# Treatment and prophylaxis of lung cancer-associated VTE

이화의대 호흡기내과 최명근

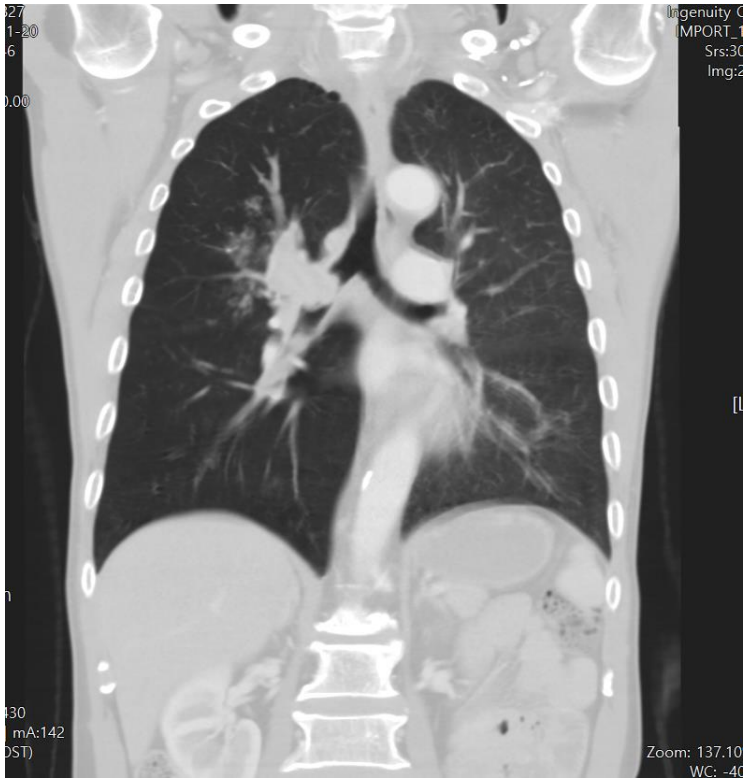
# Case

67/M

# Case 67/M: dyspnea

## OPD

- C.C: dyspnea, mMRC 2, 3 months ago
- Weight loss, - 10 kg during 3 mo
- Past medical history: HTN
- Smoking: 40PYs, current smoker




1. Right hilar mass occluding right main bronchus and RUL bronchus
   - High probability of lung cancer
   - with air trapping in right lung due to check valve obstruction with mucus plugging in central bronchi
2. Suspicious enlarged lymph node in right lower paratracheal area (4 R)
   - Limited evaluation current 5 5mm slice CT scan

-> 1. , 2. : high probability of lung cancer (T2N2Mx)

Rec: Contrast enhanced thin section CT scan and bronchoscopic biopsy

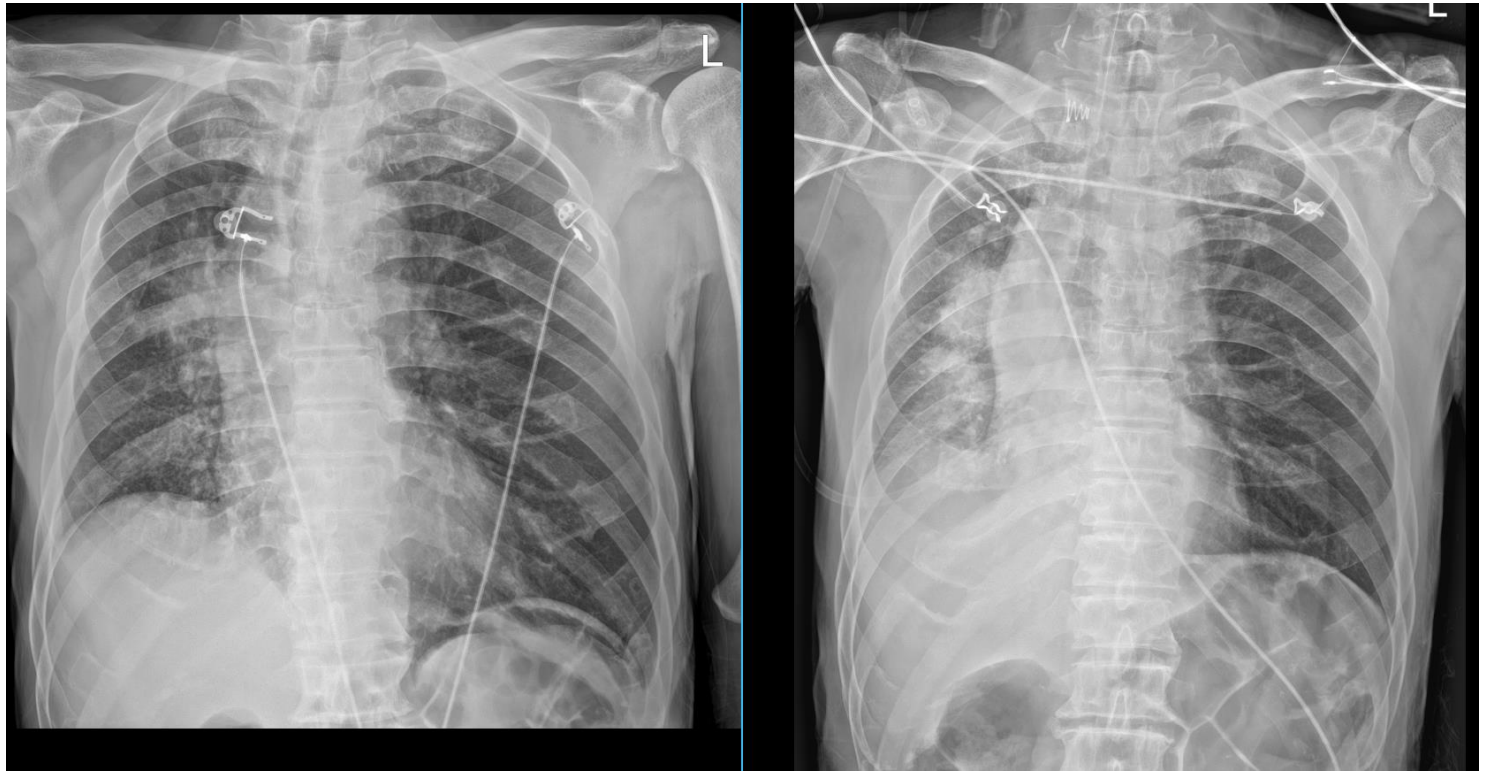
# Case 67/M: dyspnea

## HD #2

- Nasal prong 2L -> HFNC FiO2 100% / 60L
- Intubation

| | |
|---|---|
| pH, arterial | 7.455 |
| $pCO_2$, arteria | 32.5 |
| $pO_2$, arterial | 56.5 |
| Bicarbonate, | 22.3 |
| Base excess, | -1.6 |
| $CO_2$content, | 23.3 |
| $O_2$ saturate, | 90.6 |
| Lactate, artei | 11.7 |
| FiO2 | 100.0 |
| Hct, arterial | 41 |
| Hb, arterial | 14.0 |

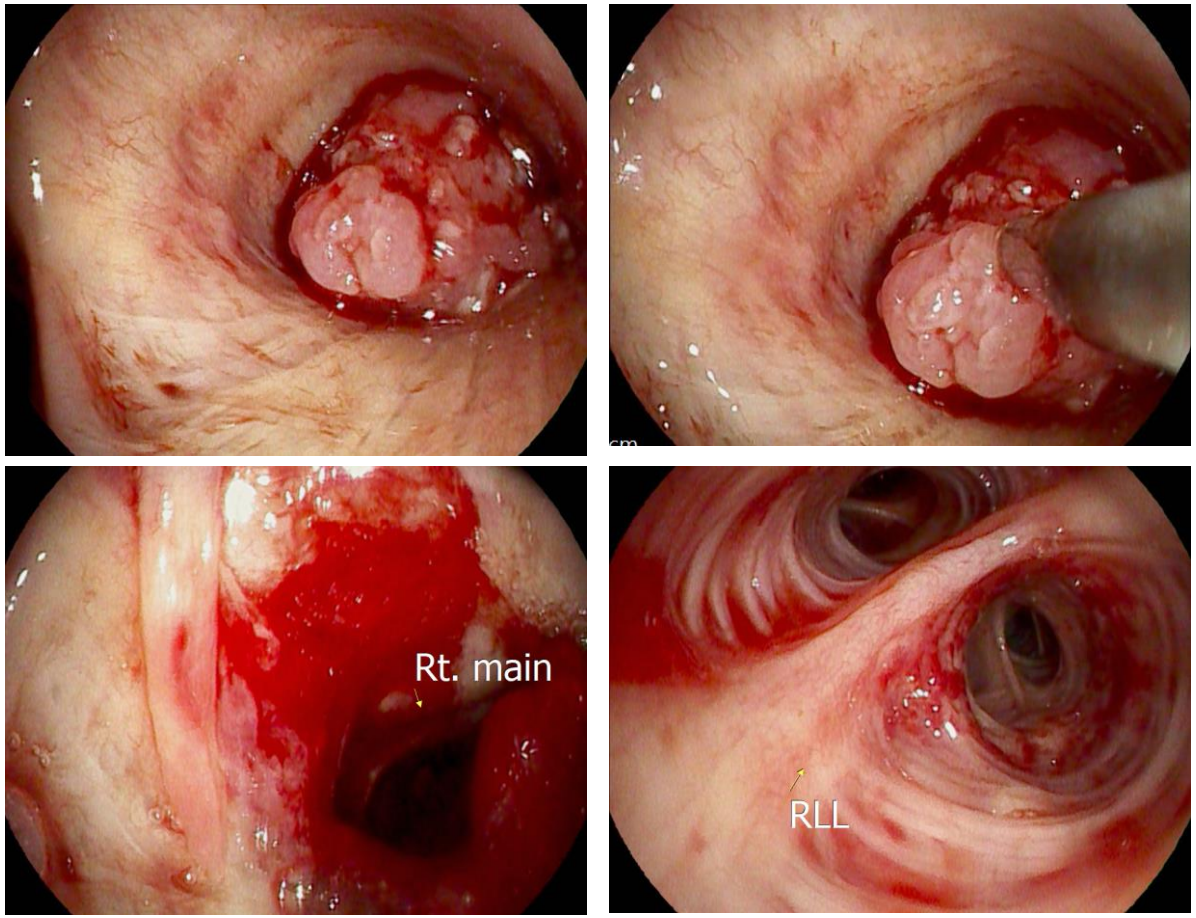
| | |
|---|---|
| pH, arterial | 7.345 |
| $pCO_2$, arteria | 41.8 |
| $pO_2$, arterial | 43.9 |
| Bicarbonate, | 22.3 |
| Base excess, | -3.4 |
| $CO_2$content, | 23.6 |
| $O_2$ saturate, | 75.9 |
| Lactate, artei | 15.2 |
| FiO2 | 100.0 |
| Hct, arterial | 42 |
| Hb, arterial | 14.3 |

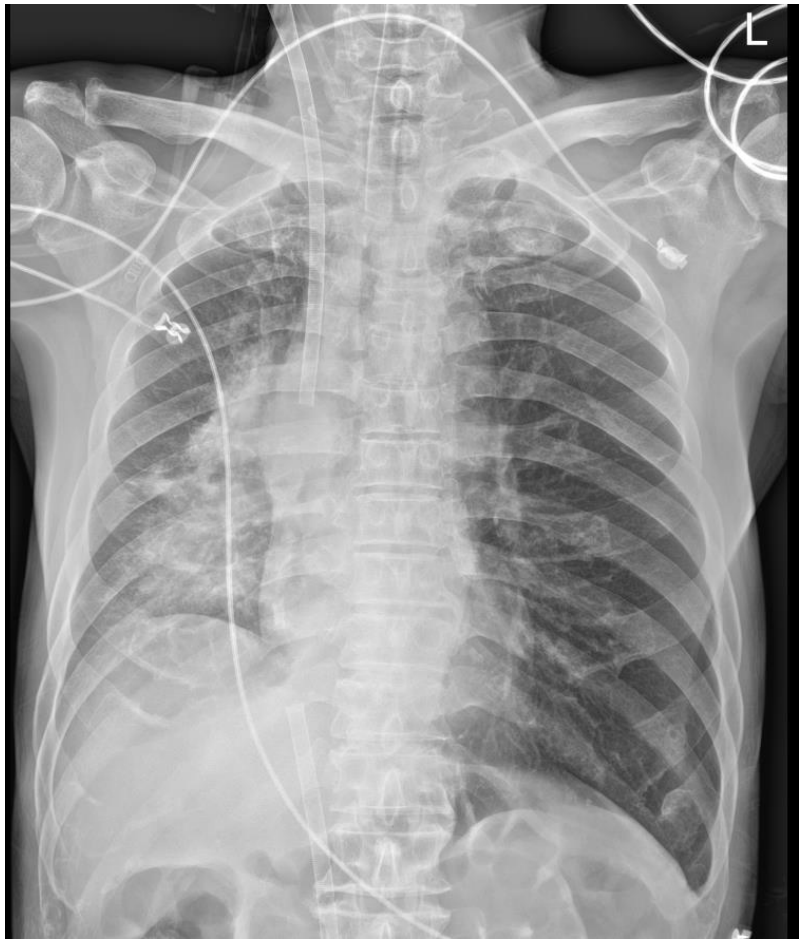


# Case 67/M: dyspnea

## HD #2

- V-V ECMO
- Bronchoscopy with cryobiopsy



# Case 67/M: dyspnea

## HD #4

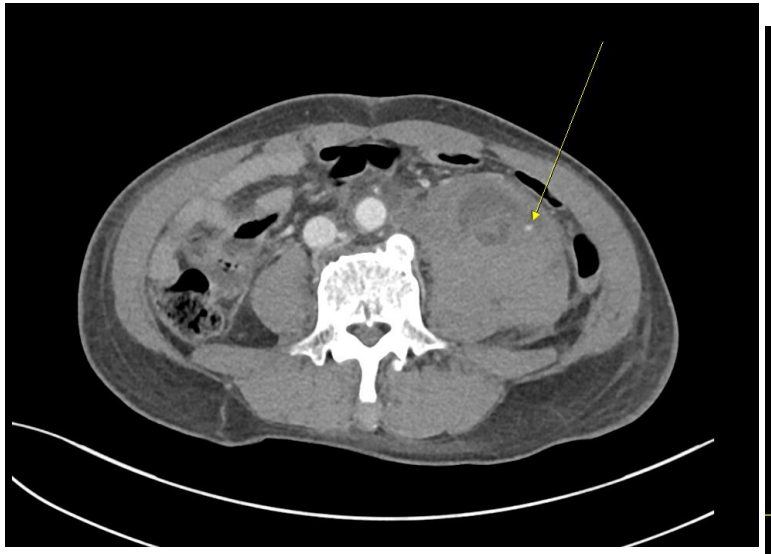
- V-V ECMO weaning
- Pulmonary embolism CT
  - Enoxaparin 60mg bid SC
- Extubation: HD #6

