Θεραπεία και Πρόληψη Θρομβώσεων και Πνευμονικών Εμβολών
Τι μάθαμε το 2017; Τι περιμένουμε το 2018;

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Disclosures

Lecture honoraria: Bayer HealthCare, Boehringer Ingelheim, MSD, Pfizer – Bristol-Myers Squibb, Servier

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Institutional research support: Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer, Actelion

1) (Re)defining low, intermediate and high risk
2) Risk-adapted acute-phase treatment
3) Optimal duration (and dose) of anticoagulation
4) How to follow patients after acute PE?
### 2014-2016: 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>Both positive</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interm-low</td>
<td>One (or none) positive</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Gaps in definition of intermediate versus low risk

• 31 year-old man; obese (BMI: 36 kg/m²), no history of previous disease

• **Presented at ED:** Increasing dyspnoea over 7 days; syncope

**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
### Pulmonary Embolism Severity Index (PESI) ‘versus’ RV...

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version</th>
<th>Simplified version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age &gt;80 years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
<td>-</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10</td>
<td>1</td>
</tr>
<tr>
<td>Pulse rate ≥110 b.p.m.</td>
<td>+20</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mmHg</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate &gt;30 breaths per minute</td>
<td>+20</td>
<td>-</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20</td>
<td>-</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
<td>-</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>+20</td>
<td>1</td>
</tr>
</tbody>
</table>
Assess severity of PE, assess comorbidity

Clinical suspicion of PE

Shock / Hypotension?

Yes  No

Diagnostic algorithm as for suspected high-risk PE

Diagnostic algorithm as for suspected not high-risk PE

PE confirmed

Assess clinical risk (PESI or sPESI)

PE confirmed

Intermediate risk

RV function (echo or CT)

Laboratory testing

High risk

Intermediate-high risk

Low risk

Primary reperfusion

A/C; monitoring: consider rescue reperfusion

A/C; hospitalization

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

Intermediate-low risk

Consider further risk stratification

Both positive

Both positive or both negative

One positive or both negative

PESI Class III-V or sPESI ≥1

PESI Class I-II or sPESI = 0

Intermediate risk

1) Defining low, intermediate and intermediate-high risk

2) Risk-adapted acute-phase treatment
   - Reperfusion candidates
   - Initial anticoagulation
   - Patients with cancer
PEITHO 2014: Benefits vs risks of systemic thrombolysis

<table>
<thead>
<tr>
<th>All-cause mortality or haemodynamic collapse within 7 days of randomization</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>13</td>
<td>(2.6)</td>
<td>28</td>
<td>(5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-intracranial bleeding</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>32</td>
<td>(6.3)</td>
<td>6</td>
</tr>
<tr>
<td>Minor</td>
<td>165</td>
<td>(32.6)</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strokes by day 7</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>12</td>
<td>(2.4)</td>
<td>1</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

ITT population

ESC 2014: Candidates for reperfusion in PE

Clinical suspicion of PE

Shock / Hypotension?

Yes

Diagnostic algorithm as for suspected high-risk PE

PE confirmed

Intermediate risk

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

No

Diagnostic algorithm as for suspected not high-risk PE

PE confirmed

Assess clinical risk (PESI or sPESI)

PESI Class III-V or sPESI ≥1

PESI Class I-II or sPESI = 0

RV function (echo or CT) Laboratory testing

One positive or both negative

Both positive

Consider further risk stratification

PE confirmed

Intermediate risk

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 @Massachusetts General Hospital
2012-2017

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

A/C: 65%
VCI 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
Inclusion criteria: rationale

Clinical criteria of pulmonary embolism severity

<table>
<thead>
<tr>
<th>Clinical criteria of pulmonary embolism severity</th>
<th>Placebo arm (n=499)</th>
<th>Tenecteplase arm (n=506)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence in treatment arm</strong></td>
<td>Clinical outcome with vs without criterion</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td>SBP ≤110 mmHg</td>
<td>82 (16.6%)</td>
<td>9 (11.0%) vs 24 (5.8%)</td>
</tr>
<tr>
<td>Respiratory rate &gt;20 breaths/min</td>
<td>181 (46.2%)</td>
<td>21 (11.6%) vs 6 (2.8%)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>26 (5.3%)</td>
<td>6 (23.1%) vs 26 (5.6%)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>32 (6.7%)</td>
<td>6 (18.7%) vs 6 (2.4%)</td>
</tr>
<tr>
<td>At least one severity criterion</td>
<td>250 (50.2%)</td>
<td>27 (10.8%) vs 6 (2.4%)</td>
</tr>
<tr>
<td>At least 2 criteria</td>
<td>64 (12.9%)</td>
<td>13 (20.3%) vs 20 (4.6%)</td>
</tr>
<tr>
<td>At least 3 criteria</td>
<td>7 (1.4%)</td>
<td>2 (28.6%) vs 31 (6.3%)</td>
</tr>
</tbody>
</table>

