Diagnosi, profilassi e terapia del tromboembolismo venoso (TEV) in oncologia

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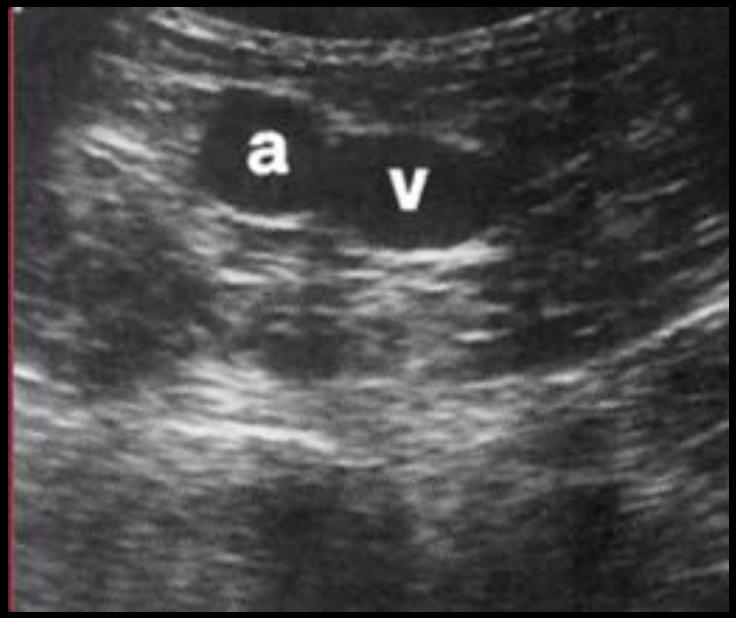
Diagnosis

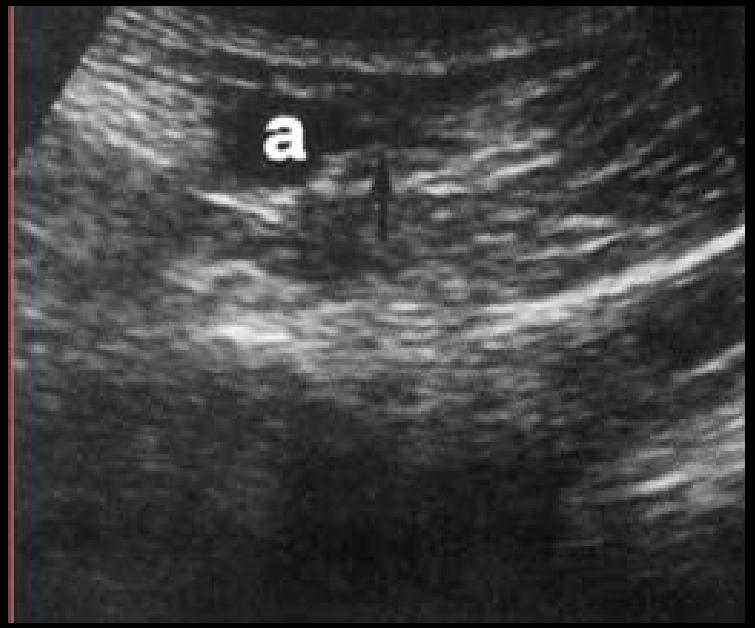
Need for diagnosis of VTE

- Treatment is with anticoagulants
- Adverse effect – bleeding complications

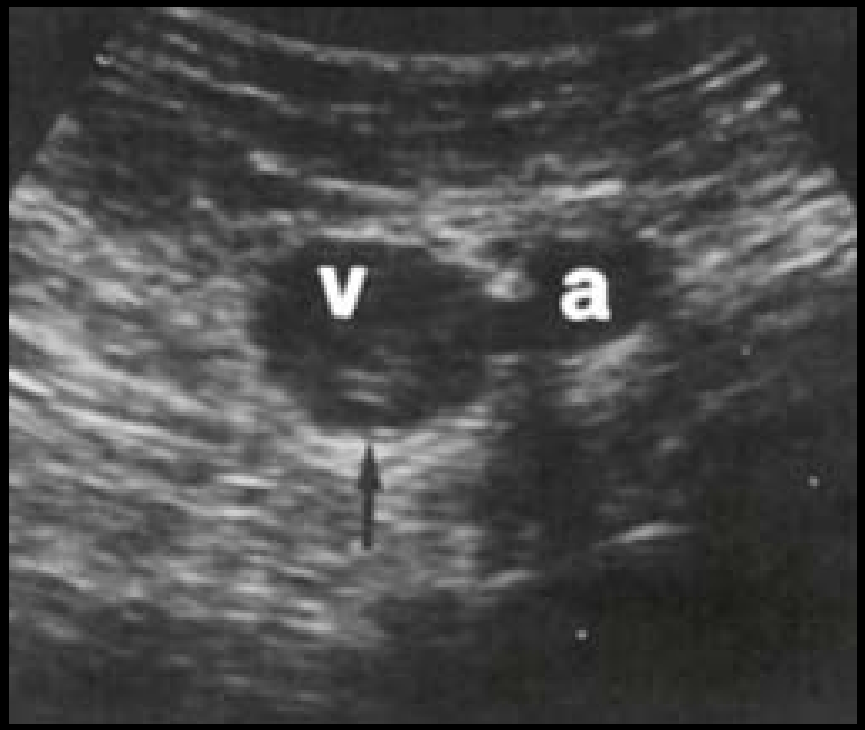
- Clinical picture is non-specific
- Incorrect treatment is to be avoided
- Thus correct diagnosis / refuting of VTE is necessary

