79.
- 40 Kaminuma Y, Tanahashi M, Suzuki E, *et al.* Venous thromboembolism in non-small cell lung cancer patients who underwent surgery after induction therapy. *Gen Thorac Cardiovasc Surg* 2020;68:1156–62.
- 41 Li Y-P, Shen L, Huang W, *et al.* Prevalence and risk factors of acute pulmonary embolism in patients with lung cancer surgery. *Semin Thromb Hemost* 2018;44:334–40.
- 42 Deschênes-Simard X, Richard C, Galland L, *et al.* Venous thrombotic events in patients treated with immune checkpoint inhibitors for non-small cell lung cancer: a retrospective multicentric cohort study. *Thromb Res* 2021;205:29–39.
- 43 Icht O, Darzi N, Shimony S, *et al.* Venous thromboembolism incidence and risk assessment in lung cancer patients treated with immune checkpoint inhibitors. *J Thromb Haemost* 2021;19:1250–8.
- 44 Khorana AA, Kuderer NM, Culakova E, *et al.* Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111:4902–7.
- 45 Mansfield AS, Tafur AJ, Wang CE, *et al.* Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost* 2016;14:1773–8.
- 46 Rupa-Matysek J, Lembicz M, Rogowska EK, *et al.* Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. *Med Oncol* 2018;35:63.
- 47 Vathiotis I, Dimakakos EP, Boura P, *et al.* Khorana score: vew predictor of early mortality in patients with lung adenocarcinoma. *Clin Appl Thromb Hemost* 2018;24:1347–51.
- 48 Kuderer NM, Poniewierski MS, Culakova E, *et al.* Predictors of venous thromboembolism and early mortality in lung cancer: results from a global prospective study (CANTARISK). *Oncologist* 2018;23:247–55.
- 49 Alexander M, Ball D, Solomon B, *et al.* Dynamic thromboembolic risk modelling to target appropriate preventative strategies for patients with non-small cell lung cancer. *Cancers (Basel)* 2019;11:50.
- 50 van Es N, Ventresca M, Di Nisio M, *et al.* The Khorana score for prediction of venous thromboembolism in cancer patients: an individual patient data meta-analysis. *J Thromb Haemost* 2020;18:1940–51.
- 51 Li S, Gao P, Qiu J, *et al.* A modified Khorana score as a risk assessment tool for predicting venous thromboembolism in newly diagnosed advanced lung cancer. *J Thromb Thrombolysis* 2021;52:898–903.
- 52 Gerotziapas GT, Taher A, Abdel-Razeq H, *et al.* A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-cancer-associated thrombosis study. *Oncologist* 2017;22:1222–31.
- 53 Xiong W, Zhao Y, Du H, *et al.* Optimal authoritative risk assessment score of cancer-associated venous thromboembolism for hospitalized medical patients with lung cancer. *Thromb J* 2021;19:95.
- 54 Syrigos K, Grapsa D, Sangare R, *et al.* Prospective assessment of clinical risk factors and biomarkers of hypercoagulability for the identification of patients with lung adenocarcinoma at risk for cancer-associated thrombosis: the observational ROADMAP-CAT study. *Oncologist* 2018;23:1372–81.
- 55 Li Z, Zhang G, Zhang M, *et al.* Development and validation of a risk score for prediction of venous thromboembolism in patients with lung cancer. *Clin Appl Thromb Hemost* 2020;26:107602962091079.
- 56 Castellón Rubio VE, Segura PP, Muñoz A, *et al.* High plasma levels of soluble p-selectin and factor viii predict venous thromboembolism

- in non-small cell lung cancer patients: the thrombo-nsclc risk score. *Thromb Res* 2020;196:349–54.
- 57 Tsubata Y, Hotta T, Hamai K, *et al.* A new risk-assessment tool for venous thromboembolism in advanced lung cancer: a prospective, observational study. *J Hematol Oncol* 2022;15:40.
 - 58 Zhang L, Liu X, Yang R, *et al.* The diagnostic value of the systemic immune-inflammation index for venous thromboembolism in lung cancer patients: a retrospective study. *Mediators of Inflammation* 2022;2022:1–8.
 - 59 Cronin M, Dengler N, Krauss ES, *et al.* Completion of the updated caprini risk assessment model (2013 version). *Clin Appl Thromb Hemost* 2019;25:107602961983805.
 - 60 Hachey KJ, Hewes PD, Porter LP, *et al.* Caprini venous thromboembolism risk assessment permits selection for postdischarge prophylactic anticoagulation in patients with resectable lung cancer. *The Journal of Thoracic and Cardiovascular Surgery* 2016;151:37–44.
