Πνευμονική Εμβολή
Αναπάντητα ερωτήματα και προτεραιότητες ένα χρόνο πριν από τις νέες Ευρωπαϊκές Κατευθυντήριες Οδηγίες

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Disclosures

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Consultancy honoraria: Bayer AG, Boehringer Ingelheim, Actelion, Pfizer – Bristol-Myers Squibb

Institutional research support: AG, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer, Actelion
Difficult cases, specific populations in PE

1) Determine the patient’s risk: Low-risk or intermediate-risk PE? And why does it matter?

2) Anticoagulation in specific patient groups and clinical situations

3) Anticoagulation after PE in the patient with cancer

4) How to choose the optimal duration (and dose) of anticoagulation?
### ESC Guidelines 2014: Risk classes of acute PE

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
<th>Death at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PESI class III-V or sPESI ≥1</td>
<td>RV dysfunction (imaging)</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Interm-high</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Interm-low</td>
<td>+</td>
</tr>
<tr>
<td>Low</td>
<td>–</td>
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Case 1 - What is the risk of this patient?

- 31 year-old man; obese (BMI: 36 kg/m²), no history of previous disease
- **Presented at ED:** Increasing dyspnoea over 7 days

**Clinical findings at presentation:**
- BP, 100/70 mm Hg; HR, 105/min; resp. rate, 24/min; SO₂, 91% on room air
- Heart and lung exam OK
Low, intermediate-low, or intermediate-high risk?

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RV/LV ratio 2.6:1 !!
Algorithms are educational, but do NOT forget the RV!

Clinical suspicion of PE

Shock / Hypotension?

Yes

Diagnostic algorithm as for suspected high-risk PE

PE confirmed

Diagnostic algorithm as for suspected not high-risk PE

PE confirmed

Assess clinical risk (PESI or sPESI)

PESI Class III-V or sPESI ≥1

Intermediate risk

RV function (echo or CT) Laboratory testing

One positive or both negative

Intermediate-low risk

A/C; hospitalization

Both positive

Intermediate-high risk

A/C; monitoring: consider rescue reperfusion

Low risk

A/C; consider early discharge and home treatment, if feasible

Intermediate risk

Consider further risk stratification

High risk

Primary reperfusion

PESI Class I-II or sPESI = 0

Low risk

A/C; hospitalization

Intermediate-low risk

A/C; hospitalization

Intermediate-high risk

A/C; monitoring: consider rescue reperfusion

High risk

Primary reperfusion

No

PE confirmed

Intermediate-

Implications: Candidates for monitoring, perhaps thrombolysis.

**Clinical suspicion of PE**

- **Shock / Hypotension?**
  - Yes
    - Diagnostic algorithm as for suspected high-risk PE
  - No
    - Diagnostic algorithm as for suspected not high-risk PE

**PE confirmed**

- **Intermediate risk**
  - RV function (echo or CT) Laboratory testing
    - One positive or both negative
    - Consider further risk stratification

**High risk**
- Primary reperfusion

**Intermediate-high risk**
- A/C; monitoring: consider rescue reperfusion

**Intermediate-low risk**
- A/C; hospitalization

**Low risk**
- A/C; consider early discharge and home treatment, if feasible

---

Patient with suspected pulmonary embolism (PE)

Anticoagulation initiated, unless contraindicated

Acute PE confirmed by CT scan

Multidisciplinary PE response team (PERT) alerted: Interventionalist, cardiac surgeon, radiology, pulmonary/critical care medicine

PERT members review the available medical information and develop optimal treatment plan

Medical therapy

Catheter directed therapy

Surgical embolectomy

PERT experience at Massachusetts General Hospital 2012-2017

760 PERT sessions over 5 years, 16% ▲ every 6 months

A/C: 65%

IVC filters: 15%

CDT: 9.2%

i.v. lysis: 2.5%

Aspiration: 1.1%

ECMO: 2.2%

Surgery: 3.8%

Rosovsky RP; personal communication Feb 1, 2018

Case 2 - What is the risk of this patient?

- 36 year old lady, arrives at the hospital alone, on foot
- Presents with a swollen leg, mild retrosternal discomfort.
- Patient’s family doctor just diagnosed DVT by CUS and sent her to the hospital.

At the hospital:
- BP: 130/80 mm Hg; HR: 80/min, regular
- SO$_2$: 98% under room air
- Heart and lungs normal

Patient wants to go home right away, she “feels good”!
What to do now?

Patient with confirmed DVT and dyspnoea:

a) CTPA is now necessary to diagnose PE.
b) No further tests necessary, this patient has DVT, and thus VTE, and is stable; start rivaroxaban and let her go home right away!
c) I will keep her in the hospital and on the monitor for 2 days to make sure she will not decompensate
d) I need more information to decide
Patient with dyspnoea and diagnosed DVT: What do the Guidelines say?