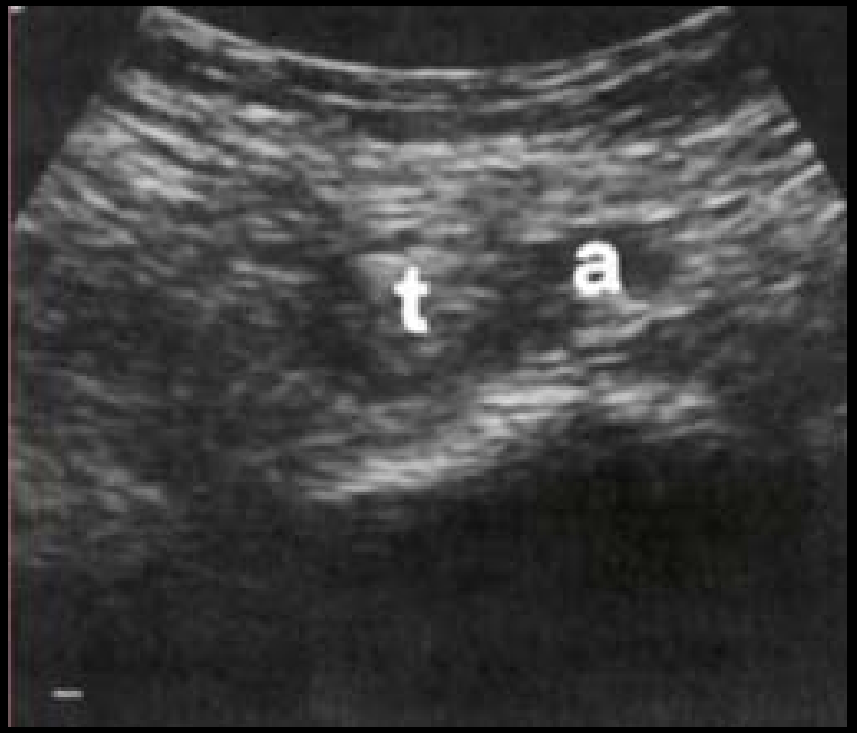
Compression ultrasound (normal)





Compression ultrasound (not compressible)





Suspicion of Pulmonary Embolism

- Wide clinical spectrum
  - Most symptoms shared with other diseases
  - No single ‘pathognonomic’ symptom
  - Also ‘first line tests’
    - Oxygenation of blood
    - ECG-Right Ventricular strain
    - Chest X-ray

      are not ‘sensitive’ or specific’

Signs and symptoms of PE

- Thoracic pain associated with breathing
- Shortness of breath (on exertion)
- Coughing
- Speckles of blood in sputum
- (Sub-) febrile temperature

A Practical Approach to PE

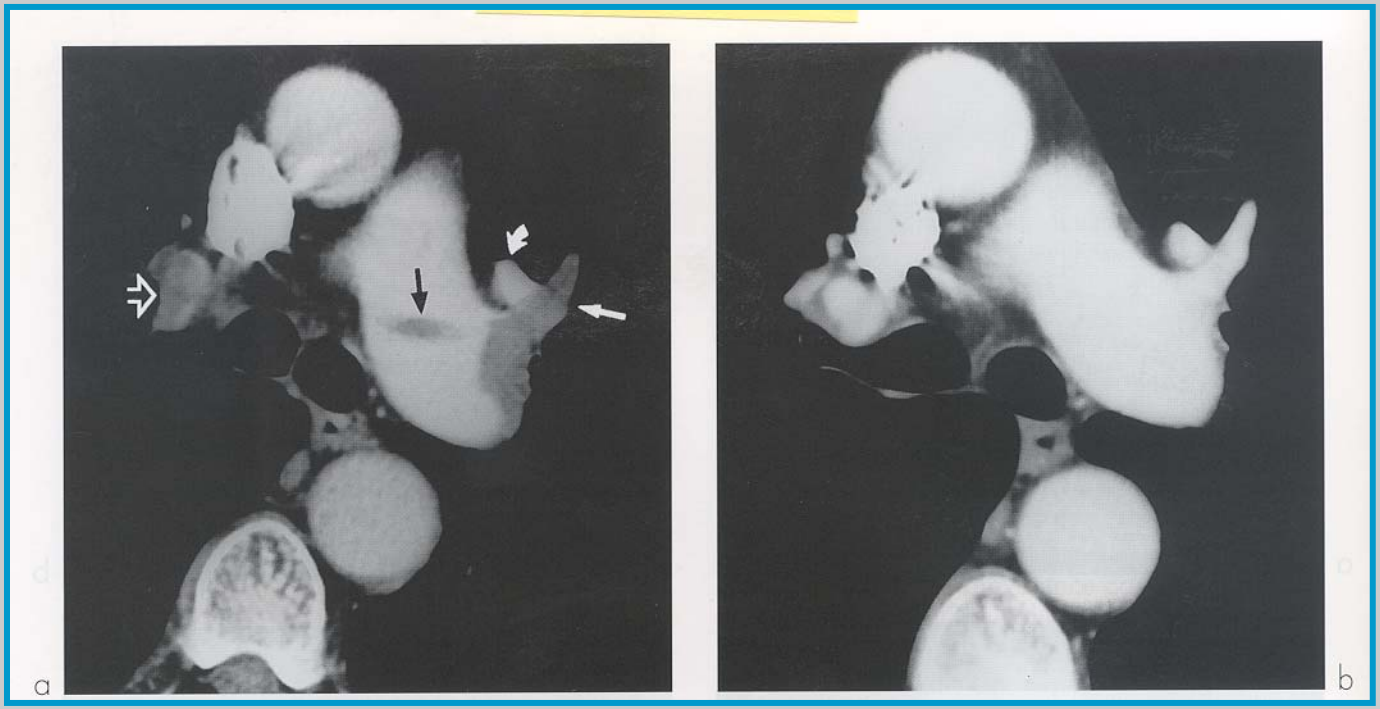
- Always consider the diagnosis, especially:
  - Discrepancy Chest X-ray – clinical presentation
  - Chest X-ray – ECG provide no alternative diagnosis
  - Presence of known risk-factors