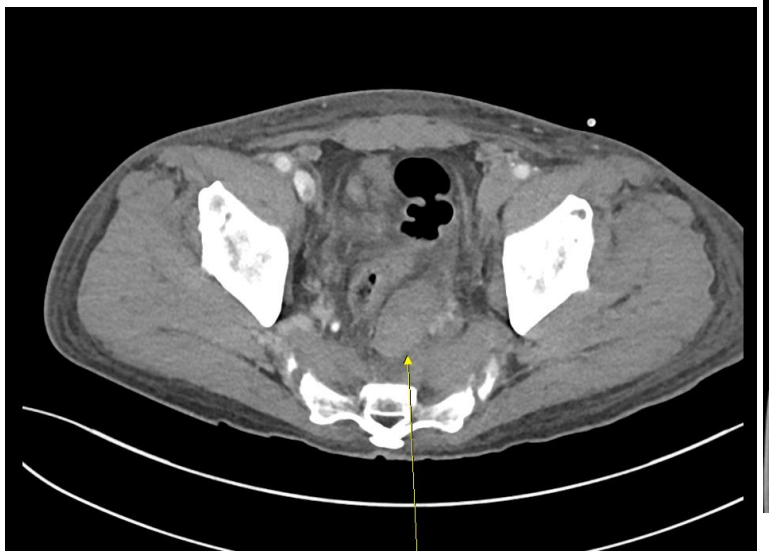
# Case 67/M: dyspnea

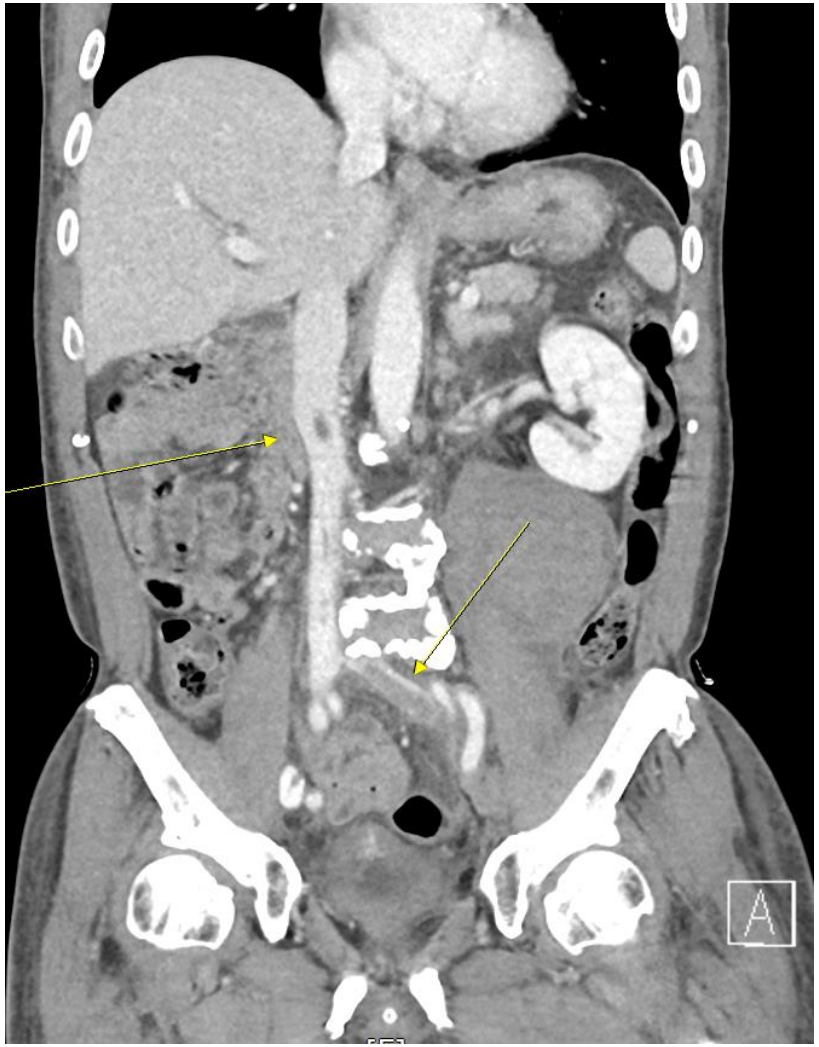
## HD #8

- Hb 10.2 -> Hb 6.7
- APCT

1. Hematoma at left iliopsoas muscle
   - With active bleeding
2. Hematoma at perirectal area
3. Thrombus at IVC and below left common iliac vein level
4. Right renal cyst
5. Scanned lower thorax : increased consolidation at LUL, suspicious pneumonia



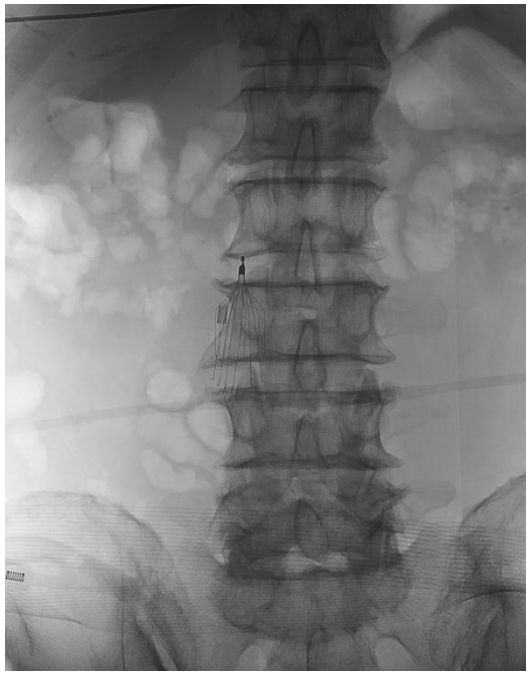


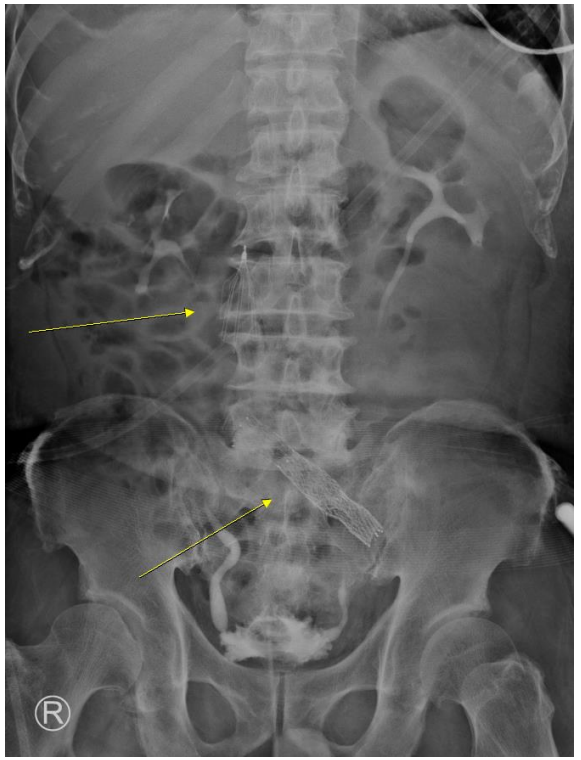


# Case 67/M: dyspnea

## HD #8

- IVC filter insertion
- thrombectomy with PTA and stent insertion (left femoral ~ iliac vein)
- Embolization, s/p left iliolumbar artery and left 3rd ~ 4rd lumbar artery





# Lung cancer

Lung, "right main bronchus endobronchial lesion", bronchoscopic biopsy:

SQUAMOUS CELL CARCINOMA

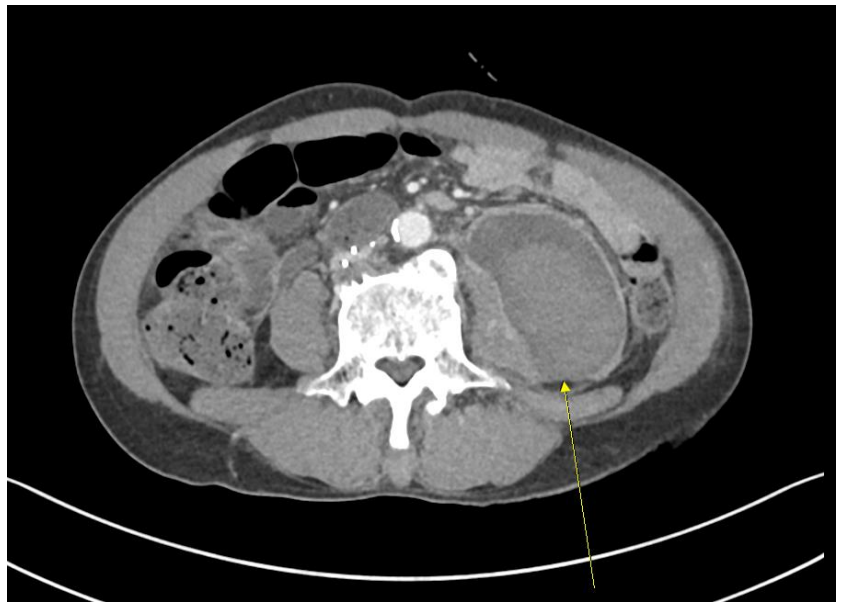
- cT2N2M0
- EGFR wild type, ALK wild type, PD-L1 SP263 40%
- FEV1 46%/1.36L, DLco 55 mL/mmHg/min

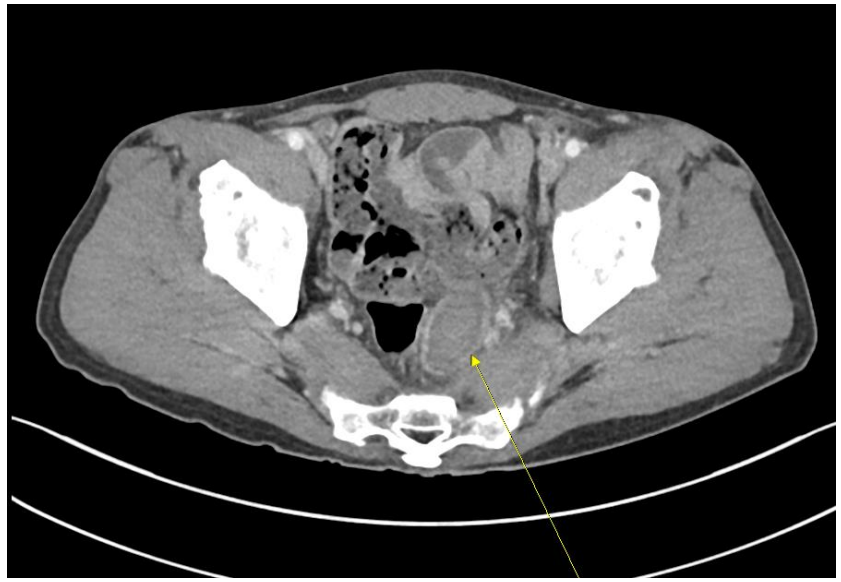
- Plan: Definitive CCRT followed by durvalumab maintain

# Case 67/M: dyspnea

## HD #15

- APCT f/u
  - liquefied hematoma
  - No evidence of active bleeding
- Enoxaparin 60mg bid restart

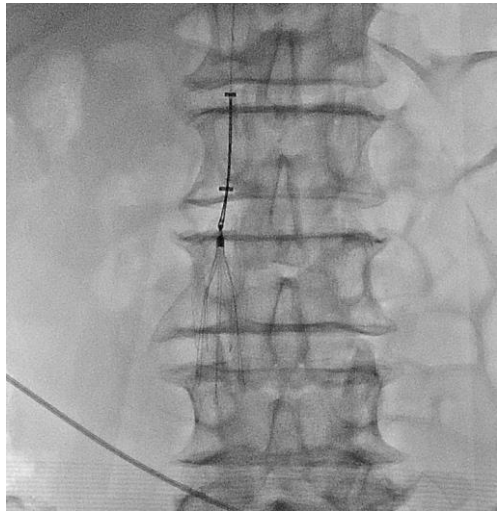


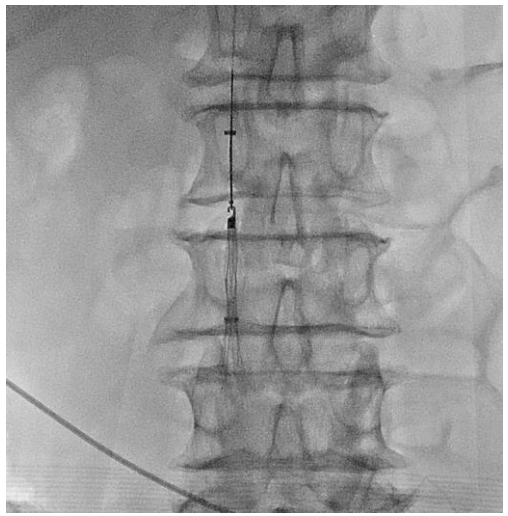


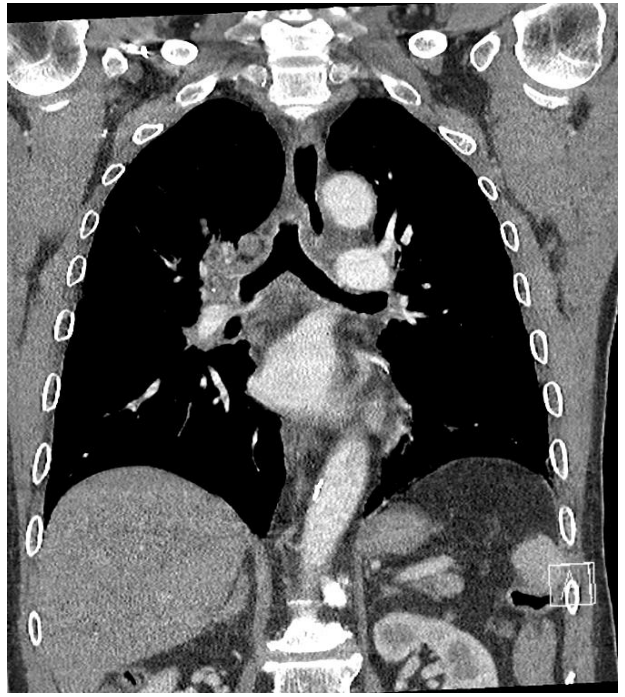
# Case 67/M: dyspnea

## Discharge

- Enoxaparin 60mg bid -> Rivaroxaban 20mg qd
- IVC filter removal
- Rivaroxaban 10mg qd







2024.09.25 Durvalumab #14

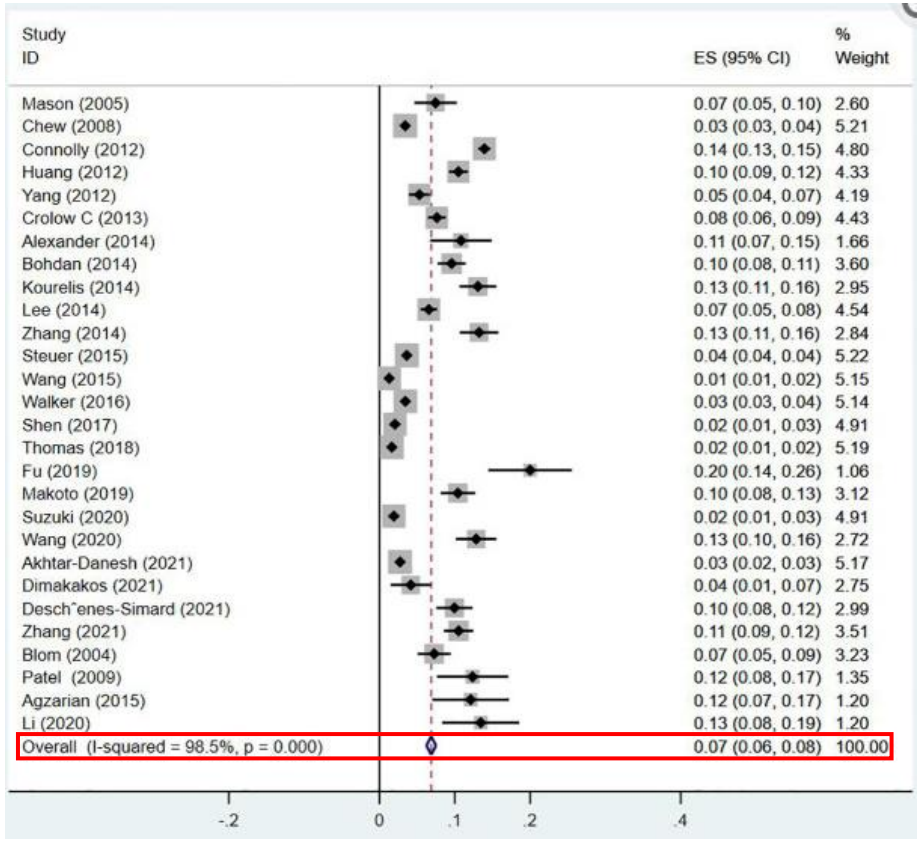
# Contents

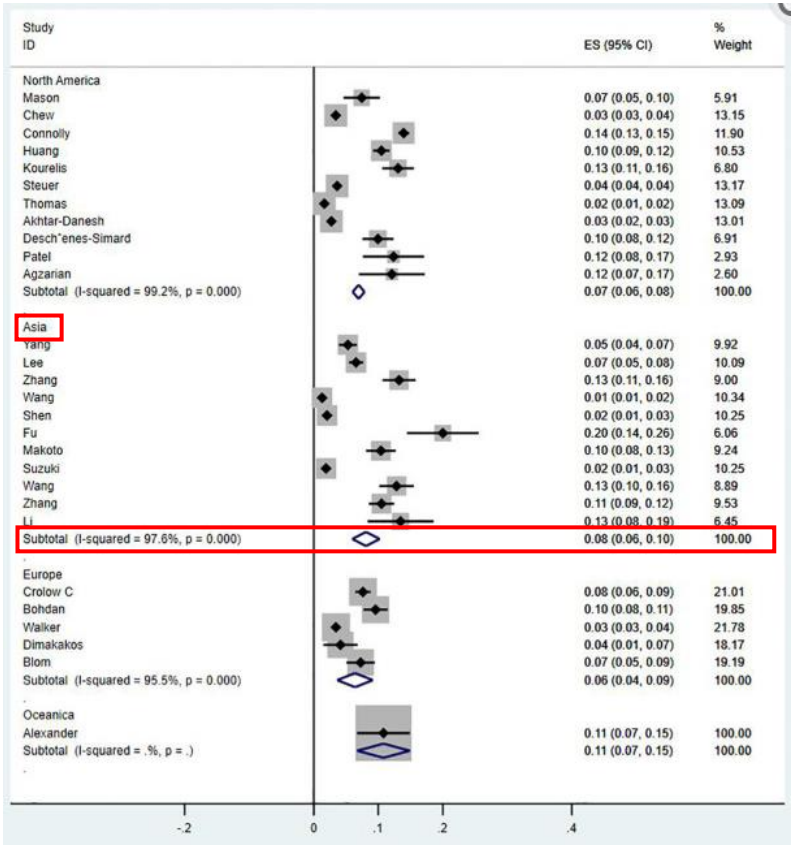
- Epidemiology
- Mechanism of VTE in lung cancer
- Risk factor
- Current guidelines for VTE treatment and prophylaxis in lung cancer
- Summary

# Epidemiology

- Prevalence of VTE in patients with lung cancer
- Meta-analysis
- 35 studies involving 742,156 patients

- Overall: 7%
- Asia: 8%




Front Oncol. 2024; 14: 1405147.