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<td><strong>Exclusion of PE</strong></td>
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<tr>
<td>Negative result, highly sensitive assay</td>
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</tr>
<tr>
<td>Negative result, moderately sensitive assay</td>
<td>+</td>
</tr>
<tr>
<td><strong>Chest CT angiography</strong></td>
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<td>Normal multidetector CT alone</td>
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<tr>
<td><strong>V/Q scan</strong></td>
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<td>Normal perfusion lung scan</td>
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<td>Non-diagnostic lung scan and negative proximal CUS</td>
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<tr>
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**BUT:** assessment of risk always necessary in PE!

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Patients with low risk may be candidates for home treatment

Clinical suspicion of PE

Shock / Hypotension?

Yes

Diagnosis algorithm as for suspected high-risk PE

PE confirmed

Intermediate risk

RV function (echo or CT)

Laboratory testing

Both positive

A/C; monitoring: consider rescue reperfusion

A/C; consider early discharge and home treatment, if feasible

Low risk

One positive or both negative

Intermediate-low risk

A/C; hospitalization

Intermediate-high risk

High risk

Primary reperfusion

Assess clinical risk (PESI or sPESI)

PE confirmed

PESI Class III–V or sPESI ≥1

PESI Class I–II or sPESI = 0

No

Diagnostic algorithm as for suspected not high-risk PE

PE confirmed

Intermediate risk

Consider further risk stratification

Home treatment: Check risk, feasibility AND RV status!

- ✓ NO haemodynamic instability
- ✓ NO need for oxygen
- ✓ NO need for parenteral analgesia
- ✓ NO extreme obesity
- ✓ NO serious comorbidity

- ✓ Patient compliance with treatment
- ✓ Support from family/social environment

- ✓ NO RV dysfunction on CT or echo!
Large ongoing HoT-PE study (555 patients enrolled!)

Haemodynamically stable patient admitted with clinically suspected PE:

❖ Start parenteral anticoagulation

❖ Confirm PE within 24 hours of admission
  (Chest CT, V/Q scan or pulmonary angiogram)

Enrolment after eligibility criteria verified and informed consent

❖ First dose of rivaroxaban in hospital

Additional baseline tests (echocardiography, CUS of leg veins)
  – recommended, not compulsory

❖ Discharge within 48 hours

3-month follow-up

CUS, compression ultrasound

Difficult cases, specific populations in PE

1) Determine the patient’s risk: Low-risk or intermediate-risk PE? And why does it matter?

2) Anticoagulation in specific patient groups and clinical situations

3) Anticoagulation after PE in the patient with cancer

4) How to choose the optimal duration (and dose) of anticoagulation?
Current (2018) anticoagulation regimens for PE and DVT

**Initial treatment schemes with non-VKA oral anticoagulants**

**Single drug approach**
- **Rivaroxaban** 15 mg bid × 21 days, then 20 mg od **OR** **Apixaban** 10 mg bid × 7 days, then 5 mg bid

**Initial parenteral anticoagulation**
- **Dabigatran** 150 mg bid **OR** **Edoxaban** 60 mg od

**Acute**
- UFH, LMWH, fondaparinux, ≥5 days

**Overlap**

**Prevention**
- **VKA (INR 2.0–3.0)** ≥3 months

**Extended use**
- Long-term secondary prevention
  - **VKA (INR 2.0–3.0)**, indefinite with periodic assessment

Which anticoagulant to start with, depending on patient’s risk?

Clinical suspicion of PE

Shock / Hypotension?

Yes

Diagnostic algorithm as for suspected high-risk PE

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Laboratory testing

High risk

Primary reperfusion

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A/C; consider early discharge and home treatment, if feasible

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Diagnostic algorithm as for suspected not high-risk PE

PE confirmed

Assess clinical risk (PESI or sPESI)

PESI Class III-V or sPESI ≥1

One positive or both negative

PESI Class I-II or sPESI = 0

Both positive

Consider further risk stratification

Which anticoagulant to start with, NOAC or heparin?

- **3%** In high-risk PE (unstable patient) → start UFH
- **15%** → after stabilization, switch to (N)OAC possible.
- **50%** In intermediate-high-risk PE → start UFH/LMWH
  → monitor for 2-3 days, if no decompensation, switch to (N)OAC* possible.
- **25%** In intermediate-high-risk, or DVT treated in hospital
  → LMWH and switch to (N)OAC*, or single oral drug regimen with rivaroxaban/apixaban.
- **3%** In low-risk PE and ambulatory DVT treatment
  → single oral drug (apixaban, rivaroxaban) may be more attractive.