  And finally:
  - Treated for other diagnosis, but no improvement

Spiral C(omputed) T(omography)

How to be performed?

- injection of contrast medium
- 30 sec breathhold
- 5 (or 3) mm slices caudocranial
- contrast timing



Six view V/Q lung scan

How to be performed?

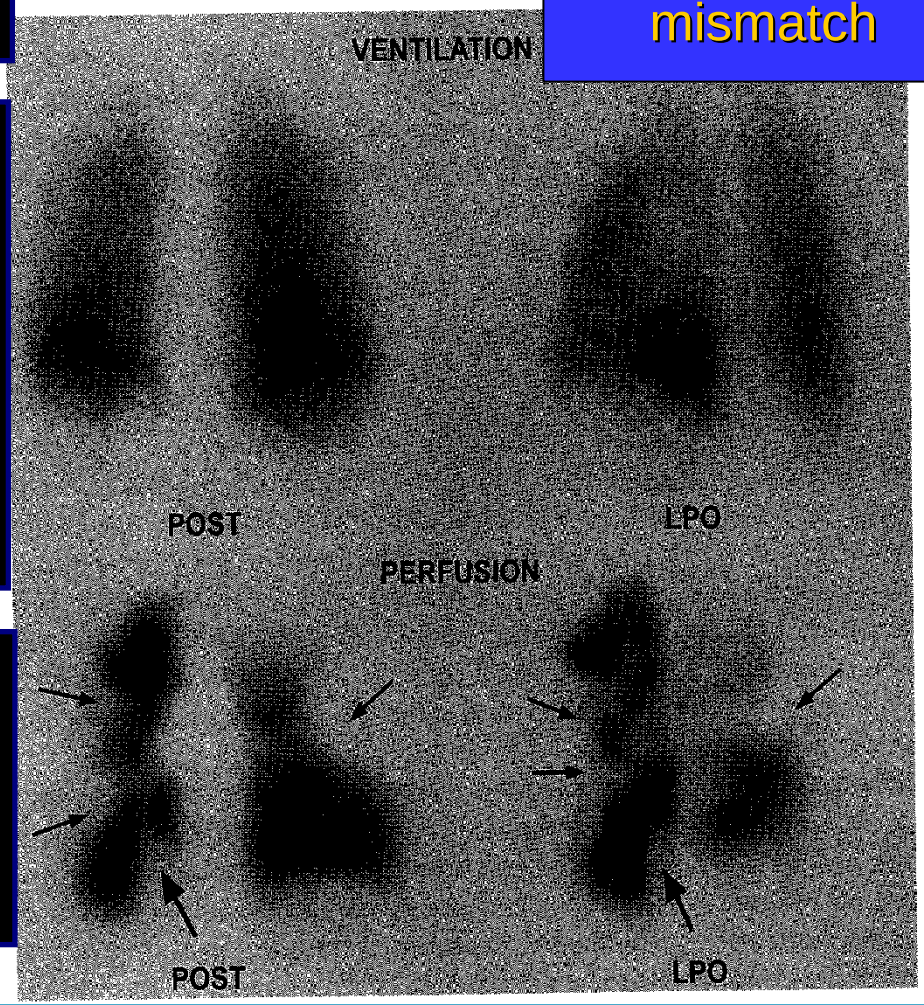
Inhalation of xenon, krypton or radio-labeled aerosol formulations