# Epidemiology

- Department of Veterans Affairs health care system in US
- Retrospective cohort study
- 434,203 patients

- Overall cumulative VTE incidence in lung cancer: 6.9% at 12mo


Table 2. Multivariable Cox Regression Analysis for Association With Cancer-Associated Thrombosis

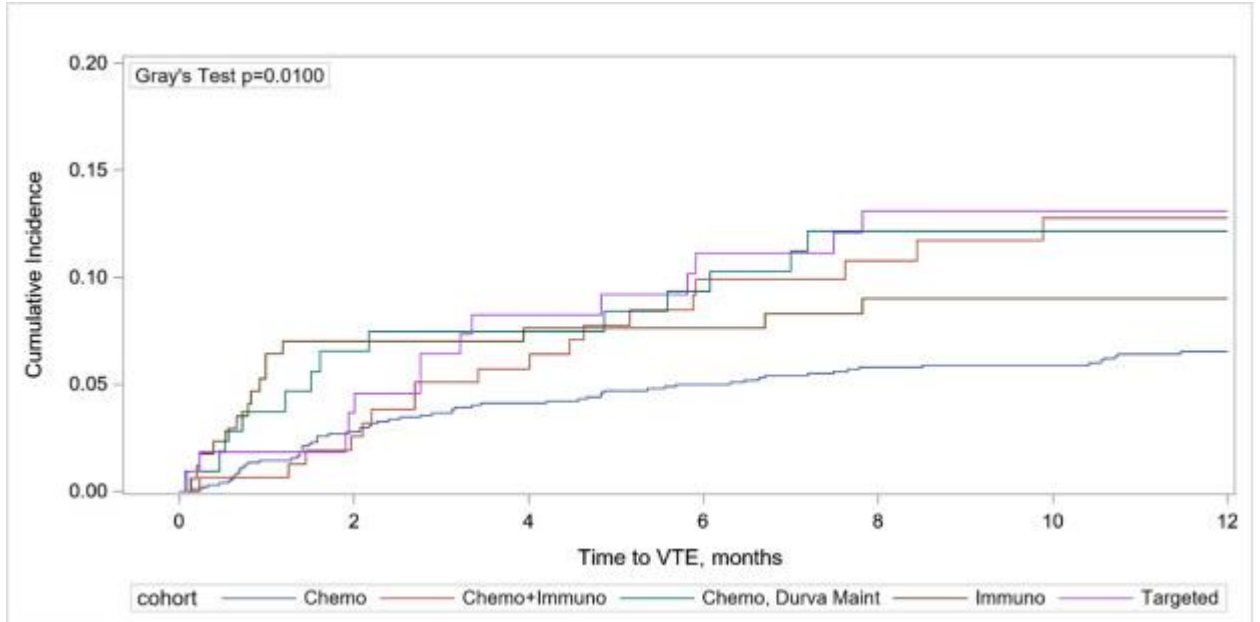
| Variables | HR (95% CI) | |
|---|---|---|
| | Overall VTE incidence | PE or LE-DVT incidence |
| Prostate | 1 [Reference] | 1 [Reference] |
| Chronic myeloid leukemia | 0.57 (0.49-0.66) | 0.51 (0.43-0.60) |
| Chronic lymphocytic leukemia | 0.77 (0.68-0.87) | 0.72 (0.63-0.83) |
| Myelodysplastic syndrome | 0.76 (0.66-0.87) | 0.64 (0.55-0.75) |
| Thyroid | 1.05 (0.90-1.22) | 0.97 (0.82-1.16) |
| Head and neck | 1.32 (1.24-1.41) | 1.01 (0.94-1.09) |
| Indolent non-Hodgkin lymphoma | 1.38 (1.26-1.51) | 1.18 (1.06-1.30) |
| Melanoma | 1.38 (1.26-1.52) | 1.35 (1.22-1.49) |
| Multiple myeloma | 1.72 (1.57-1.87) | 1.60 (1.45-1.76) |
| Breast | 1.85 (1.62-2.10) | 1.60 (1.37-1.86) |
| Liver | 1.84 (1.70-2.00) | 1.92 (1.76-2.09) |
| Neuroendocrine | 1.97 (1.78-2.18) | 1.84 (1.64-2.06) |
| Hodgkin lymphoma | 2.00 (1.68-2.38) | 1.55 (1.25-1.92) |
| Acute myeloid leukemia | 2.10 (1.82-2.41) | 1.35 (1.12-1.62) |
| Colon | 2.45 (2.31-2.59) | 2.31 (2.17-2.45) |
| Kidney | 2.17 (2.02-2.33) | 2.12 (1.97-2.29) |
| Testicular | 2.49 (1.91-3.25) | 2.18 (1.60-2.98) |
| Aggressive non-Hodgkin lymphoma | 2.65 (2.43-2.89) | 2.25 (2.04-2.48) |
| Bladder | 2.76 (2.57-2.96) | 2.65 (2.46-2.86) |
| Sarcoma | 2.82 (2.46-3.23) | 2.56 (2.20-2.98) |
| Gynecologic | 2.93 (2.35-3.61) | 3.39 (2.69-4.27) |
| Miscellaneous solid | 3.21 (2.98-3.47) | 2.95 (2.71-3.21) |
| Lung | 3.23 (3.08-3.39) | 3.10 (2.94-3.27) |
| Gastric and esophageal | 4.03 (3.78-4.30) | 3.65 (3.40-3.93) |
| Bile and gallbladder | 4.38 (3.84-4.98) | 4.42 (3.85-5.08) |
| Acute lymphoblastic leukemia | 4.98 (3.71-6.68) | 3.37 (2.35-4.85) |
| Brain | 5.65 (4.96-6.44) | 6.32 (5.51-7.25) |
| Pancreas | 6.42 (5.98-6.90) | 6.45 (5.97-6.97) |
| Cancer stage | | |
| I | 1 [Reference] | 1 [Reference] |
| II | 1.47 (1.41-1.54) | 1.43 (1.37-1.50) |
| III | 1.88 (1.80-1.97) | 1.82 (1.73-1.90) |
| IV | 2.78 (2.68-2.90) | 2.79 (2.67-2.91) |
| Unknown | 1.44 (1.36-1.52) | 1.40 (1.32-1.48) |
| First-line systemic therapy within 3 mo[c] | | |
| None | 1 [Reference] | 1 [Reference] |
| Chemotherapy | 1.44 (1.40-1.49) | 1.34 (1.30-1.39) |
| Immune checkpoint inhibitor | 1.49 (1.22-1.82) | 1.38 (1.11-1.71) |
| Targeted therapy | 1.21 (1.13-1.30) | 1.23 (1.14-1.33) |
| Endocrine therapy | 1.20 (1.12-1.28) | 1.18 (1.09-1.26) |

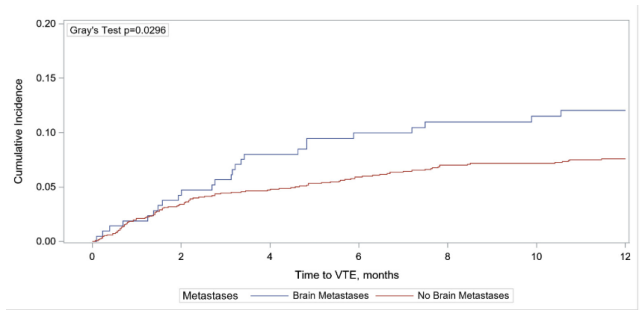
JAMA Netw Open. 2023;6(6):e2317945.

# Epidemiology

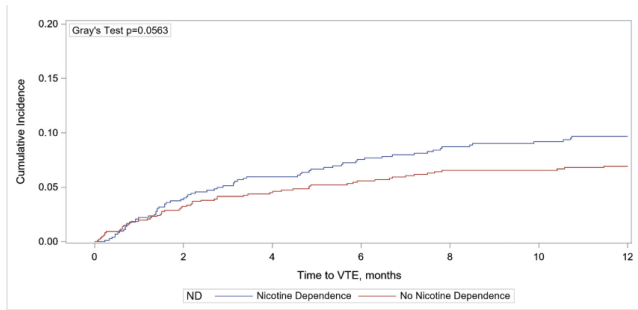
- 1,587 patients with NSCLC who received first-line treatment in US
- Retrospective cohort study

- Lung cancer patients receiving **targeted therapies** had the highest thrombosis rate.

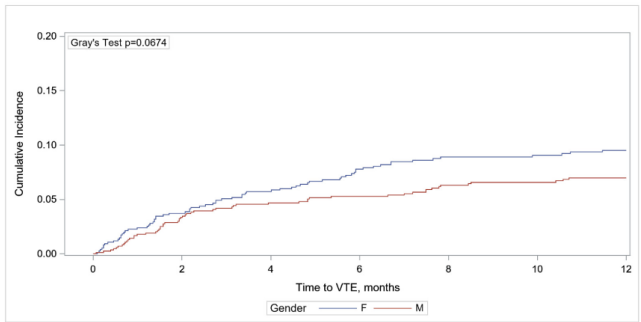



a




b



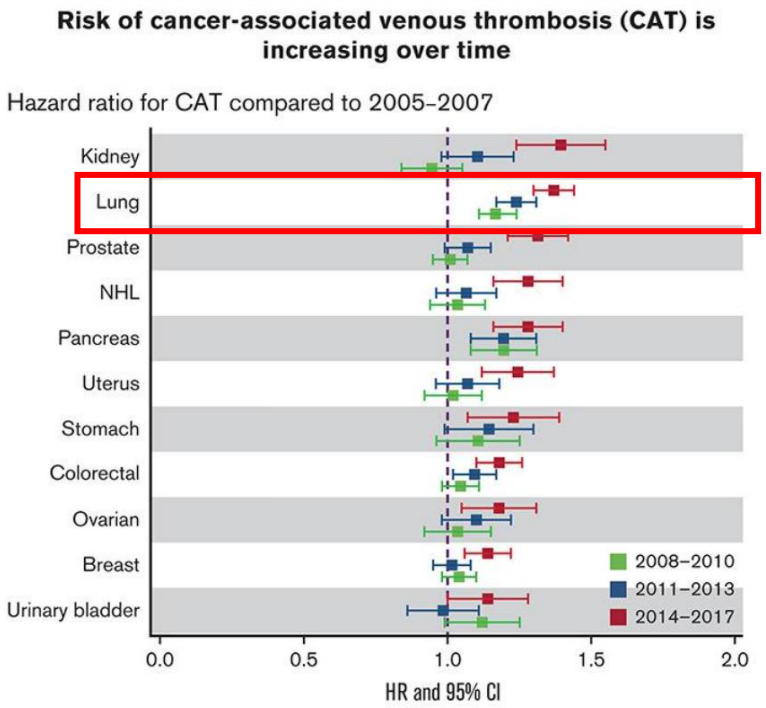

c

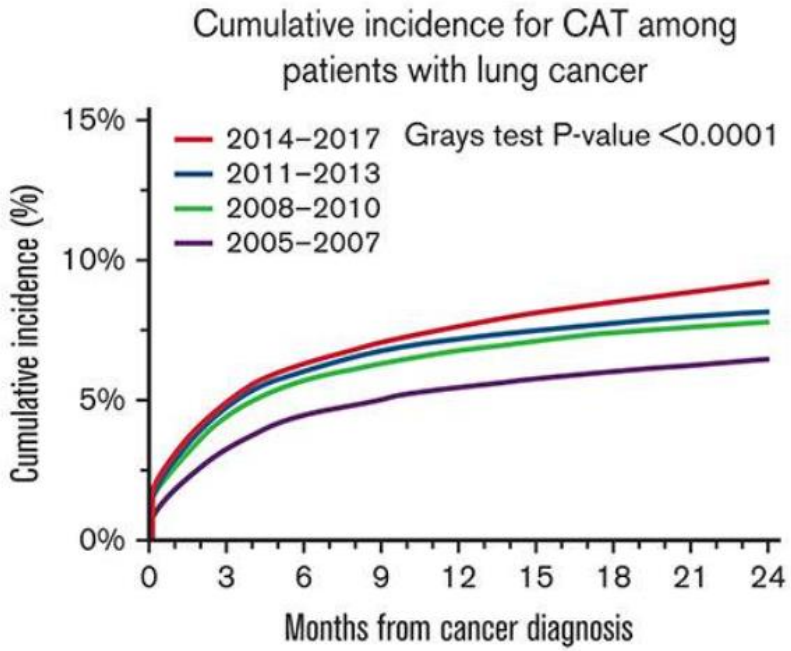
Thromb Res. 2021 Dec:208:71-78.

# Epidemiology

- The California Cancer Registry
- Retrospective cohort study
- Lung cancer (N = 135,075) diagnosed between 2005 and 2017

- Cancer-associated thrombosis (CAT) is increasing over time.
  - Increased detection during routine disease assessment
  - Immunotherapy
  - Intensive combination chemotherapy
  - Improved survival



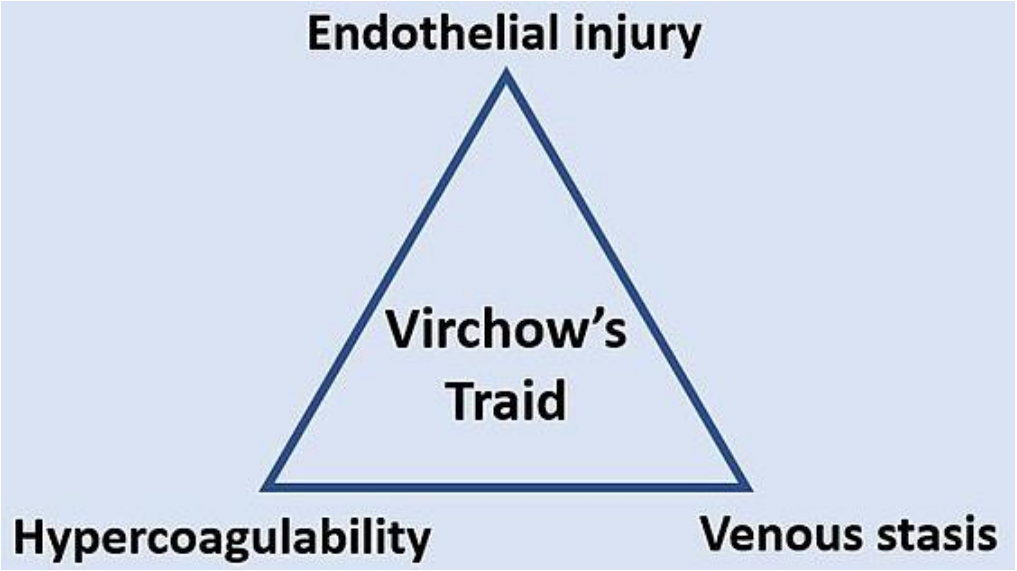



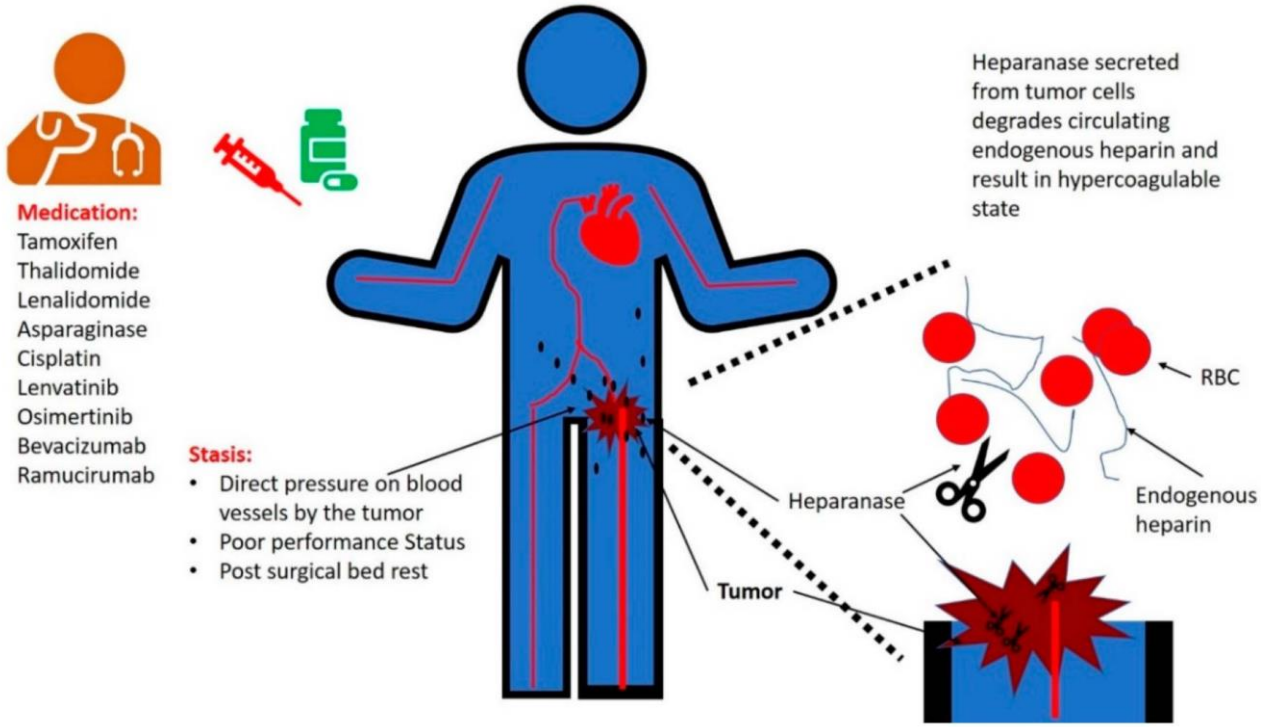

Blood Adv. 2022 Jan 11; 6(1): 307–320.