 - 61 Li Y, Shen L, Ding J, *et al.* Derivation and validation of a nomogram model for pulmonary thromboembolism in patients undergoing lung cancer surgery. *Transl Lung Cancer Res* 2021;10:1829–40.
 - 62 Streiff MB, Holmstrom B, Angelini D, *et al.* Cancer-associated venous thromboembolic disease, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2021;19:1181–201.
 - 63 Macbeth F, Noble S, Evans J, *et al.* Randomized phase III trial of standard therapy plus low molecular weight heparin in patients with lung cancer: FRAGMENT trial. *JCO* 2016;34:488–94.
 - 64 Yu Y, Lv Q, Zhang B, *et al.* Adjuvant therapy with heparin in patients with lung cancer without indication for anticoagulants: a systematic review of the literature with meta-analysis. *J Can Res Ther* 2016;12:37.
 - 65 Fuentes HE, Oramas DM, Paz LH, *et al.* Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer. *Thromb Res* 2017;154:28–34.
 - 66 Thein KZ, Yeung S-CJ, Oo TH. Primary thromboprophylaxis (PTP) in ambulatory patients with lung cancer receiving chemotherapy: a systematic review and meta-analysis of randomized controlled trials (rots). *Asia Pac J Clin Oncol* 2018;14:210–6.
 - 67 Liu Z-L, Wang Q, Wang M, *et al.* Low molecular weight heparin in treating patients with lung cancer received chemotherapy: a meta-analysis. *J Cancer Res Ther* 2018;14:S437–43.
 - 68 Ek L, Gezelius E, Bergman B, *et al.* Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial. *Ann Oncol* 2018;29:398–404.
 - 69 Thein KZ, Quick DP, Htut TW, *et al.* Impact of primary ambulatory thromboprophylaxis (PATP) with low-molecular weight heparins (lmwhs) on survival in patients with lung cancer receiving chemotherapy. *Lung* 2020;198:575–9.
 - 70 Schünemann HJ, Ventresca M, Crowther M, *et al.* Evaluating prophylactic heparin in ambulatory patients with solid tumours: a systematic review and individual participant data meta-analysis. *Lancet Haematol* 2020;7:e746–55.
 - 71 Meyer G, Besse B, Doubre H, *et al.* Anti-tumour effect of low molecular weight heparin in localised lung cancer: a phase III clinical trial. *Eur Respir J* 2018;52:1801220.
 - 72 Tsubata Y, Hotta T, Hamai K, *et al.* Incidence of venous thromboembolism in advanced lung cancer and efficacy and safety of direct oral anticoagulants: a multicenter, prospective, observational study (rising-VTE/NEJ037 study). *Ther Adv Med Oncol* 2022;14:17588359221110171.
 - 73 Agzarian J, Linkins L-A, Schneider L, *et al.* Practice patterns in venous thromboembolism (VTE) prophylaxis in thoracic surgery: a comprehensive Canadian Delphi survey. *J Thorac Dis* 2017;9:80–7.
 - 74 Smith D, Raices M, Diego C, *et al.* Incidence of venous thromboembolism and bleeding after pulmonary lobectomy: evaluating the timing for thromboprophylaxis. *J Thromb Thrombolysis* 2021;51:997–1004.
 - 75 Shargall Y, Schneider L, Linkins L-A, *et al.* Double blind pilot randomized trial comparing extended anticoagulation to placebo following major lung resection for cancer. *Semin Thorac Cardiovasc Surg* 2021;33:1123–34.
 - 76 A-Lai G-H, Zhuo Z-G, Li G, *et al.* Safety profile of preoperative administration of low-molecular-weight heparin on minimally invasive lung cancer surgery: a randomized controlled trial. *BMC Surg* 2021;21:250.
 - 77 Raskob GE, van Es N, Verhamme P, *et al.* Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;378:615–24.
 - 78 Agnelli G, Becattini C, Meyer G, *et al.* Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med* 2020;382:1599–607.
 - 79 Lee JH, Hyun D, Choi CM, *et al.* A retrospective study on efficacy and safety of rivaroxaban and dalteparin for long-term treatment of venous thromboembolism in patients with lung cancer. *Respiration* 2019;98:203–11.
 - 80 Howlett J, Benzenine E, Fagnoni P, *et al.* Are direct oral anticoagulants an economically attractive alternative to low molecular weight heparins in lung cancer associated venous thromboembolism management? *J Thromb Thrombolysis* 2020;50:642–51.