Mixing of radio-labeled material with alveolar gas

Wash-in, equilibrium, wash-out phase
Serial images in time

Injection of radio-labeled albumin particles

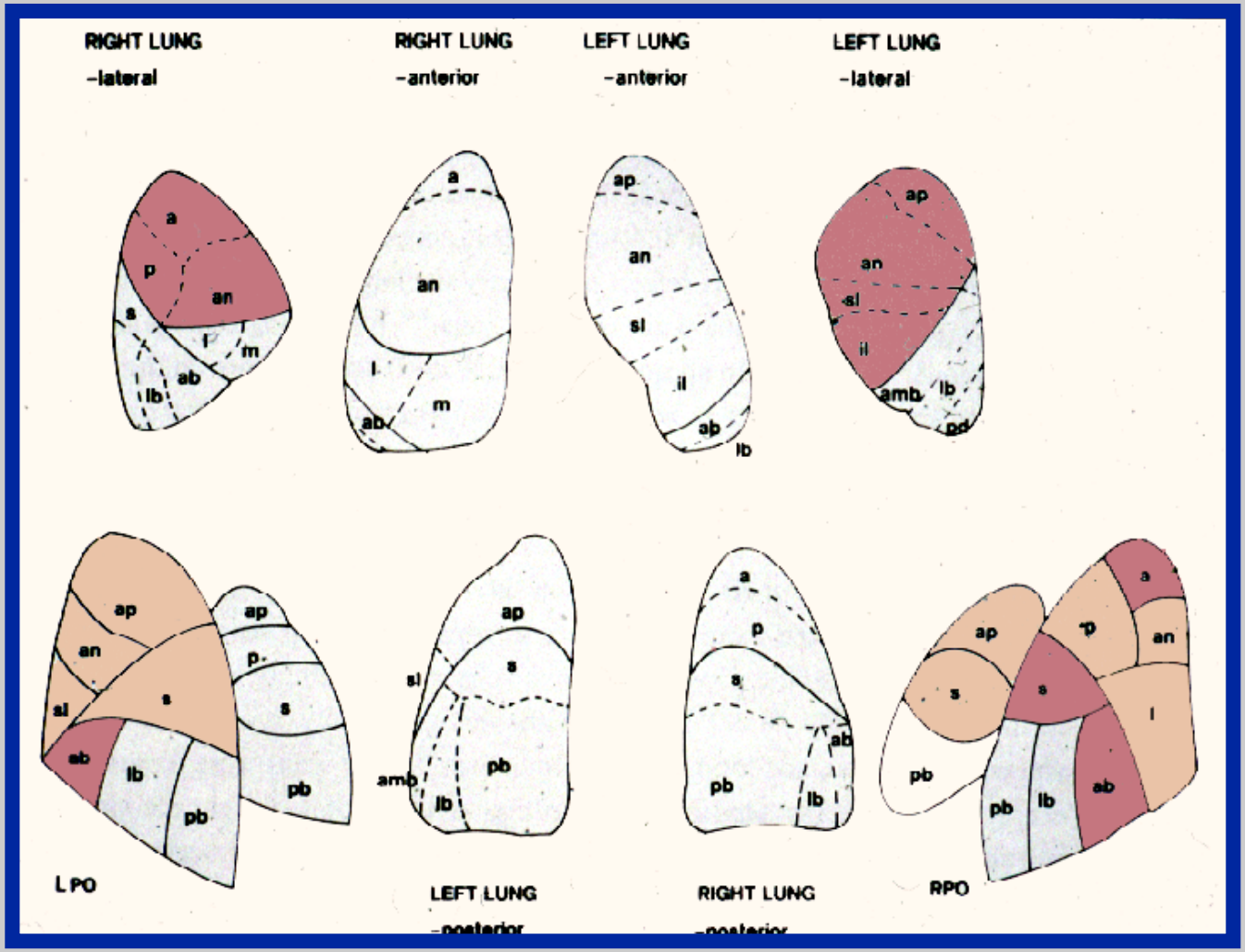
Particles entrapped in pulmonary circulation



V/Q scan

6 view scans:

anterior
posterior
right/left oblique
right/left lateral



Take Home Messages

- Pulmonary Embolism should always be on the shortlist, when seeing a patient with pulmonary symptoms
- Multiple diagnostic strategies can be used depending on local expertise/availability
- D-dimer can be useful (to rule out VTE) in case of low clinical probability

Prophylaxis

Prophylaxis of VTE in patients with cancer: surgery

ACCP Guidelines, Chest 2008; 133

- We recommend prophylaxis appropriate for the type of surgery **Grade 1A**
- For selected high-risk surgery patients, including some of those who have undergone major cancer surgery, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered **Grade 2A**

A Clinical Outcome-Based Prospective Study on Venous Thromboembolism After Cancer Surgery

The @RISTOS Project

Giancarlo Agnelli, MD, Giorgio Bolis, MD,† Lorenzo Capussotti, MD,‡*
Roberto Mario Scarpa, MD,§ Francesco Tonelli, MD,|| Erminio Bonizzoni, PhD,¶ Marco Moia, MD,‡‡
Fabio Parazzini, MD,† Romina Rossi, MD, Francesco Sonaglia, MD,* Bettina Valarani, PhD,***
Carlo Bianchini, MD,†† and Gualberto Gussoni, MD, PhD††

Ann Surg 2006;243: 89–95

Prophylaxis regimens

In-hospital prophylaxis	**81.7%**
LMWH	60.7%
UFH	15.3%
Physical methods	8.5%
Post-discharge prophylaxis	**30.7%**
LMWH	23.7%
UFH	1.2%
Physical methods	1.7%
ASA	3.3%
Oral anticoagulants	1.2%