# Contents

- Epidemiology
- Mechanism of VTE in lung cancer
- Risk factor
- Current guidelines for VTE treatment and prophylaxis in lung cancer
- Summary

# Mechanism of VTE in lung cancer

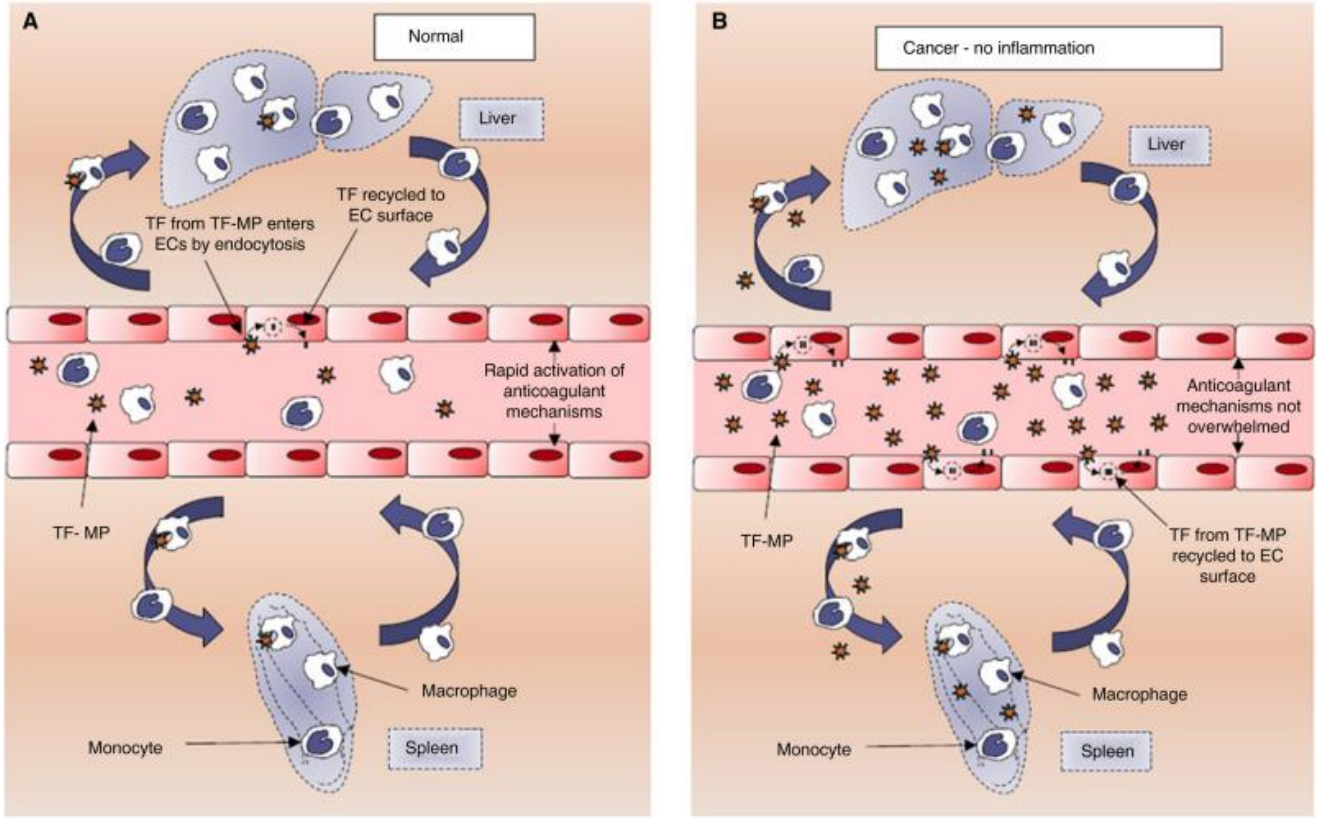



Cancers. 2020;12(3):566.

# Mechanism of VTE in lung cancer

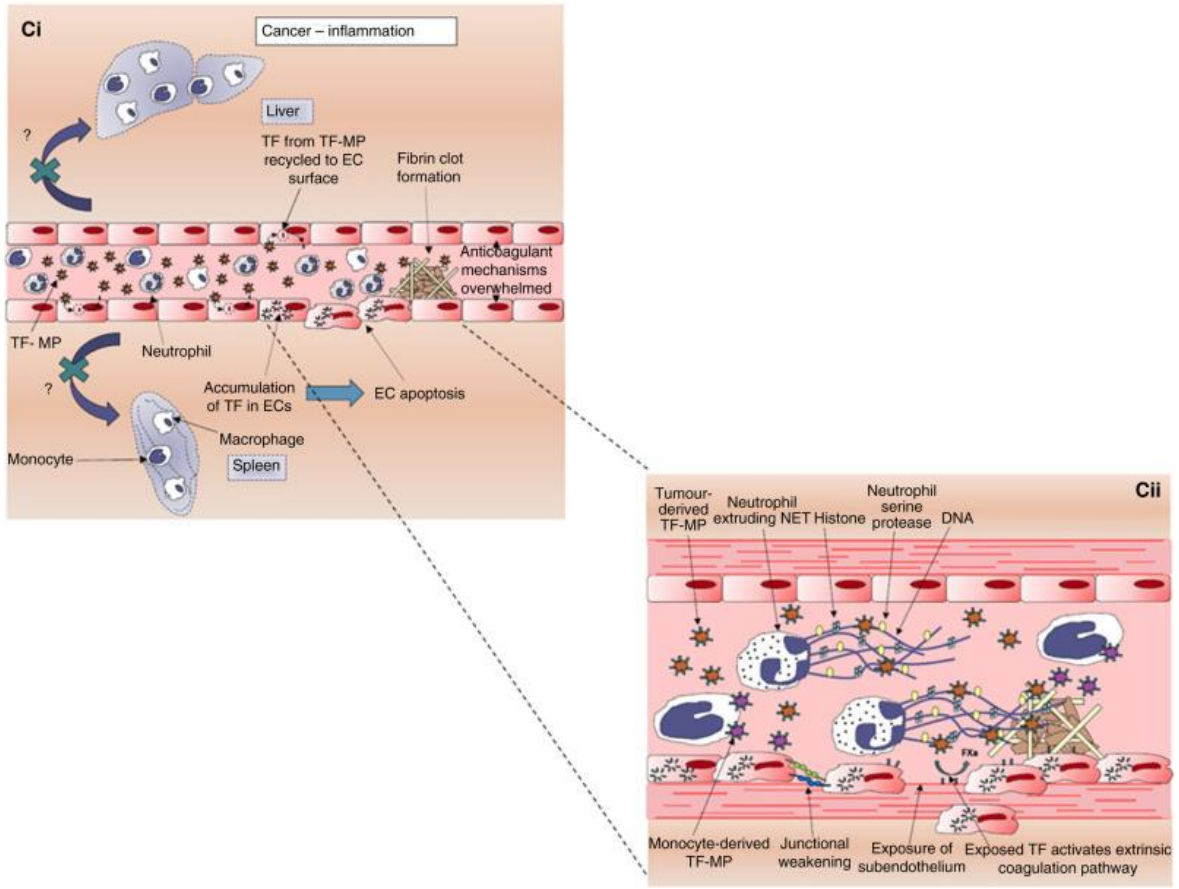
- Lung cancer cells
  - Tissue factor
  - Microparticles
  - Cancer procoagulant
  - Inflammatory factors
  - Cytokines




J Thromb Haemost. 2017 Dec;15(12):2289-2299.

# Mechanism of VTE in lung cancer

- Lung cancer cells
  - Tissue factor
  - Microparticles
  - Cancer procoagulant
  - Inflammatory factors
  - Cytokines




J Thromb Haemost. 2017 Dec;15(12):2289-2299.

# Contents

- Epidemiology
- Mechanism of VTE in lung cancer
- Risk factor
- Current guidelines for VTE treatment and prophylaxis in lung cancer
- Summary

# Risk factors

- Patient-related
- Cancer-related
- Therapy-related

**Table 1** Summary of Risk Factors and Biomarkers for Lung Cancer-Associated VTE

| |
|---|
| 1.Patient-related risk factors<br>·Demographics: age<br>·Comorbidities: lower extremity varicose vein, cardiovascular disease, hypertension, atrial fibrillation |
| 2.Cancer-related risk factors<br>·Genetic alterations: EGFR mutation/ALK-rearrangement/KRAS mutation/ROS1-rearrangement<br>·Histological type: lung adenocarcinoma<br>·Clinical stage: advanced stage, regional and distant lymph node metastases<br>·Time interval after diagnosis/chemotherapy: within 6 months after lung cancer diagnosis |
| 3.Therapy-related risk factors<br>·Surgery: lobectomy<br>·Chemotherapy: platinum-based chemotherapy<br>·Targeted therapy:EGFR-tyrosine kinase inhibitors (TKI), anti-angiogenic agents<br>·Other treatment: Central venous catheters (CVC) |
| 4.Biomarkers<br>·D-dimer<br>·Platelet<br>·P-selectin<br>·Microparticle<br>·More hematological parameters:Neutrophil/lymphocyte ratio (NLR), Platelet/lymphocyte ratio (PLR), thrombin factor VIII, serum albumin, thrombin-antithrombin III complex (TAT), Plasminogen activator inhibitor type I (PAI-1), inflammatory cytokines |

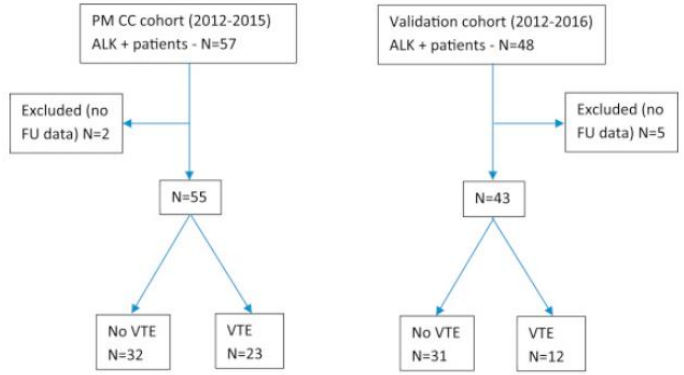
**Table 2** Summary of Risk Assessment Models for Lung Cancer-Associated VTE

| RAM | Khorana Score | Vienna (CATS) Score | PROTECHT Score | ONKOTEV Score | COMPASS-CAT Score | Tic-ONCO Score |
|---|---|---|---|---|---|---|
| Factors | Site of cancer | Site of cancer | Site of cancer | Khorana score >2 | Anthracycline/anti-hormonal therapy | Site of cancer |
| | Platelet count | Platelet count | Platelet count | Personal history of VTE | Time since cancer diagnosis | Genetic risk score |
| | Hemoglobin count | Hemoglobin count | Hemoglobin count | Metastatic disease | Central venous catheter | Hemoglobin count |
| | Leukocyte count | Leukocyte count | Leukocyte count | Vascular/lymphatic macroscopic compression | Stage of cancer | Leukocyte count |
| | Body mass index | Body mass index | Body mass index | | Presence of cardiovascular risk | Body mass index |
| | | D-dimer | Cisplatin/carboplatin-based chemotherapy or gemcitabine | | Platelet count | Platelet count |
| | | Soluble P-selectin | | | Recent hospitalization for acute medical illness | |
| | | | | | Personal history of VTE | |
| Reference | [45] | [47] | [50] | [52] | [54] | [55] |

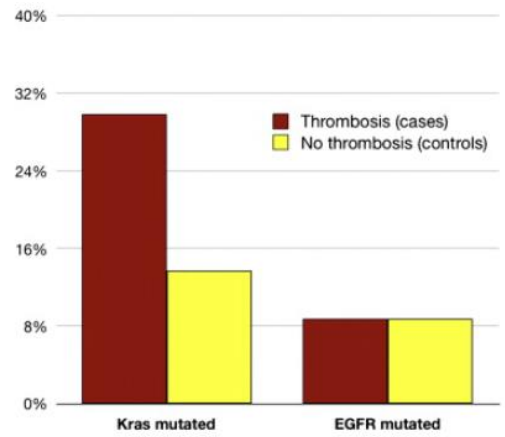
Cancer Manag Res. 2021; 13: 8317–8327.

# Risk factors

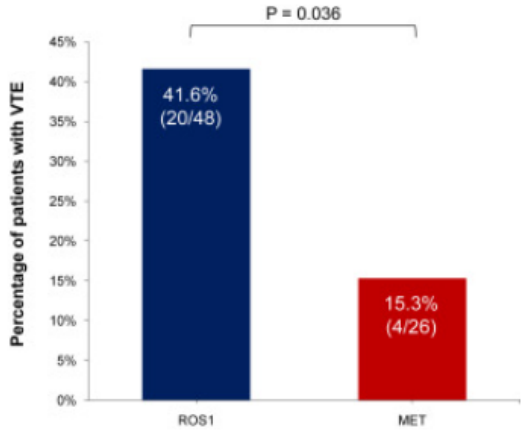
- Cancer-related
  - Genetic alteration
    - ALK rearrangement, KRAS, ROS-1, EGFR
  - Histologic type: adenocarcinoma
  - Clinical stage
  - Time interval after diagnosis/chemotherapy: <6 mo



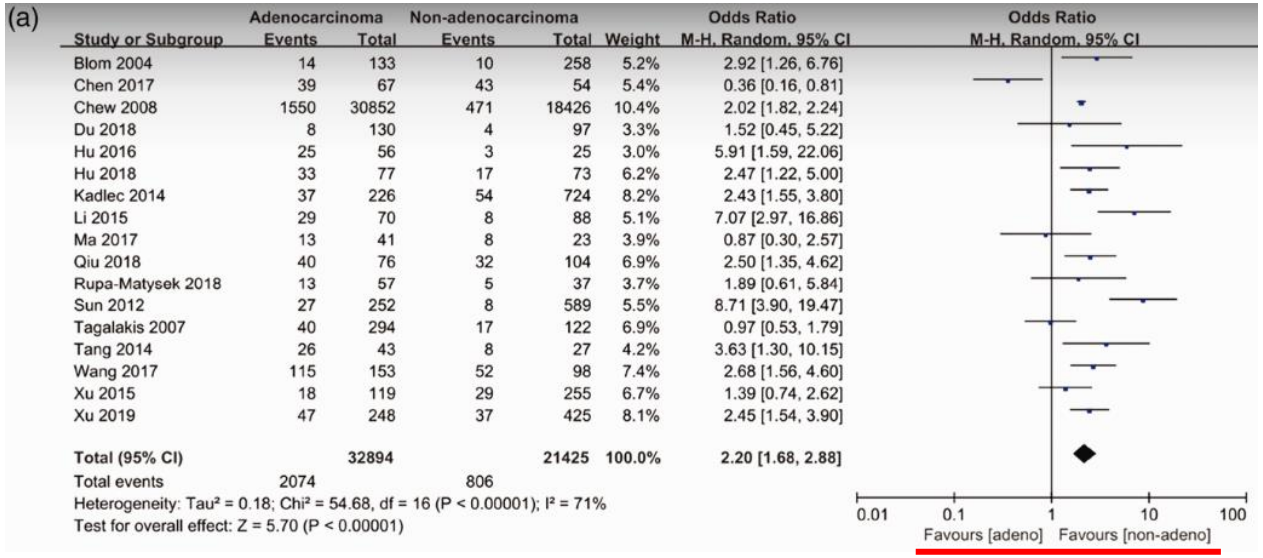

ALK+: 42%




KRAS: OR 2.67, p=0.014




ROS-1: 41.6%





Clin Lung Cancer. 2017;18(2):156–161.
Thromb Res. 2014;133(1):48–51.
Clin Lung Cancer. 2020;21(1):15–20.
J Int Med Res. 2020;48(1):300060519896919.