* Dabigatran or edoxaban may be started no earlier than 5 days after initiation of LMWH treatment. Apixaban or rivaroxaban must be taken at the higher dosage until day 7 or day 21 is reached, respectively.
Venous thromboembolism: case fatality ▼, incidence ▲

**FIGURE 2** Global Trends in PE Incidence and Case Fatality Rates

(Left) Pulmonary embolism (PE) incidence. (Right) Case fatality rates. Data shown here were retrieved from studies of trends in pulmonary embolism (61-64,66,68,70). In case of duplicate or overlapping data, only the most recent publication was included. *Pulmonary embolism was listed as principal diagnosis. †Any listed code for pulmonary embolism was considered.

Overdiagnosis of PE a “side effect” of modern CT methods?

Retrospective studies: sub-segmental PE on local reading, without associated DVT, no anticoagulation

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Recurrent VTE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pena 2012</td>
<td>18</td>
<td>0</td>
<td>(0-18.5)</td>
</tr>
<tr>
<td>Goy 2015</td>
<td>37**</td>
<td>0</td>
<td>(0-9.5)</td>
</tr>
</tbody>
</table>

Ongoing study:
Withholding anticoagulation in patients with subsegmental PE and no cancer, who have negative serial bilateral lower extremity ultrasound tests and are carefully followed over 3 months (NCT01455818)

*: 25 with follow-up among 32 patients
**: no systematic search for DVT

Photos: Courtesy K F Kreitner, University Medical Center Mainz, DE

Donato AA, et al. Thromb Res 2010; 126: e266–70
Difficult cases, specific populations in PE

1) Determine the patient’s risk: Low-risk or intermediate-risk PE? And why does it matter?
2) Anticoagulation in specific patient groups and clinical situations
3) Anticoagulation after PE in the patient with cancer
4) How to choose the optimal duration (and dose) of anticoagulation?
Specific subgroup: PE and cancer (2014 Guidelines)

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<tr>
<td>Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3 to 6 months.</td>
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<td>For patients with PE and cancer, extended anticoagulation (beyond the first 3 to 6 months) should be considered for an indefinite period or until the cancer is cured.</td>
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NOACs for cancer? Recent edoxaban Hokusai VTE Cancer trial

**Recurrent VTE (mITT, n=1046)**

- Objectively confirmed VTE
  - Stratified randomization for
    - Bleeding risk
    - Dose adjustment
  - PROBE design

**Major bleeding (mITT, n=1046)**

- LMWH → edoxaban 60 mg od
- dalteparin 200 IU/kg → dalteparin 150 IU/kg
- Day 0 → Day 5 → Day 30 → Month 12

NOACs for cancer? Recent rivaroxaban select-d trial

*15 mg bid for 21 days followed by 20 mg od; for patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; if a patient’s platelet counts falls to <50,000/mm³, rivaroxaban should be discontinued until the platelet count recovers to above 50,000/mm³; *200 IU/kg od for the first 30 days of treatment followed by 150 IU/kg od; if a patient’s platelet count falls to 50,000–100,000/mm³ the daily dose of dalteparin should be reduced by 2500 IU until platelet count returns to ≥100,000/mm³; if a patient’s platelet count falls to <50,000/mm³, dalteparin should be discontinued until the platelet count recovers to above 50,000/mm³

IIR, Investigator Initiated Research; FU, follow-up; R, randomization; RVT, residual vein thrombosis

http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/select-d/; EudraCT number: 2012-005589-37

Difficult cases, specific populations in PE

1) Determine the patient’s risk: Low-risk or intermediate-risk PE? And why does it matter?

2) Anticoagulation in specific patient groups and clinical situations

3) Anticoagulation after PE in the patient with cancer

4) How to choose the optimal duration (and dose) of anticoagulation?
A patient presenting 6 months after PE

- 63 year-old lady, 163 cm, 60 kg
- She was healthy until March 2018
- She suffered acute PE after flying from Athens to London (a little less than 4 hours)
- Was given rivaroxaban 20 mg once daily; treatment well tolerated
- Came to our PE outpatient service last week: She would like to stop the anticoagulant, but she is also afraid of a new PE episode
What is your advice?

a) Yes, she can stop now, this was provoked PE (economy class syndrome!)

b) No, she should continue treatment lifelong, this prevents life-threatening PE recurrence!

c) I would continue, but the dose can be reduced now to 10 mg once daily

d) I do not know, let the patient decide
### Recommendations

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High risk of VTE recurrence: highly effective prevention by VKA

BUT: Bleeding frequent and potentially dangerous while on chronic VKA treatment

33 studies; 10,757 patients; 4,374 patient-years of OAC

After the first 3 months of OAC:

- Major bleeding rate: 2.74%/yr
- Intracranial bleeding: 0.65%/yr
- Fatal bleeding rate: 0.63%/yr
- Case fatality rate: 9.1%

Recurrence versus bleeding risk: What was done in clinical practice in the VKA era?