30-day / in-hospital mortality

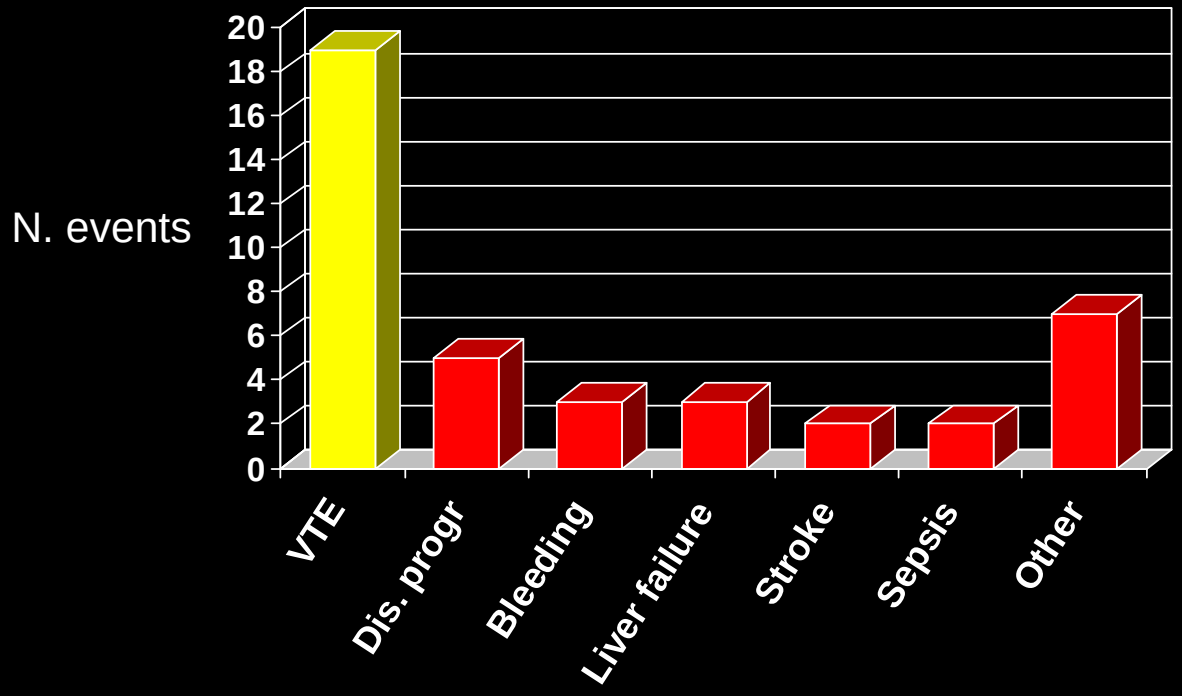
Overall mortality: 1.72

VTE-related: 46.3%

General surgery: 2.91%

Urology: 0.58%

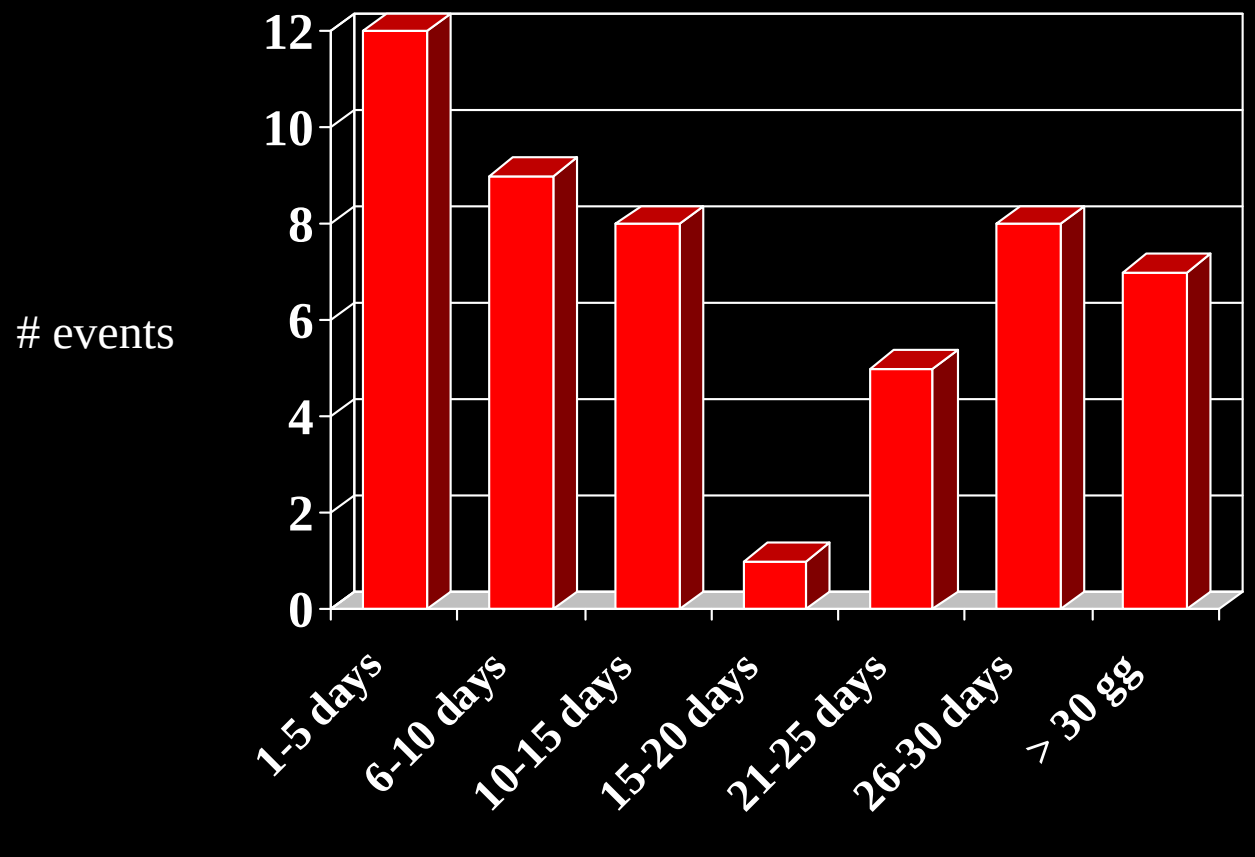
Gynecology: 0.22%



@ristos

VTE timing

Event timing: 40% > 21 days after surgery



@ristos

VTE and risk factors

Multivariate logistic regression analysis

Variable	Effect	OR	95%CI
Age	≥ 60 vs < 60 years	2.6	1.2 - 5.7
Previous VTE	Yes vs No	6.0	2.1 - 16.8
Anesthesia	≥ 2 vs < 2 hours	4.5	1.1 - 19.1
Staging	Adv. vs non-advanced	2.7	1.4 - 5.2
Bed resting	≥ 4 vs < 4 days	4.4	2.4 - 7.8

Thromboprophylaxis in major abdominal surgery for cancer

Negus JJ et al, Eur J Surg Oncol, 2006

- Systematic review of the literature
- Patients with cancer are at substantially higher risk for VTE than patients without cancer
- Prolonged thromboprophylaxis (up to 4 weeks) is more effective than short-term
- Graduated compression stockings have a synergistic effect on the reduction in VTE risk