# Risk factors

- Therapy-related
  - Surgery
  - Chemotherapy
    - Platinum based chemotherapy
    - Osimertinib
  - Central venous catheter

| Cancer Type and Treatment Regimen | No. of Patients* | % |
|---|---|---|
| Cancer diagnosis | | |
| Colorectal/anal/small bowel | 5/13 | 38.5 |
| Pancreatic | 29/79 | 36.7 |
| Gallbladder/ampullary | 3/10 | 30.0 |
| Gastric/GE junction | 31/114 | 27.2 |
| Cholangiocarcinoma | 5/18 | 27.8 |
| Ovarian | 12/57 | 21.0 |
| Bladder | 6/33 | 18.2 |
| Sarcoma | 2/11 | 18.2 |
| Germ cell/seminoma | 7/39 | 18.0 |
| Esophageal | 8/46 | 17.4 |
| Endometrial | 3/22 | 13.6 |
| Melanoma | 9/69 | 13.0 |
| Head and neck | 12/94 | 12.8 |
| Lung | 24/204 | 11.8 |
| Cervical/uterine/vulvar | 4/39 | 10.3 |
| Hematologic malignancies | 1/11 | 9.1 |
| Neuroendocrine/carcinoid | 0/11 | 0 |
| Other | 8/62 | 12.9 |
| Chemotherapy regimens | | |
| Cisplatin + docetaxel + fluorouracil/leucovorin + bevacizumab | 11/16 | 68.8 |
| Cisplatin + docetaxel + fluorouracil/leucovorin | 7/11 | 63.6 |
| Cisplatin IP + paclitaxel IV/IP + bevacizumab | 6/13 | 46.2 |
| Cisplatin + docetaxel + fluorouracil | 5/17 | 29.4 |
| Cisplatin + gemcitabine | 38/134 | 28.4 |
| Cisplatin + paclitaxel + ifosfamide | 2/11 | 18.2 |
| Cisplatin + irinotecan | 15/89 | 16.9 |
| Cisplatin + pemetrexed | 6/43 | 14 |
| Cisplatin + etoposide | 10/80 | 12.5 |
| Cisplatin + fluorouracil + epirubicin | 2/16 | 12.5 |
| Cisplatin + vinblastine + temozolomide | 7/57 | 12.3 |
| Cisplatin + pemetrexed + bevacizumab | 4/33 | 12.1 |
| Cisplatin + radiation | 9/94 | 9.6 |
| Cisplatin IP + paclitaxel IV/IP | 3/33 | 9.1 |
| Other cisplatin-based regimens | 44/285 | 15.4 |

**Table 7.** Adverse events reported with osimertinib

| Adverse event | Any grade, *n* (%) | G3/G4, *n* (%) | G1/G2, *n* (%) |
|---|---|---|---|
| **Any** | **110 (87.3)** | **42 (33.3)** | **68 (54.0)** |
| ILD/pneumonitis | 12 (9.5) | 3 (2.4) | 9 (7.1) |
| **Diarrhea** | **49 (38.9)** | 4 (3.2) | 45 (35.7) |
| Stomatitis | 17 (13.5) | 1 (0.8) | 16 (12.7) |
| Keratitis | 7 (5.6) | 0 (0.0) | 7 (5.6) |
| **Rash** | **42 (33.3)** | 2 (1.6) | 40 (31.7) |
| **Dry skin** | **24 (19.0)** | 0 (0.0) | 24 (19.0) |
| **Paronychia** | **33 (26.2)** | 1 (0.8) | 32 (25.4) |
| Pruritus | 12 (9.5) | 0 (0.0) | 12 (9.5) |
| QTcProlonged | 2 (1.6) | 1 (0.8) | 1 (0.8) |
| Platelet count decrease | 18 (14.3) | 3 (2.4) | 15 (11.9) |
| Leucopenia | 17 (13.5) | 1 (0.8) | 16 (12.7) |
| Neutropenia | 9 (7.1) | 0 (0.0) | 9 (7.1) |
| **Venous thromboembolism** | **12 (9.5)** | **10 (7.9)** | **2 (1.6)** |
| Creatinine increased | 26 (20.6) | 0 (0.0) | 26 (20.6) |
| Heart failure | **2 (1.6)** | **1 (0.8)** | **1 (0.8)** |
| Arterial thromboembolism | **3 (2.4)** | **2 (1.6)** | **1 (0.8)** |
| Myocardial infarction | 2 (1.6) | 2 (1.6) | 0 (0) |
| Atrial fibrillation | 2 (1.6) | 0 (0.0) | 2 (1.6) |
| Pericardial effusion | 2 (1.6) | 0 (0.0) | 2 (1.6) |
| Anemia | 7 (5.6) | 0 (0.0) | 7 (5.6) |
| Asthenia | 9 (7.1) | 0 (0.0) | 9 (7.1) |
| AST and ALT increased | 10 (7.9) | 0 (0.0) | 10 (7.9) |
| Nausea | 7 (5.6) | 1 (0.8) | 6 (4.8) |
| Oral dysesthesia | 1 (0.8) | 0 (0.0) | 1 (0.8) |
| Hyponatriemia | 3 (2.4) | 0 (0.0) | 3 (2.4) |
| Oral hemorrhage | 1 (0.8) | 0 (0.0) | 1 (0.8) |
| Bilirubin increase | 1 (0.8) | 0 (0.0) | 1 (0.8) |
| Skin ulceration | 2 (1.6) | 1 (0.8) | 1 (0.8) |
| Alopecia | 2 (1.6) | 0 (0.0) | 2 (1.6) |
| Endocarditis | 1 (0.8) | 1 (0.8) | 0 (0) |
| Hemorrhoids | 2 (1.6) | 1 (0.8) | 1 (0.8) |
| Gastric pyrosis | 2 (1.6) | 0 (0.0) | 2 (1.6) |
| Abdominal pain | 1 (0.8) | 0 (0.0) | 1 (0.8) |
| Constipation | 2 (1.6) | 0 (0.0) | 2 (1.6) |
| Peripheral sensory neuropathy | 1 (0.8) | 0 (0.0) | 1 (0.8) |

Significant values are highlighted in bold.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; G3/G4, grade 3/grade 4; ILD, Interstitial Lung Disease; QTcProlonged, electrocardiogram QT corrected interval prolonged.

J Clin Oncol. 2011 Sep 1;29(25):3466-73.
Thromb Res. 2022 Feb:210:63-66.

# Contents

- Epidemiology
- Mechanism of VTE in lung cancer
- Risk factor
- Current guidelines for VTE treatment and prophylaxis in lung cancer
- Summary

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- 2019 ESC guideline

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.[360–363] | IIa | A |
| Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[366] | IIa | B |
| Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[367] | IIa | C |
| For patients with PE and cancer, extended anticoagulation (beyond the first 6 months)[c] should be considered for an indefinite period or until the cancer is cured.[378] | IIa | B |
| In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.[376,377] | IIa | B |



Eur Heart J. 2020 Jan 21;41(4):543-603.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

## Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline☆

A. Falanga[1,2], C. Ay[3], M. Di Nisio[4], G. Gerotziafas[5], L. Jara-Palomares[6,7], F. Langer[8], R. Lecumberri[9,10], M. Mandala[11], A. Maraveyas[12], I. Pabinger[3], M. Sinn[8], K. Syrigos[13], A. Young[14] & K. Jordan[15,16], on behalf of the ESMO Guidelines Committee*

ASCO special articles

## Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Guideline Update

Nigel S. Key, MBChB[1]; Alok A. Khorana, MD[2]; Nicole M. Kuderer, MD[3]; Kari Bohlke, ScD[4]; Agnes Y.Y. Lee, MD, MSc[5]; Juan I. Arcelus, MD, PhD[6]; Sandra L. Wong, MD, MS[7]; Edward P. Balaban, DO[8]; Christopher R. Flowers, MD, MS[9]; Leigh E. Gates, BA, CPHQ[10]; Ajay K. Kakkar, MD, PhD[11]; Margaret A. Tempero, MD[12]; Shilpi Gupta, MD[13]; Gary H. Lyman, MD, MPH[14]; and Anna Falanga, MD[15]

## 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19

*Dominique Farge*, Corinne Frere*, Jean M Connors, Alok A Khorana, Ajay Kakkar, Cihan Ay, Andres Muñoz, Benjamin Brenner, Pedro H Prata, Dialina Brilhante, Darko Antic, Patricia Casais, María Cecilia Guillermo Esposito, Takayuki Ikezoe, Syed A Abutalib, Luis A Meillon-García, Henri Bounameaux, Ingrid Pabinger, James Douketis, the International Initiative on Thrombosis and Cancer (ITAC) advisory panel*

CLINICAL GUIDELINES

blood advances

## American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

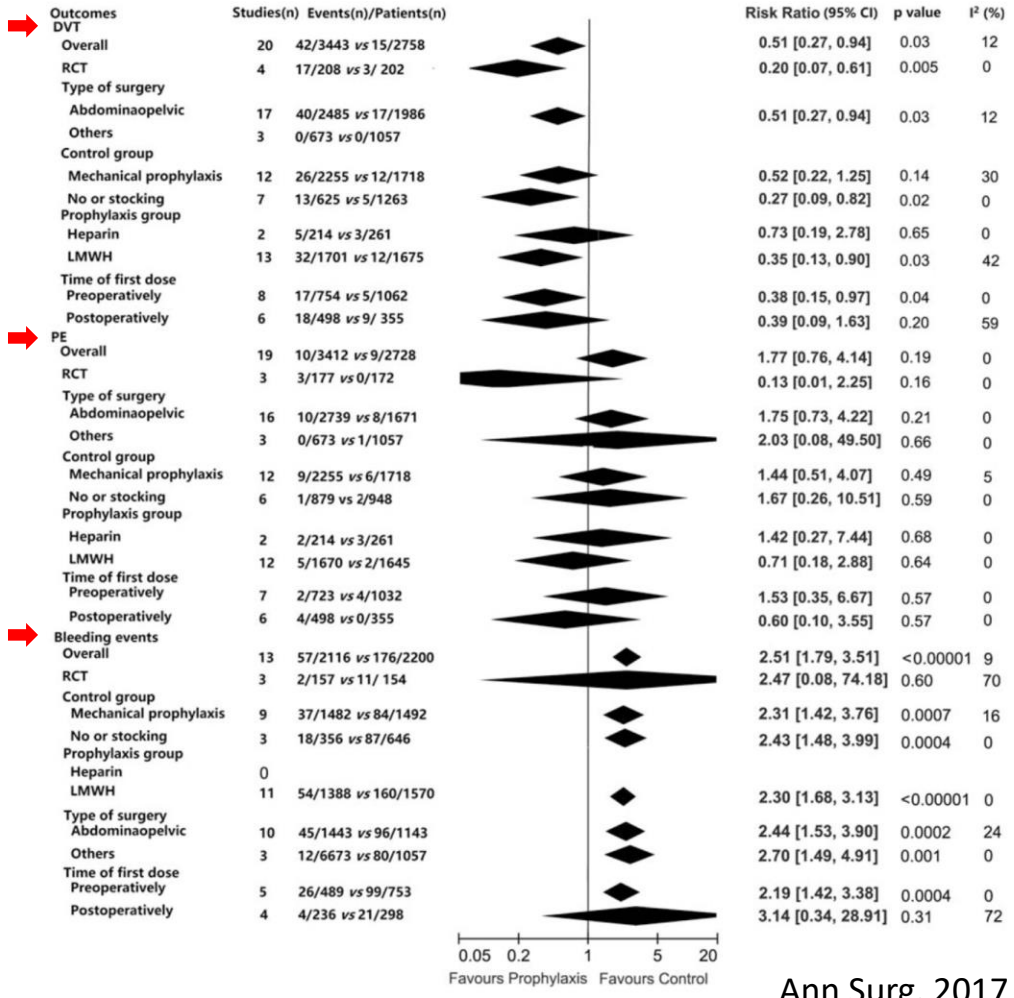
Gary H. Lyman,[1,2,*] Marc Carrier,[3,*] Cihan Ay,[4] Marcello Di Nisio,[5] Lisa K. Hicks,[6] Alok A. Khorana,[7] Andrew D. Leavitt,[8,9] Agnes Y. Y. Lee,[10,11] Fergus Macbeth,[12] Rebecca L. Morgan,[13] Simon Noble,[14] Elizabeth A. Sexton,[15] David Stenehjem,[16] Wojtek Wiercioch,[13] Lara A. Kahale,[17,†] and Pablo Alonso-Coello[18,†]

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Perioperative setting (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - Pharmacological VTE prophylaxis with LMWH (preferred) or UFH is recommended in patients undergoing major cancer surgery 2-12 h preoperatively and at least 10 days post-operatively. (ASCO, ESMO, ITAC, ASH)

- Meta-analysis including 39 studies and 16,366 patients
- Solid tumor
- Pharmacological prophylaxis versus non-drug studies

- Thromboprophylaxis is associated with lower VTE events, there is a higher incidence of clinically significant bleeding events



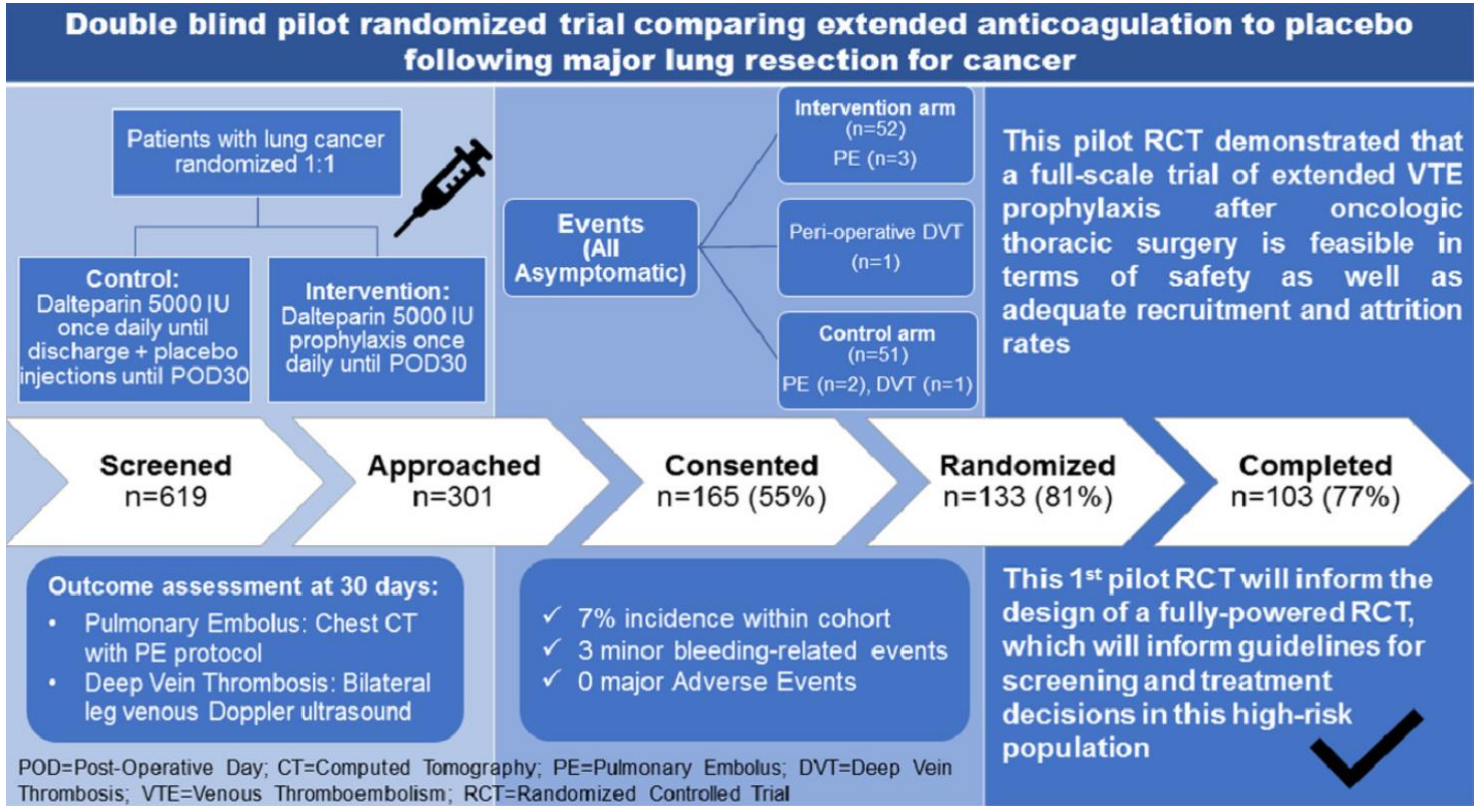

Ann Surg. 2017 Jun;265(6):1087-1093.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Perioperative setting (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - Pharmacological VTE prophylaxis with LMWH (preferred) or UFH is recommended in patients undergoing major cancer surgery 2-12 h preoperatively and at least 10 days post-operatively. (ASCO, ESMO, ITAC, ASH)

- A pilot double blind RCT
- 103 patients undergoing lung resection
- POD 1 – Discharge: LMWH
- Discharge – POD 30: LVWH vs. Placebo

- "The thoracic surgery community eagerly awaits well-conducted, adequately powered studies."