RIETE Registry (N=6944)

Cumulative Incidence (%)

Days

55%

19%

Extended treatment with *low-dose* NOAC: AMPLIFY-EXT

- Two doses of apixaban (2.5 mg and 5 mg twice daily*) versus placebo
- Pts with VTE who had completed 6–12 months of anticoagulation
- Study drugs were given for 12 months
- 2482 pts included in ITT

**Recurrent VTE/VTE-related death:** 8.8% in placebo vs. 1.7% in each apixaban dose

*Only the 2.5 mg BID dose of apixaban is licensed for prevention of recurrent DVT/PE

ITT: intention-to-treat

Extended treatment with *low-dose* NOAC: AMPLIFY-EXT

- Two doses of apixaban (2.5 mg and 5 mg twice daily*) versus placebo
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- 2482 pts included in ITT
- **Recurrent VTE/VTE-related death:** 8.8% in placebo vs. 1.7% in each apixaban dose

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**Major or clinically relevant non-major bleeding**

*Only the 2.5 mg bid dose of apixaban is licensed for prevention of recurrent DVT/PE*

CRNM: clinically relevant non-major bleeding; ITT: intention-to-treat

Safety and efficacy of extended prophylaxis with *standard-dose* and *half-dose* rivaroxaban: EINSTEIN CHOICE

**Efficacy***

- Rivaroxaban 20 mg od vs ASA:
  - 17/1107 (1.5%) vs 50/1131 (4.4%)
  - HR=0.34 (95% CI 0.20–0.59), p<0.001

- Rivaroxaban 10 mg od vs ASA:
  - 13/1127 (1.2%) vs 50/1131 (4.4%)
  - HR=0.26 (95% CI 0.14–0.47), p<0.001

**Major bleeding***

- Rivaroxaban 20 mg od vs ASA:
  - 6/1107 (0.5%) vs 3/1131 (0.3%)
  - HR=2.01 (95% CI 0.50–8.04), p=0.32

- Rivaroxaban 10 mg od vs ASA:
  - 5/1127 (0.4%) vs 3/1131 (0.3%)
  - HR=1.64 (95% CI 0.39–6.84), p=0.50

*Intention-to-treat analysis; #safety analysis; ‡no events after Day 360 up to Day 480

Pulmonary embolism 2018: Most patients candidates for extended (low-dose) anticoagulation

**STOP after 3 months:**
PE provoked by a strong reversible risk factor

- Major, especially orthopaedic surgery (anaesthesia > 30 min)
- Major trauma with/without surgical treatment
- Immobilization in hospital for acute severe illness

**CONSIDER CONTINUING:**
All other transient or permanent factors

- More than one VTE event (without strong reversible factor)
- Cancer
- Antiphospholipid syndrome (only VKA!)
- Inflammatory bowel disease
- Active autoimmune disease
- Family history of VTE, or major hereditary thrombophilia
- Minor surgery (anaesthesia < 30 min), or (leg) trauma
- Long-haul flight
- Oestrogen contraception or replacement therapy
- Male sex
- Age
- Obesity (BMI > 30 kg/m²)
- Location of index VTE: PE or proximal DVT (not distal DVT)
- No identifiable risk factor!
Regular follow-up, repeated assessment of recurrence versus bleeding risk remains necessary!

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Follow-up also intended to assess CTEPH risk!

- Acute PE
  - Follow-up at 3-6 months, ON A/C
    - Are you short of breath? Are you limited in your daily activities? Is it worse than before PE?
      - YES, I have symptoms / functional limitation
        - Echo, lab (NT-proBNP), CPET(?)
      - NO, I am fine

1) Determine the patient’s risk class, do NOT forget to **assess the RV**: Distinguishing low-risk from intermediate-risk PE matters for hospitalization, monitoring, initial anticoagulation, possibly thrombolysis!

2) NOACs increasingly preferred for anticoagulation, also in “vulnerable” patients

3) In acute **subsegmental PE**, “watchful waiting” may be preferable to routine anticoagulation, unless the patient has cancer

4) For the patient with **cancer**, the NOACs edoxaban and rivaroxaban now an alternative to low molecular weight heparin, **unless high risk of gastrointestinal or genitourinary bleeding**; apixaban data coming 2019

5) **Extended anticoagulation** increasingly preferred after PE (unless major reversible risk factor caused the index episode); bleeding risk with low-dose NOACs now very low; do NOT forget REGULAR follow-up and re-evaluation!
Thank you!!