Prophylaxis of VTE in cancer patients

ACCP Guidelines, Chest 2008; 133

- Cancer patients who are bedridden with an acute medical illness: we recommend routine thromboprophylaxis with LMWH, LDUH, or fondaparinux **Grade 1A**
- If there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with GCS or IPC **Grade 1A**

Study design

Randomization (1 : 2)

Double-blind

Placebo

Nadroparin 3800 IU

up to 4 months

4-month primary efficacy analysis

1-year clinical follow-up

PROTECHT

Prophylaxis of VTE in cancer patients with CVC

ACCP Guidelines, Chest 2008; 133

- We recommend that clinicians not use either prophylactic doses of LMWH, or minidose warfarin **Grade 1B**

Treatment

Tretament of VTE
Common goals for DVT and PE

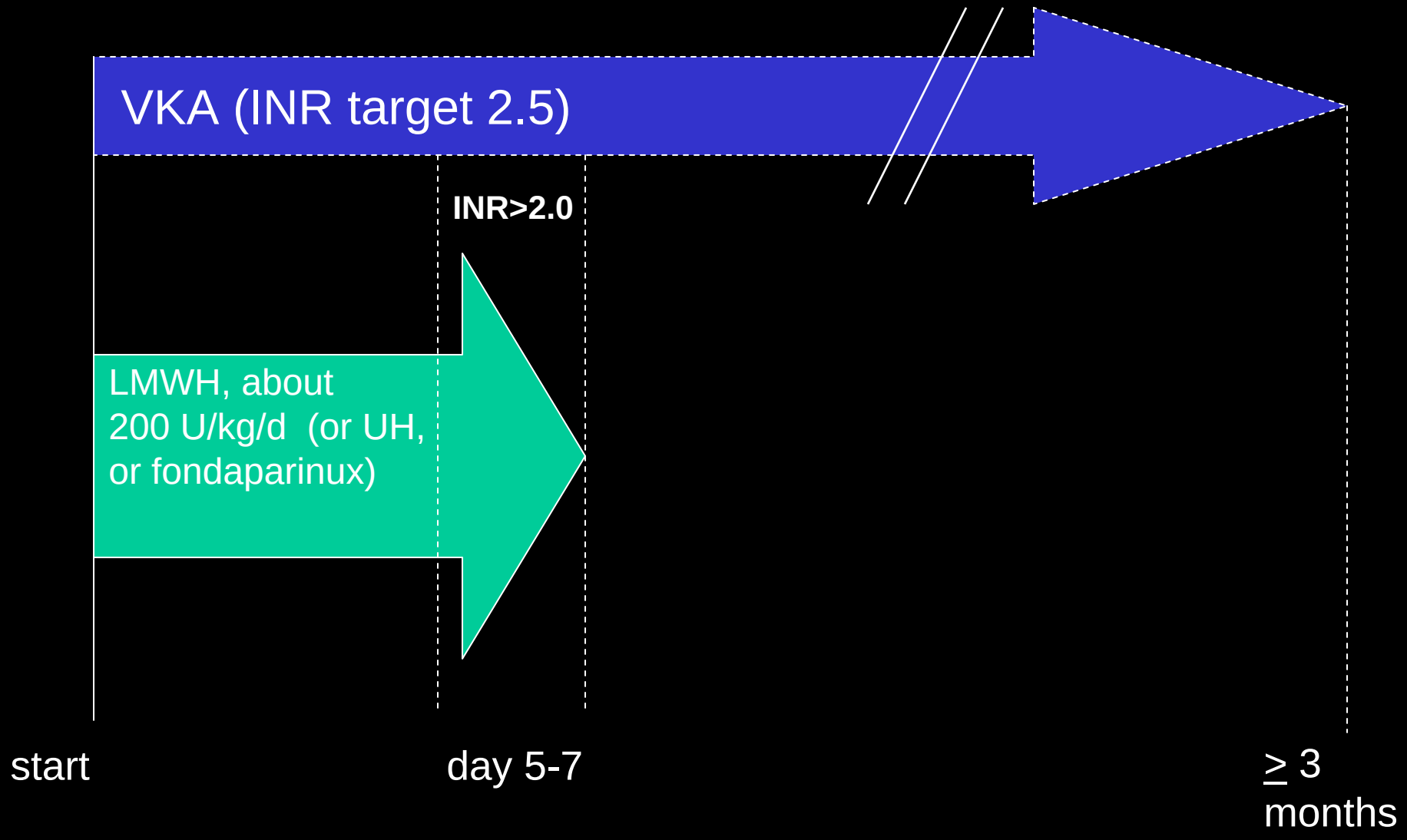
- To reduce thrombus formation and/or to favour thrombolysis
- To prevent (further) embolization
- To reduce the risk of death
  - At low risk of bleeding
  - Without admission
- To reduce the risk of recurrence