Semin Thorac Cardiovasc Surg. 2021 Winter;33(4):1123-1134.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Chemotherapy (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - In ambulatory cancer patients starting systemic anticancer treatment who have a high thrombosis risk, apixaban, rivaroxaban or LMWH may be considered for primary thromboprophylaxis for a maximum of 6 months. (ESMO, ASCO)
  - Primary pharmacological prophylaxis of VTE with LMWH is NOT recommended for patients treated with systemic chemotherapy. (ITAC)

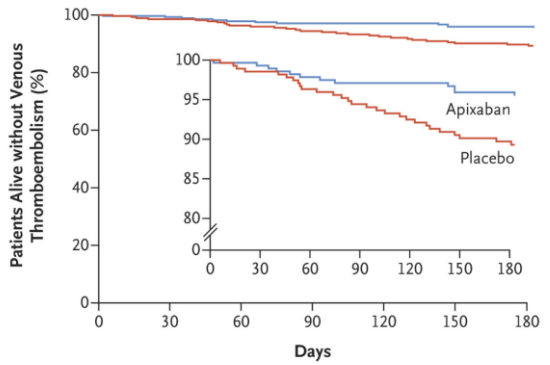
- AVERT and CASSINI studies randomized 574 and 841 patients
- Khorana score ≥2
- Apixaban or Rivaroxaban vs. Placebo

- DOAC resulted in a significantly lower rate of venous thromboembolism among intermediate-to-high-risk ambulatory patients with cancer starting chemotherapy.
- The rate of major bleeding episodes was higher.

ORIGINAL ARTICLE

**Apixaban to Prevent Venous Thromboembolism in Patients with Cancer**

Authors: Marc Carrier, M.D., Karim Abou-Nassar, M.D., Ranjeeta Mallick, Ph.D., Vicky Tagalakis, M.D., Sudeep Shivakumar, M.D., Ariah Schattner, M.D., Philip Kuruvilla, M.D., +16, for the AVERT Investigators* Author Info &

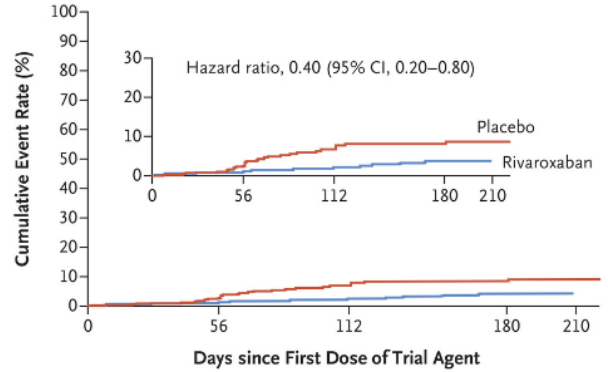



| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Apixaban | 288 | 276 | 265 | 256 | 249 | 244 | 229 |
| Placebo | 275 | 268 | 259 | 244 | 237 | 228 | 215 |

ORIGINAL ARTICLE

**Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer**

Authors: Alok A. Khorana, M.D., Gerald A. Soff, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Saroj Vadhan-Raj, M.D., M.H.C.M., C.M.Q., Hanno Riess, M.D., Ph.D., Ted Wun, M.D., Michael B. Streiff, M.D., +15, for the CASSINI



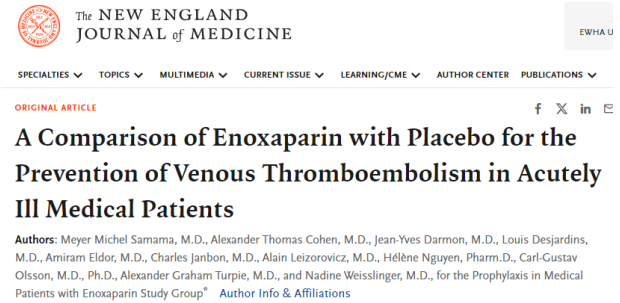

| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Placebo | 421 | 336 | 263 | 169 | 1 |
| Rivaroxaban | 420 | 338 | 274 | 172 | 0 |

N Engl J Med 2019;380:711-719
N Engl J Med 2019;380:720-728

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Hospitalized patients (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH or fondaparinux is recommended during hospitalization. (ASCO, ESMO, ITAC)
  - Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion. (ASCO)

- 3 RCTs
- Acutely ill medical patients
- LMWH or fondaparinux vs. Placebo


The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

A Comparison of Enoxaparin with Placebo for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients

Authors: Meyer Michel Samama, M.D., Alexander Thomas Cohen, M.D., Jean-Yves Darmon, M.D., Louis Desjardins, M.D., Amiram Eldor, M.D., Charles Janbon, M.D., Alain Leizorovicz, M.D., Hélène Nguyen, Pharm.D., Carl-Gustav Olsson, M.D., Ph.D., Alexander Graham Turpie, M.D., and Nadine Weisslinger, M.D., for the Prophylaxis in Medical Patients with Enoxaparin Study Group* Author Info & Affiliations


Circulation

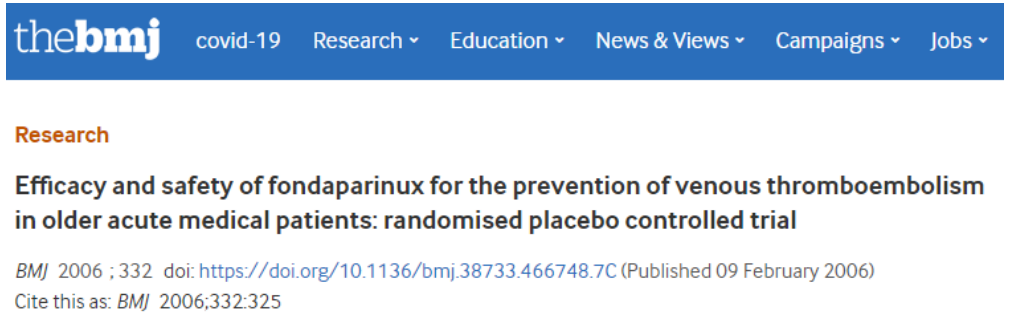
CURRENT ISSUE | ARCHI

RESEARCH ARTICLE | Originally Published 2 August 2004 |

Randomized, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients

Alain Leizorovicz, MD, Alexander T. Cohen, MD, Alexander G.G. Turpie, MD, Carl-Gustav Olsson, MD, Paul T. Vaitkus, MD, MBA, Samuel Z. Goldhaber, MD, and for the PREVENT Medical Thromboprophylaxis Study Group | AUTHOR INFO & AFFILIATIONS

- The recommendation of pharmacological thromboprophylaxis to prevent VTE for inpatients with cancer is based on the results from large clinical trials of hospitalized medical patients.


thebmj covid-19 Research Education News & Views Campaigns Jobs

Research

Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial

*BMJ* 2006 ; 332 doi: https://doi.org/10.1136/bmj.38733.466748.7C (Published 09 February 2006)
Cite this as: *BMJ* 2006;332:325

N Engl J Med 341:793-800, 1999
Circulation 110:874-879, 2004
BMJ 332:325-329, 2006

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Hospitalized patients (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH or fondaparinux is recommended during hospitalization. (ASCO, ESMO, ITAC)
  - Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion. (ASCO)

- RASTEN trial, RCT
- Newly diagnosed SCLC
- LMWH vs. Placebo

- Enoxaparin in addition to standard therapy did not improve OS in SCLC patients.
- The incidence of VTE was significantly reduced in the LMWH arm.
- Hemorrhagic events were more frequent in the LMWH-treated group.

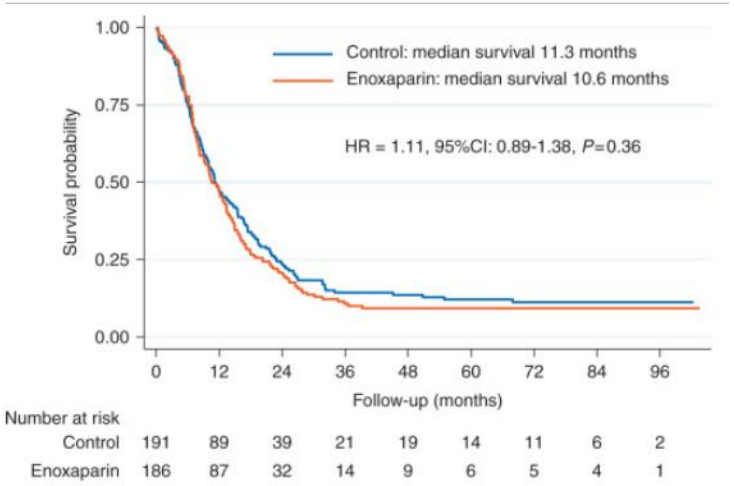
- Addition of LMWH cannot be generally recommended in the management of SCLC patients

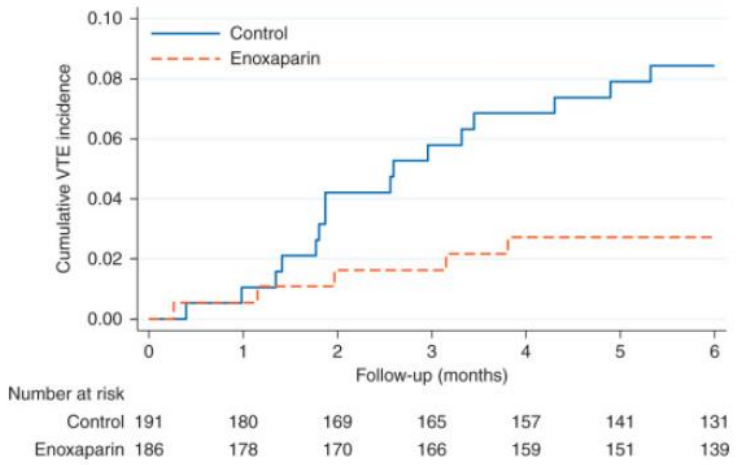
Original articles

Thoracic tumors

## Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial

L. Ek [1], E. Gezelius [2 3], B. Bergman [4], P.O. Bendahl [3], H. Anderson [5], J. Sundberg [2], M. Wallberg [1], U. Falkmer [6], S. Verma [7], M. Belting [2 3], Swedish Lung Cancer Study Group (SLUSG)



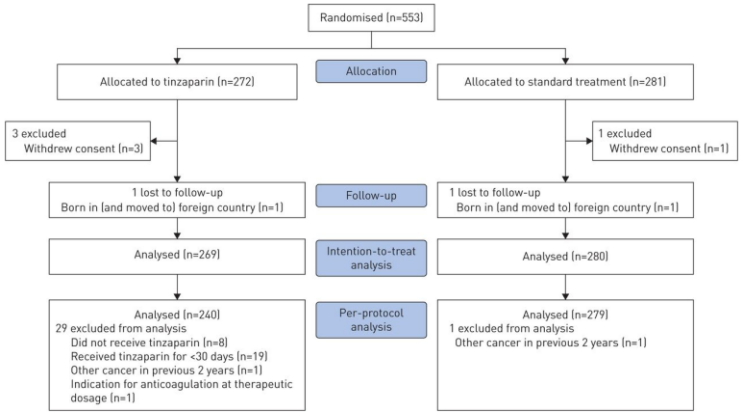

Ann Oncol 2018;29:398–404.

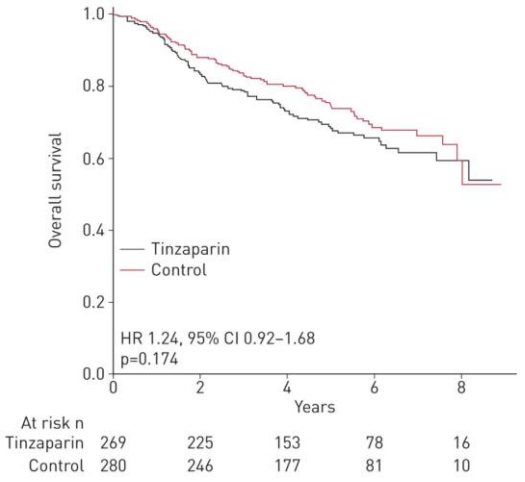
# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Hospitalized patients (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH or fondaparinux is recommended during hospitalization. (ASCO, ESMO, ITAC)
  - Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion. (ASCO)

- A phase III RCT
- Patients with completely resected stage I, II or IIIA NSCLC
- LMWH (tinzaparin) (n=269) for 12 weeks vs. placebo (n=280)

- Adjuvant tinzaparin had no detectable impact on OS of patients with completely resected stage I–IIIA NSCLC.

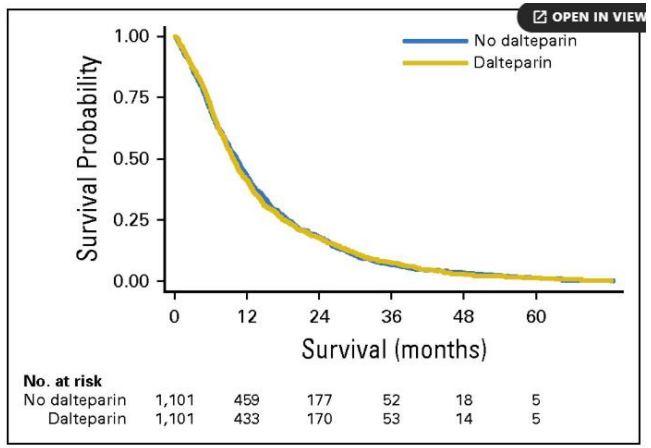

Eur Respir J 2018;52:1801220.

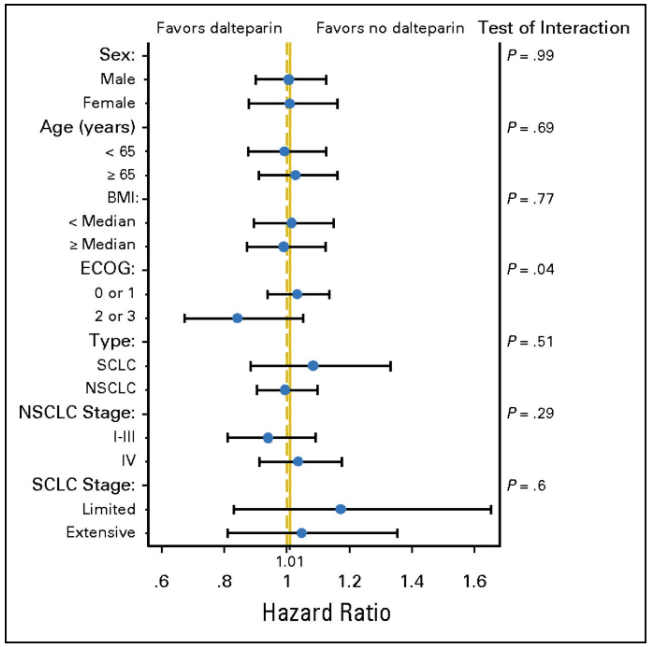
# Current guidelines for VTE treatment and prophylaxis in lung cancer

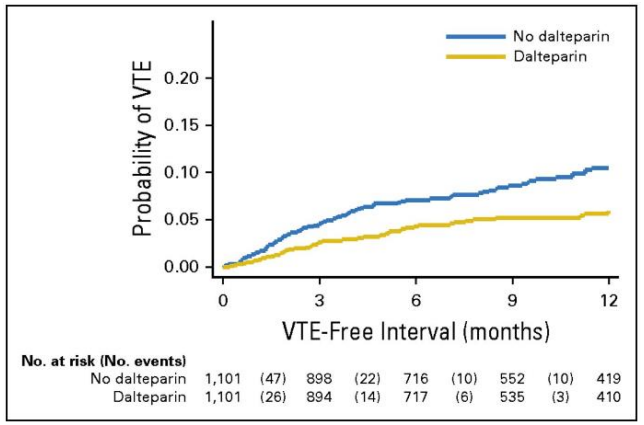
- Hospitalized patients (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH or fondaparinux is recommended during hospitalization. (ASCO, ESMO, ITAC)
  - Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion. (ASCO)

- A multicenter, open-label, randomized trial
- Newly diagnosed lung cancer of any stage and histology
- A primary prophylactic dose of LMWH for 24 weeks (n=1101) vs. placebo (n=1101)

- LMWH did not improve overall survival in the patients with lung cancer in this trial.
- A significant reduction in VTE is associated with an increase in clinically relevant nonmajor bleeding.