Treatment of VTE
Specific goals for DVT and PE

- DVT: to reduce the risk of the post-thrombotic syndrome (elastic stockings, exercise, …)
- PE: to reduce the risk of pulmonary hypertension (recurrence of PE)

Treatment of VTE

- LMWH (from 115 to 200 U/kg/d, depending on the molecule) for at least 5 days; alternatives are UH or fondaparinux
- VKA (warfarin or acenocoumarol) from the first day, for at least 3-6 months
- LMWH should not be stopped earlier than 48 hours from INR at target (INR 2.5, range 2.0-3.0)


VKA (INR target 2.5)
INR>2.0
LMWH, about
200 U/kg/d (or UH,
or fondaparinux)
start
day 5-7
≥ 3
months

When VKA should be delayed or avoided

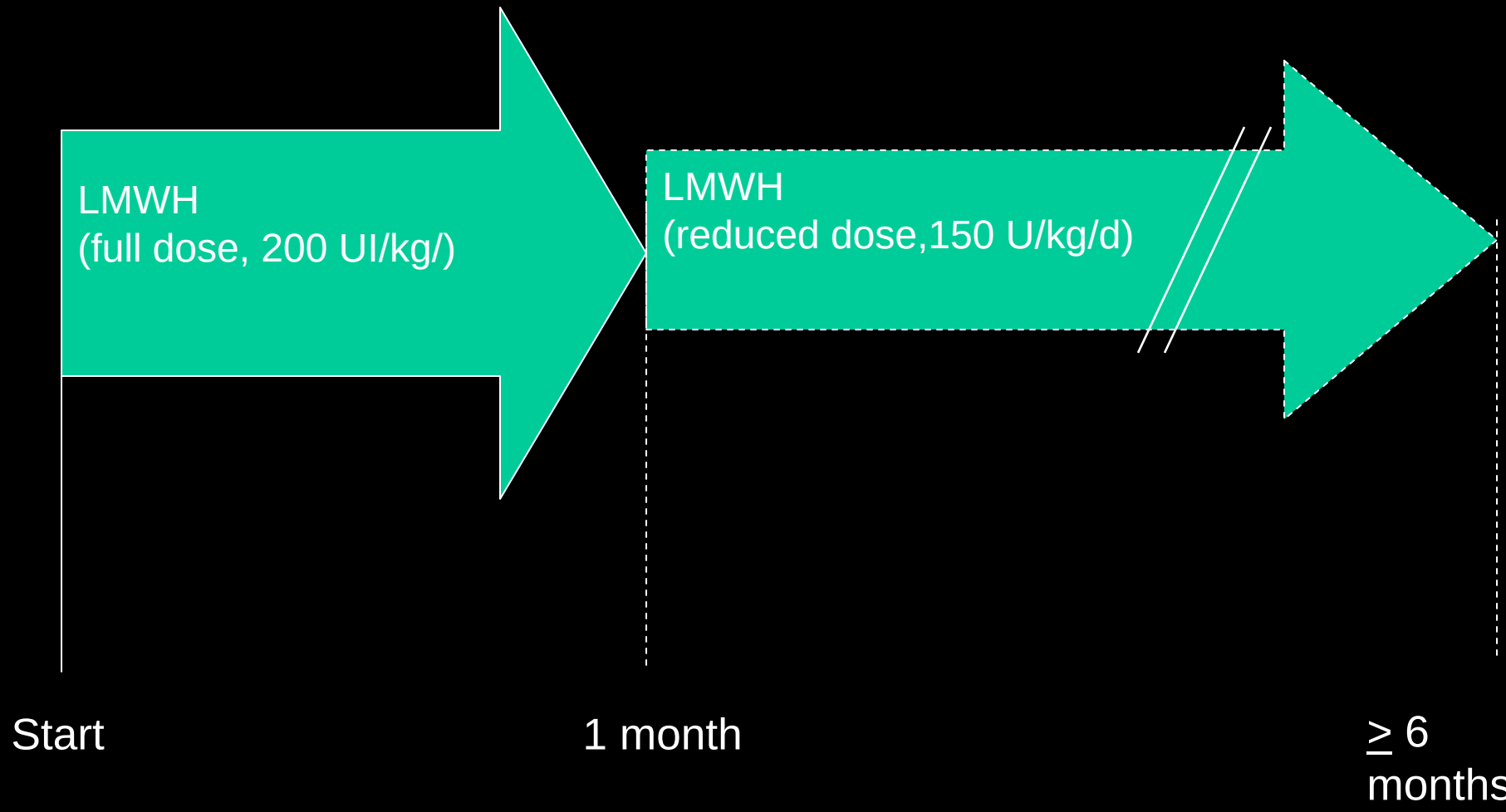
- Contraindications to VKA
- Low compliance (check !)
- Active bleeding
- Invasive procedure
- Overt cancer

Treatment of VTE in patients with cancer

ACCP Guidelines, Chest 2008; 133

- We recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy **Grade 1A** and subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved **Grade 1C**
- In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals **Grade 1C**

VTE treatment in cancer patients



Lee AYY et al, N Engl J Med 2003;349:146-53

LMWH vs VKA for Long-Term Treatment of VTE in Patients With Active Cancer

Author/yr (Acronym)	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Recurrent DVT or PE, No./Total (%)	Major Bleeding, No./Total (%)	Total Mortality, No./Total (%)	Comments
Meyer et al[213]/2002	VKA (INR, 2.0–3.0) for 3 mo after initial enoxaparin	75/75	3 mo	3/75 (4%)	12/75 (16%)	17/75 (23%)	Population: DVT (proportion with calf DVT not known) or PE and active cancer; all fatal bleedings (n = 6) were in VKA group.
	Enoxaparin at 1.5 mg/kg once daily for 3 mo	71/71	3 mo.	2/71 (3%) RR, 0.7 (95% CI, 0.1–4.1)	5/71 (7%) RR, 0.4 (95% CI, 0.2–1.2)	8/71 (11%) RR, 0.5 (95% CI, 0.2–1.1)	
Lee et al[211]/2003 (CLOT)	VKA (INR, 2.0–3.0) for 6 mo after initial dalteparin	336/338	6 mo	53/336 (16%)	12/335 (4%)	136/336 (40%)	Population: Proximal DVT or PE and active cancer
	Dalteparin at 200 U/kg once daily for 1 mo followed by 150 U/kg for 5 mo	336/338	6 mo	27/336 (8%) RR, 0.5 (95% CI, 0.3–0.8)	19/338 (6%) RR, 1.6 (95% CI, 0.8–3.2)	130/336 (37%) RR, 1.0 (95% CI, 0.8–1.2)	Difference in efficacy mainly due to recurrent DVT (14 vs 37 episodes)
Hull et al[221] /2006 (Main LITE-cancer)	VKA (INR 2.0–3.0) for 3 mo after initial IV UFH	100/100	3 mo	10/100 (10%)	7/100 (7%)	19/100 (19%)	Population: Proximal DVT and active cancer
	Tinzaparin at 175 mg/kg once for 3 mo	100/100	3 mo.	6/100 (6%) RR, 0.6 (95% CI, 0.2–1.6)	7/100 (7%) RR, 1.0 (95% CI, 0.4–2.8)	20/100 (20%) RR, 1.0 (95% CI, 0.6–1.9)	Prespecified, stratification, subgroup within a larger trial; Outcomes at 12 mo were also reported
Summary				RR, 0.7 (95% CI, 0.4–0.8)	RR, 1.0 (95% CI, 0.6–1.6)	RR, 0.9 (95% CI, 0.8–1.1)	

Treatment of DVT: useful

- Elevated legs
- Elastic stockings
- Ultrasound before stopping treatment
- Search for causes (cancer, thrombophilic state)

Treatment of DVT: useless

- Bedrest
- Antibiotics
- NSAID
- To frighten the patient

Vena Cava Filters

ACCP Guidelines, Chest 2008; 133

- For most patients with DVT, **we recommend against** the routine use of a vena cava filter in addition to anticoagulants **Grade 1A**
- We recommend placement of an inferior vena caval filter in patients with a **contraindication for, or a complication of anticoagulant treatment** **Grade 1C**

Take home messages

- In patients with high suspicion of VTE start treatment (LMWH) while waiting for diagnostic confirmation/exclusion
- In patients with PE, evaluate the risk/benefit ratio of a more aggressive approach:
  - In patients hemodinamically unstable: prefer thrombolysis
  - In all the other patients, prefer anticoagulant treatment