J Clin Oncol. 2016 Feb 10;34(5):488-94.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Hospitalized patients (prophylaxis)
  - No mention of prophylaxis specific for lung cancer
  - In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH or fondaparinux is recommended during hospitalization. (ASCO, ESMO, ITAC)
  - Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion. (ASCO)

**Table 1. VTE prophylaxis options in cancer patients**

| Options | Hospitalised patients | Surgical patients | Ambulatory patients |
|---|---|---|---|
| Heparins[a] | | | |
| UFH | 5000 IU every 8 h | 5000 IU 2-4 h preoperatively and every 8 h thereafter | — |
| Bemiparin | 3500 anti-Xa IU o.d. | 3500 anti-Xa IU starting 2 h preoperatively or 6 h post-operatively and 3500 anti-Xa IU o.d. thereafter | 3500 anti-Xa IU o.d.[b] |
| Dalteparin | 5000 anti-Xa IU o.d. | 5000 anti-Xa IU 12 h preoperatively and 5000 anti-Xa IU o.d. thereafter | 5000 anti-Xa IU o.d.[b,c] |
| Enoxaparin | 4000 anti-Xa IU o.d. | 4000 anti-Xa IU 12 h preoperatively and 4000 anti-Xa IU o.d. thereafter | 4000 anti-Xa IU o.d.[b] |
| Nadroparin | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU/kg o.d.) | 2850 anti-Xa IU 2-4 h preoperatively and 2850 anti-Xa IU o.d. thereafter | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU o.d.)[b] |
| Tinzaparin | 4500 anti-Xa IU o.d. | 4500 anti-Xa IU o.d., beginning 12 h post-operatively | 4500 anti-Xa IU o.d.[b] |
| Selective parenteral indirect factor Xa inhibitor | | | |
| Fondaparinux | 2.5 mg o.d. | 2.5 mg o.d. beginning 6-8 h post-operatively | Not studied in the outpatient prophylaxis setting |
| DOACs | | | |
| Apixaban | Not recommended | Not recommended | 2.5 mg orally b.i.d.[b] |
| Rivaroxaban | Not recommended | Not recommended | 10 mg orally o.d.[b] |
| Mechanical prophylaxis | | | |
| IPC | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| Venous foot pump | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| GCSs | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |

Ann Oncol. 2023 May;34(5):452-467.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Initial treatment
  - LMWH, UFH, fondaparinux, apixaban or rivaroxaban are recommended treatments for the acute phase. (ESMO, ASCO, ITAC, ASH)
  - LMWH is preferred over UFH or fondaparinux.
  - UFH may be considered in patients with CAT and severe renal impairment. (defined as CrCl <30 ml/min)
  - In patients with luminal GI or GU cancer, LMWH is preferred for treating CAT.
  - For patients without GI or GU cancer, rivaroxaban or apixaban (in the first 10 days), or edoxaban (started after at least 5 days of parenteral anticoagulation) can also be used. (ITAC)

- A systematic review and meta-analysis
- 15 RCTs including 1615 participants with cancer and VTE.
- LMWH vs. UFH
- Fondaparinux vs. heparin (UFH or LMWH)

- LMWH is possibly superior to UFH in the initial treatment of VTE in people with cancer.

Cochrane Database of Systematic Reviews | Review - Intervention

**Anticoagulation for the initial treatment of venous thromboembolism in people with cancer**

Maram B Hakoum, Lara A Kahale, Ibrahim G Tsolakian, Charbel F Matar, Victor ED Yosuico, Irene Terrenato, Francesca Sperati, Maddalena Barba, Holger Schünemann, ✉ Elie A Akl Authors' declarations of interest

Version published: 24 January 2018 Version history

LMWH vs. UFH

| Outcomes | No of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with UFH initial treatment | Risk difference with LMWH initial treatment |
| **Mortality** follow-up: 3 months | 418 (5 RCTs) | ⊕⊕⊕⊖ **Moderate**[1] | **RR 0.66** (0.40 to 1.10) | Study population | |
| | | | | 168 per 1000 | 57 fewer per 1000 (101 fewer to 17 more) |
| **Recurrent VTE** follow-up: 3 months | 422 (3 RCTs) | ⊕⊕⊕⊖ **Moderate**[2] | **RR 0.69** (0.27 to 1.76) | Study population | |
| | | | | 96 per 1000 | 30 fewer per 1000 (70 fewer to 73 more) |

Fondaparinux vs. heparin (UFH or LMWH)

| Outcomes | No of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with Heparin initial treatment | Risk difference with Fondaparinux initial treatment |
| Mortality follow-up: 3 months | 477 (1 RCT) | ⊕⊕⊕⊖ Moderate [1] | RR 1.25 (0.86 to 1.81) | Study population | |
| | | | | 172 per 1,000 | 43 more per 1,000 (24 fewer to 139 more) |
| Recurrent VTE follow-up: 3 months | 477 (1 RCT) | ⊕⊕⊕⊖ Moderate [2] | RR 0.93 (0.56 to 1.54) | Study population | |
| | | | | 117 per 1,000 | 8 fewer per 1,000 (52 fewer to 63 more) |

Cochrane Database Syst Rev. 2018 Jan 24;1(1):CD006649.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Initial treatment
  - LMWH, UFH, fondaparinux, apixaban or rivaroxaban are recommended treatments for the acute phase. (ESMO, ASCO, ITAC, ASH)
  - LMWH is preferred over UFH or fondaparinux.
  - UFH may be considered in patients with CAT and severe renal impairment. (defined as CrCl <30 ml/min)
  - In patients with luminal GI or GU cancer, LMWH is preferred for treating CAT.
  - For patients without GI or GU cancer, rivaroxaban or apixaban (in the first 10 days), or edoxaban (started after at least 5 days of parenteral anticoagulation) can also be used. (ITAC)

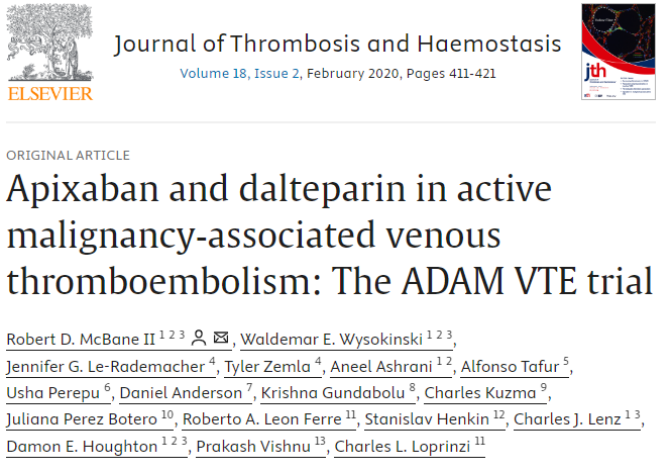
- SELECT-D
  - Dalteparin vs. rivaroxaban
  - Rivaroxaban was associated with relatively low VTE recurrence but higher nonmajor bleeding.
- ADAM-VTE
  - Dalteparin vs. apixaban
  - Oral apixaban was associated with low major bleeding and VTE recurrence rates.
- Caravaggio trial
  - Dalteparin vs. apixaban
  - Lung cancer (17.3%, n=200)
  - Oral apixaban was noninferior to subcutaneous dalteparin without an increased risk of major bleeding.


Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

FREE ACCESS | RAPID COMMUNICATION | May 10, 2018

**Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)**

Authors: Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, ... SHOW ALL ..., and Mark Levine | AUTHORS INFO & AFFILIATIONS


Journal of Thrombosis and Haemostasis
Volume 18, Issue 2, February 2020, Pages 411-421

ORIGINAL ARTICLE

**Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial**

Robert D. McBane II [1 2 3], Waldemar E. Wysokinski [1 2 3], Jennifer G. Le-Rademacher [4], Tyler Zemla [4], Aneel Ashrani [1 2], Alfonso Tafur [5], Usha Perepu [6], Daniel Anderson [7], Krishna Gundabolu [8], Charles Kuzma [9], Juliana Perez Botero [10], Roberto A. Leon Ferre [11], Stanislav Henkin [12], Charles J. Lenz [1 3], Damon E. Houghton [1 2 3], Prakash Vishnu [13], Charles L. Loprinzi [11]


The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES | TOPICS | MULTIMEDIA | CURRENT ISSUE | LEARNING/CME | AUTHOR CENTER | PUBLICATIONS

ORIGINAL ARTICLE

**Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer**

Authors: Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., +10, for the Caravaggio Investigators* Author Info & Affiliations

J Clin Oncol, 36 (20) (2018), pp. 2017-2023
J Thromb Haemost, 18 (2) (2020), pp. 411-421
N Engl J Med, 382 (17) (2020), pp. 1599-1607

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Long-term and extended phase (treatment)
  - Long-term anticoagulation for at least 6 months includes LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs. (ASCO, ESMO, ITAC, ASH)
  - After 6 months, continuation of anticoagulation should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity. (ITAC, ASH)

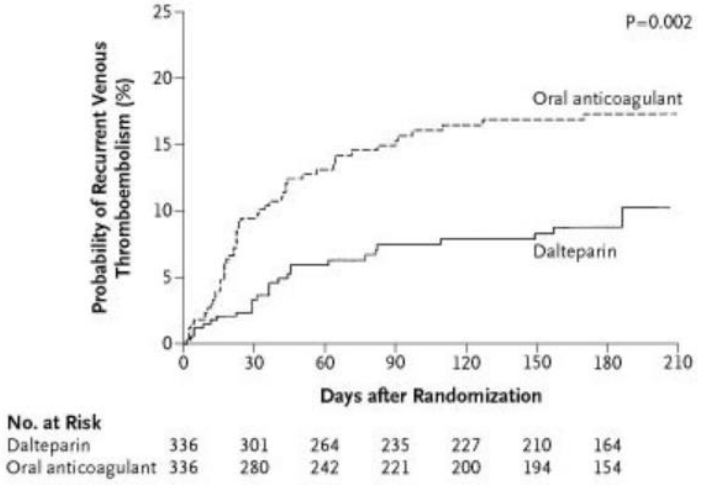
- A multicenter, randomized, open-label clinical trial
- Patients with cancer who had acute VTE
- LMWH (dalteparin) vs. VKA (coumarin)

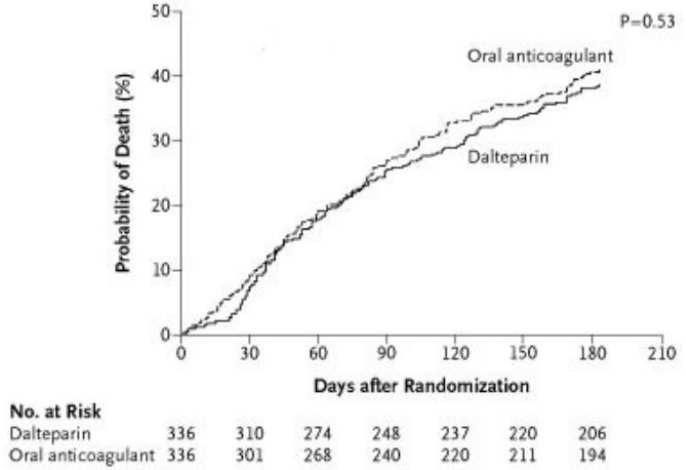
ORIGINAL ARTICLE

## Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

**Authors**: Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc., for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators* Author Info & Affiliations

- Dalteparin was more effective in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.




N Engl J Med, 349 (2) (2003), pp. 146-153

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Long-term and extended phase (treatment)
  - Long-term anticoagulation for at least 6 months includes LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs. (ASCO, ESMO, ITAC, ASH)
  - After 6 months, continuation of anticoagulation should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity. (ITAC, ASH)

- Hokusai VTE
  - LMWH (at least 5 days) followed by edoxaban 60 mg qd for 6-12 months, vs. LMWH
  - Lung cancer (14.5%, n=152)
- SELECT-D
  - Rivaroxaban 15mg bid 3 weeks, then 20 mg qd 6 months, vs. LMWH
  - Lung cancer (11.6%, n=47)
- ADAM-VTE and Caravaggio
  - apixaban 10 mg bid 7 days, followed by 5 mg bid 6 months, vs. LMWH

**Table 2. Treatment options for VTE in cancer patients**

| Drug | Initial treatment of established VTE (5-10 days) | Long-term phase (first 3-6 months) and extended phase (beyond 6 months) |
|---|---|---|
| Heparins (LMWH) | | |
| Dalteparin | 100 anti-Xa IU/kg every 12 h, or 200 anti-Xa IU/kg o.d. for the first 30 days | 150 anti-Xa IU/kg o.d. after day 30 |
| Enoxaparin | 100 anti-Xa IU/kg every 12 h, or 150 anti-Xa IU/kg o.d. | 100 anti-Xa IU/kg every 12 h, or 150 anti-Xa IU/kg o.d. |
| Tinzaparin | 175 anti-Xa IU/kg o.d. | 175 anti-Xa IU/kg o.d. |
| Nadroparin | 86 anti-Xa IU/kg every 12 h, or 171 anti-Xa IU/kg o.d. | 86 anti-Xa IU/kg every 12 h, or 171 anti-Xa IU/kg o.d. |
| Bemiparin | 115 anti-Xa IU/kg o.d. | 115 anti-Xa IU/kg o.d. |
| Heparins (UFH) | | |
| UFH | 80 IU/kg i.v. bolus, then 18 IU/kg/h i.v.; adjust dose based on aPTT | — |
| DOACs | | |
| Edoxaban | — | 60 mg, o.d.<br>30 mg, o.d. if: (i) CrCl <50 ml/min, (ii) ≤60 kg or (iii) patients receiving P-glycoprotein inhibitors |
| Rivaroxaban | 15 mg every 12 h for 3 weeks | 20 mg o.d. |
| Apixaban | 10 mg every 12 h for 7 days | 5 mg every 12 h |
| Vitamin K antagonists | | |
| Acenocoumarol | — | Adjust dose to maintain INR 2-3 |
| Phenprocoumon | — | Adjust dose to maintain INR 2-3 |
| Warfarin | — | Adjust dose to maintain INR 2-3 |

Xa, activated coagulation factor X; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; INR, international normalised ratio; i.v., intravenous; LMWH, low-molecular-weight heparin; o.d., once daily; UFH, unfractionated heparin; VTE, venous thromboembolism.

N Engl J Med, 378 (7) (2018), pp. 615-624
J Clin Oncol, 36 (20) (2018), pp. 2017-2023
J Thromb Haemost, 18 (2) (2020), pp. 411-421
N Engl J Med, 382 (17) (2020), pp. 1599-1607

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Long-term and extended phase (treatment)
  - Long-term anticoagulation for at least 6 months includes LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs. (ASCO, ESMO, ITAC, ASH)
  - After 6 months, continuation of anticoagulation should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity. (ITAC, ASH)

- A single-center retrospective study
- 204 patients with primary lung cancer
- rivaroxaban (n = 131) vs. dalteparin (n = 73) for VTE

- There was no difference in the safety and efficacy profile of rivaroxaban compared with dalteparin.

RESEARCH ARTICLES | MAY 16 2019

**A Retrospective Study on Efficacy and Safety of Rivaroxaban and Dalteparin for Long-Term Treatment of Venous Thromboembolism in Patients with Lung Cancer**

Subject Area: Pharmacology , Pneumology

Jang Ho Lee; Dong-gon Hyun; Chang Min Choi; Jae Cheol Lee; Woo Sung Kim; Yeon-Mok Oh; Sang-Do Lee; Jae Seung Lee

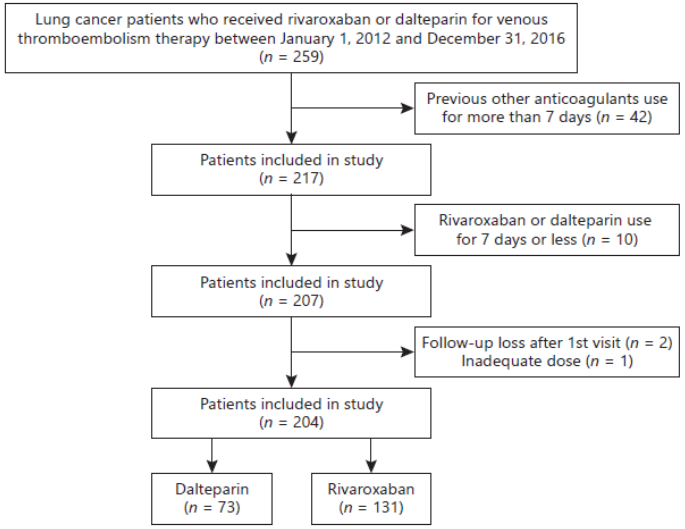



**Table 2.** Primary and secondary endpoints in both groups

| | Dalteparin ($n$ = 73), $n$ (%) | Rivaroxaban ($n$ = 131), $n$ (%) | $p$ value |
|---|---|---|---|
| Composite event | 12 (16.4) | 38 (29.0) | 0.045 |
| Recurrence* | 2 (2.7) | 7 (5.3) | 0.495 |
| Symptomatic recurrence* | 2 (2.7) | 4 (3.1) | >0.999 |
| Bleeding | 10 (13.7) | 31 (23.7) | 0.089 |
| Major bleeding* | 2 (2.7) | 8 (6.1) | 0.500 |
| CRNM bleeding | 8 (11.0) | 23 (17.6) | 0.208 |
| All-cause mortality | 64 (87.7) | 106 (80.9) | 0.215 |
| PE-related mortality* | 2 (2.7) | 3 (2.3) | >0.999 |
| Bleeding-related mortality* | 0 (0.0) | 3 (2.3) | 0.554 |

* Variables analyzed by Fisher's exact test.
Difference between both groups was analyzed by the chi-square test or Fisher's exact test.
CRNM, clinically relevant nonmajor; PE, pulmonary embolism.

Respiration (2019) 98 (3): 203–211.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Incidental and subsegmental VTE (treatment)
  - For incidentally detected VTE, the same treatment as for symptomatic VTE is recommended. (ESMO, ASCO, ASH)
  - Anticoagulant therapy is suggested for most of the patients with subsegmental PE. (ESMO, ASCO)

- A pooled analysis of 926 patients
- Cancer patients with incidental PE
- Weighted pooled 6-month risks of recurrent VTE

- Recurrence risk is comparable after subsegmental and more proximally localized IPE.

ORIGINAL ARTICLE

**Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients**

| Thrombus location | Pooled 6-month risk of recurrent VTE % (95%CI) |
|---|---|
| Central | 5.6 (3.1-8.7) |
| Peripheral | 6.6 (3.5-11) |

| Thrombus location | Pooled 6-month risk of recurrent VTE % (95%CI) |
|---|---|
| Subsegmental | 7.8 (2.8-14.9) |
| More centrally located | 5.5 (2.9-8.8) |

**HR of 1.3 (95% CI 0.57–3.0) adjusted for age, sex, type of cancer, cancer stage, and management.**

J Thromb Haemost. 2016 Jan;14(1):105-13.

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- Catheter-related VTE (treatment and prophylaxis)
  - Routine pharmacological prophylaxis of CRT is NOT recommended. (ESMO, ASH)
  - For the treatment, anticoagulation (LMWH) is recommended for a minimum of 3 months (ESMO)
  - Extended anticoagulation (>3 mo) until catheter removal is suggested, if bleeding risk is low (ESMO)
  - It is recommended to remove the catheter if it is not needed or is infected, anticoagulant treatment is contraindicated or there is clinical deterioration due to thrombus extension despite treatment. (ESMO, ITAC, ASH)

Cochrane Database of Systematic Reviews | Review - Intervention

## Anticoagulation for people with cancer and central venous catheters

Lara A Kahale, Ibrahim G Tsolakian, Maram B Hakoum, Charbel F Matar, Maddalena Barba, Victor ED Yosuico, Irene Terrenato, Francesca Sperati, Holger Schünemann, Elie A Akl Authors' declarations of interest

Version published: 01 June 2018 Version history

| Outcomes (follow-up) | Nº of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no LMWH | Risk difference with LMWH |
| **All-cause mortality** (up to 3 months) | 1236 (5 RCTs) | ⨁⨁◯◯ **Low**[a,b] | **RR 0.82** (0.53 to 1.26) | Study population | |
| | | | | 77 per 1000 | 14 fewer per 1000 (36 fewer to 20 more) |
| **Major bleeding** (up to 3 months) | 1018 (4 RCTs) | ⨁◯◯◯ **Very low**[g,h] | **RR 1.49** (0.06 to 36.28) | Study population | |
| | | | | 0 per 1000 | 0 fewer per 1000 (0 fewer to 0 fewer) |
| | | | | Low | |
| | | | | 1 per 1000 | 0 fewer per 1000 (1 fewer to 35 more) |

Full Length Article

## Systematic review of anticoagulant treatment of catheter-related thrombosis

Lisa Baumann Kreuziger [a,b,*,1], Oluwatoyosi Onwuemene [c,1], Emma Kolesar [d], Mark Crowther [e], Wendy Lim [e]

[a] Blood Center of Wisconsin, 8733 Watertown Plank Road, Milwaukee, WI 53226, United States
[b] Medical College of Wisconsin, Department of Medicine, Division of Hematology, 8701 W Watertown Plank Rd, Milwaukee, WI 53226, United States
[c] Duke University Medical Center, Department of Medicine, Division of Hematology, 40 Duke Medicine Circle, DUHS Box 3422, Durham, NC 27710, United States
[d] McMaster University Hamilton, Ontario, Canada
[e] McMaster University, Department of Medicine, Division of Hematology and Thromboembolism, 50 Charlton Ave, E, Hamilton, Ontario L8N 4A6, Canada

**Table 3**
Clinical outcomes of studies using anticoagulation to treat catheter-related thrombosis.

| Author | AC regimen (n) | AC duration (n) | Thrombus resolution | PTS | DVT recurrence | PE | Major hemorrhage | Mortality |
|---|---|---|---|---|---|---|---|---|
| CRT specific outcomes | | | | | | | | |
| Delluc [21] | LMWH (94)<br>VKA (4)<br>Rivaroxaban (11) | Range 1–62 mo<br>Median 124 d | | | 4/99[c] | 3/99 | 2/99 | |
| Frizzelli [22] | UFH → VKA (83) | 3 mo | | | | 0/83 | | |
| Kovacs [16] | LMWH → VKA (74) | 3 mo | | | 0/74 | 0/74 | 3/74 | 9% 2 mo |
| Monreal [4] | UFH → VKA (86) | At least 8 d | | | 0/86 | 2/86 | | 2% at 8 d |
| Pucheu [17] | LMWH (25)[b] | 21 d | 1/25 | | | | | 0% 21 d |
| Combined CRT and UE thrombosis outcomes | | | | | | | | |
| Aburahma [28] | UFH → VKA (45) | ≥3 mo | 4/14 | 33/45 | | | | |
| Farge [26] | LMWH (409) | Average 5 mo | | | 7/409 | 6/409 | 23/409 | 35% at 6 mo |
| Flinterman [13] | VKA (224) | <6 mo (115)<br>>6 mo (78)<br>Censored (30) | | | 30/224<br>2/56 CRT | | | 11% 1 y<br>25% 7.5 y |
| Gloviczki [29] | UFH → VKA (23) | <3 mo (4)<br>>3 mo (17) | | 6/23 | | | | 12% at 5.4 y median fu |
| Kahn [15] | UFH/LMWH → VKA (23)<br>LMWH (1) | Median 5 mo<br>(range 0–49 mo) | | 4/11 | | | | |
| Karabay [34] | LMWH → VKA (36) | Mean 4.7 mo<br>(range 3–6 mo) | 16/36<br>(>35% resolution, 10 d) | 0/36 | 0/36 at 7 d | | | 25% (12 mo mean fu) |
| Massoure [35] | VKA (15)<br>UFH/LMWH (14) | <1 mo (6)<br>1–3 mo (13)<br>3–6 mo (13)<br>>6 mo (7) | | 8/29 | 2/29 | 2/29 | 1/29 | 52% 6 mo |
| Monreal [23] | UFH/LMWH → VKA (23)<br>LMWH (75) | At least 3 mo | | | 4/104[a] | 4/104 | 4/104 | 16% 3 mo |
| Savage [25] | LMWH → VKA (40)<br>LMWH (16) | At least 12 wk | | | 1/46 | 0/46 | 1/46 | 15% 3 mo |
| Vu [27] | LMWH (80) | <1 mo (58)<br>>6 mo (20) | | | 22/139 | 5/139 | | 74% at 14 mo median fu |

AC = anticoagulation; n = number of patients included in the analysis. PTS = post-thrombotic syndrome; h = hours, d = days, wk = weeks, mo = months, y = year; fu = follow-up; NR = not reported. UFH = unfractionated heparin, LMWH = low molecular weight heparin; VKA = vitamin K antagonist; PR = partial response; UE = Upper extremity; TLC = triple lumen catheter; DL = double lumen; F = French; PICC = peripherally inserted central venous catheter.
[a] Includes DVT from stents and pacemakers.
[b] Treated with warfarin for undefined duration and [illegible]
[c] 2 events during anticoagulation.

Cochrane Database Syst Rev, 6 (6) (2018), p. CD006468
Thromb. Res., 136 (6) (2015), pp. 1103-1109

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- IVC filter
  - The insertion of IVC filters is suggested in patients with acute and life-threatening VTEs who have absolute contraindications to anticoagulant therapy or as an adjunct to anticoagulation in patients with recurrent VTE or extension of thrombosis despite optimal anticoagulant therapy. (ESMO, ASCO, ITAC)

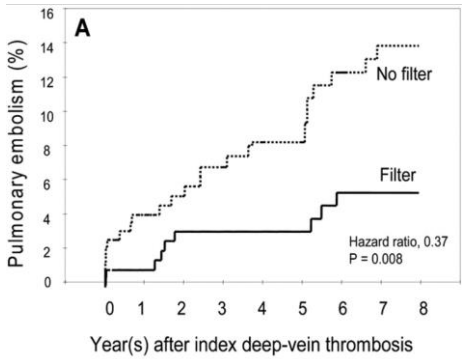
- A randomized trial
- 400 patients with proximal DVT ± PE
- Cancer (14%)
- Permanent IVC filter vs. no filter

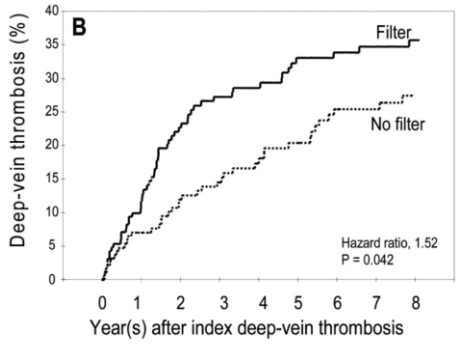
PREVENTIVE CARDIOLOGY

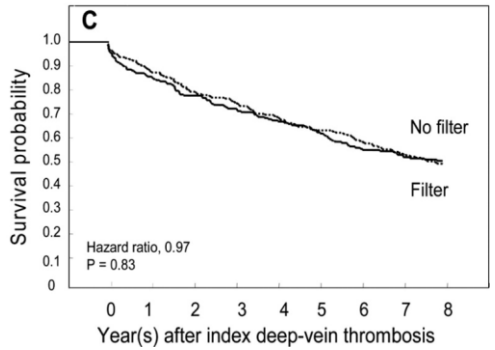
## Eight-Year Follow-Up of Patients With Permanent Vena Cava Filters in the Prevention of Pulmonary Embolism

**The PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) Randomized Study**

- IVC filters reduced PE but increased DVT and had no effect on survival.
- Systematic use in the general population with VTE is not recommended.




Circulation, 112 (3) (2005), pp. 416-422

# Current guidelines for VTE treatment and prophylaxis in lung cancer

- VTE recurrence (ITAC, ASH)
  - For LMWH, increase LMWH by 20–25% or switch to direct oral anticoagulants.
  - For DOAC, switch to LMWH.
  - For VKA, switch to LMWH or DOAC.

- Systematic studies on the management of patients with recurrent cancer associated VTE under therapeutic anticoagulation are lacking.
- Recommendations mainly are based on expert opinion and consensus.

## Recurrent Venous Thromboembolism in Patients on Anticoagulation: An Update Based on the Revised AWMF S2k Guideline

Robert Klamroth[1] Hanno Riess[2] Jan Beyer-Westendorf[3] Birgit Linnemann[4]

[1]Department of Internal Medicine and Vascular Medicine, Vivantes Hospital in Friedrichshain, Berlin, Germany
[2]Department of Haematology, Oncology and Tumour Immunology, Charité – University Medicine Berlin, Berlin, Germany
[3]Department for Hematology, Medical Faculty, University Hospital Carl Gustav – Carus, Dresden, Germany
[4]Department for Cardiology III – Angiology, University Hospital of the Johannes – Gutenberg University, Mainz, Germany

Address for correspondence Priv. Doz. Dr. med. Robert Klamroth, MD, Klinik für Innere Medizin – Angiologie und Hämostaseologie, Zentrum für Gefäßmedizin, Hämophiliezentrum/ Gerinnungssprechstunde, Vivantes Klinikum im Friedrichshain, Landsberger Allee 49, 10249 Berlin, Germany (e-mail: robert.klamroth@vivantes.de).

**Table 1** Options for patients with confirmed VTE recurrence on anticoagulation

| Pretreatment | | Therapeutic options |
|---|---|---|
| No full therapeutic anticoagulation | VKA: INR < 1.5 | VKA with target INR 2.0–3.0<br>or switch to apixaban, dabigatran, edoxaban or rivaroxaban (DOAC) |
| | Apixaban:<br>2 × 2.5 mg/d | Apixaban 2 × 10 mg/d for 7 d followed by 2 × 5 mg/d<br>or switch to an alternative DOAC |
| | Rivaroxaban:<br>1 × 10 mg/d | Rivaroxaban 2 × 15 mg/d for 21 d, followed by 1 × 20 mg/d or<br>Switch to an alternative DOAC |
| Full therapeutic anticoagulation | LMWH | LMWH: 120–125% (DOAC) |
| | VKA: INR 2.0–3.0 | LMWH: 120–125%, DOAC (VKA with higher target INR: 2.5–3.5 or 3.0–4.0) |
| | DOAC | LMWH: 120–125%<br>Switch to an alternative DOAC<br>(VKA with target INR: 2.0–3.0 or higher)<br>(DOAC in higher doses, e.g., apixaban: 2 × 10 mg/d, rivaroxaban: 2 × 15 mg/d) |
| Antiphospholipid syndrome | DOAC | VKA with target INR: 2.0–3.0 or 2.5–3.5 |
| | VKA: INR 2.0–3.0 | VKA with higher target INR (2.5–3.5 or 3.0–4.0)<br>(if necessary, addition of ASA) |
| Cancer | VKA: INR 2.0–3.0 | LMWH or apixaban, edoxaban, rivaroxaban (DXI) |
| | LMWH | LWWH: 120–125% or DXI |
| | DOAC | LMWH: 120–125% (DXI at higher dosage: apixaban: 2 × 10 mg/d, rivaroxaban: 2 × 15 mg/d) |

Abbreviations: ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; DXI, direct anti-Xa inhibitor; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism; VKA, vitamin K antagonist.
Source: Modified from Linnemann et al.[1]

Hamostaseologie. 2024 Apr;44(2):150-154.

# Summary

- Prevalence of VTE in patients with lung cancer
  - 7-8%
- Mechanism of VTE in lung cancer
  - Lung cancer cells -> tissue factor/microparticles, procoagulant, inflammatory factors, cytokines, etc.
- Risk factors
  - Patient-related
  - Cancer-related
  - Therapy-related

- Current guidelines for VTE treatment and prophylaxis in lung cancer
  - No specific guidelines for lung cancer
  - The decision could follow the general VTE treatment and prophylaxis principles of patients with all cancer types in authoritative guidelines.
  - However, VTE in lung cancer has some specific details compared to other cancer types.

# Summary (guidelines)

## Prophylaxis

### Perioperative setting

- Pharmacological VTE prophylaxis with **LMWH** (preferred) or UFH is recommended in patients undergoing **major cancer surgery** 2-12 h preoperatively and at least 10 days post-operatively. (ASCO, ESMO, ITAC, ASH)

### Chemotherapy

- In **ambulatory** cancer patients starting systemic anticancer treatment who have a **high thrombosis risk**, **apixaban, rivaroxaban or LMWH** may be considered for primary thromboprophylaxis for a maximum of 6 months. (ESMO, ASCO)

- Primary pharmacological prophylaxis of VTE with LMWH is **NOT recommended** for patients treated with systemic chemotherapy. (ITAC)

### Hospitalized patients

- In hospitalized cancer patients confined to bed with **an acute medical complication**, prophylaxis with **LMWH, UFH or fondaparinux** is recommended during hospitalization. (ASCO, ESMO, ITAC)

- Routine pharmacologic thromboprophylaxis **should NOT be offered** to patients admitted for the sole purpose of minor procedures or chemotherapy infusion. (ASCO)

## Treatment

### Initial treatment

- **LMWH, UFH, fondaparinux, apixaban or rivaroxaban** are recommended treatments for the acute phase. (ESMO, ASCO, ITAC, ASH)
- LMWH is preferred over UFH or fondaparinux.
- UFH may be considered in patients with CAT and severe renal impairment. (defined as CrCl <30 ml/min)
- In patients with luminal GI or GU cancer, LMWH is preferred for treating CAT.
- For patients **without GI or GU cancer, rivaroxaban or apixaban** (in the first 10 days), **or edoxaban** (started after at least 5 days of parenteral anticoagulation) can also be used. (ITAC)

### Long-term and extended phase

- Long-term anticoagulation for **at least 6 months** includes **LMWH, apixaban, edoxaban or rivaroxaban** which are preferred over VKAs. (ASCO, ESMO, ITAC, ASH)
- After 6 months, continuation of anticoagulation should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity. (ITAC, ASH)

### Incidental and subsegmental VTE

- For incidental VTE, the same treatment as for symptomatic VTE is recommended. (ESMO, ASCO, ASH)
- Anticoagulant therapy is suggested for most of the patients with subsegmental PE. (ESMO, ASCO)

### Catheter-related VTE (treatment and prophylaxis)

- Routine pharmacological prophylaxis of CRT is **NOT recommended**. (ESMO, ASH)
- For the treatment, anticoagulation (**LMWH**) is recommended for a minimum of **3 months** (ESMO)
- Extended anticoagulation (>3 mo) **until catheter removal** is suggested, if bleeding risk is low (ESMO)
- It is recommended to remove the catheter if it is not needed or is infected, anticoagulant treatment is contraindicated or there is clinical deterioration due to thrombus extension despite treatment. (ESMO, ITAC, ASH)

### IVC filter

- The insertion of IVC filters is suggested in patients with acute and life-threatening VTEs who have absolute contraindications to anticoagulant therapy or as an adjunct to anticoagulation in patients with recurrent VTE or extension of thrombosis despite optimal anticoagulant therapy. (ESMO, ASCO, ITAC)

### VTE recurrence (ITAC, ASH)

- For LMWH, increase LMWH by 20–25% or switch to direct oral anticoagulants.
- For DOAC, switch to LMWH.
- For VKA, switch to LMWH or DOAC.