Barco S et al, for The PEITHO Investigators. *Eur Respir J* 2018;Epub ahead of print
# Clinical criteria for ‘imminent decompensation’

**PEITHO post hoc analysis**

<table>
<thead>
<tr>
<th>Clinical criteria of pulmonary embolism severity</th>
<th>Placebo arm (n=499)</th>
<th></th>
<th>Tenecteplase arm (n=506)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence in</td>
<td>Clinical outcome</td>
<td>Relative risk</td>
<td>Prevalence in</td>
</tr>
<tr>
<td></td>
<td>treatment arm</td>
<td>with vs without</td>
<td>(95% CI)</td>
<td>treatment arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>criterion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≤110 mmHg</td>
<td>82 (16.6%)</td>
<td>9 (11.0%) vs 24</td>
<td>1.89 (0.91-3.91)</td>
<td>82 (16.3%)</td>
</tr>
<tr>
<td>Respiratory rate &gt;20 breaths/min</td>
<td>181 (46.2%)</td>
<td>21 (11.6%) vs 6</td>
<td>4.08 (1.68-9.89)</td>
<td>211 (51.3%)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td>6 (18.7%) vs 6</td>
<td>3.22 (1.43-7.26)</td>
<td></td>
</tr>
<tr>
<td>Active cancer</td>
<td>32 (6.7%)</td>
<td>6 (18.7%) vs 6</td>
<td>3.22 (1.43-7.26)</td>
<td>41 (8.4%)</td>
</tr>
<tr>
<td>At least one severity criterion</td>
<td>250 (50.2%)</td>
<td>27 (10.8%) vs 6</td>
<td>4.46 (1.88-10.62)</td>
<td>286 (56.5%)</td>
</tr>
<tr>
<td>At least 2 criteria</td>
<td>64 (12.9%)</td>
<td>13 (20.3%) vs 20</td>
<td>8.40 (3.32-21.23)</td>
<td>66 (13.0%)</td>
</tr>
<tr>
<td>At least 3 criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Barco S et al, for The PEITHO Investigators. *Eur Respir J* 2018; Epub ahead of print
Improving safety with systemic reduced-dose lysis
Hardly available data

Reduced versus standard dose
A meta-analysis of 3 studies

Improving safety with systemic reduced-dose lysis

PEITHO-III trial to start soon

Confirmed acute PE, haemodynamically stable
(including stabilisation ≤2 h of admission)

≥1 criterion of severity
- Systolic blood pressure ≤110 mmHg
- Respir. rate ≥20 rpm / SpO2 <90%
- History of chronic heart failure

RV/LV >1.0 and positive troponin

Primary Efficacy, Safety Outcomes
Secondary Outcomes
Secondary Outcomes

LMWH
Start/maintain standard oral
anticoagulation
Reduced-dose alteplase
Alteplase placebo
Start/maintain standard oral
anticoagulation

Day 0
Day ≥2
Day 30
Day 180
Year 2
Improving safety with catheter-directed low-dose local lysis
Promising, but solid evidence on efficacy needed

- Speed of lysis?
- Role of ultrasound?
- Direct comparison to lysis?
- Broad availability?? Cost? Reimbursement?
# Risk-adjusted strategies of [initial] anticoagulation

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk PE</strong> (unstable patient)</td>
<td>Start UFH. After stabilization, switch to (N)OAC possible.</td>
</tr>
<tr>
<td><strong>Intermediate-high-risk PE</strong></td>
<td>Start UFH/LMWH. Monitor for 2-3 days, if no decompensation, switch to (N)OAC* possible.</td>
</tr>
<tr>
<td><strong>Intermediate-low-risk PE</strong>, or DVT treated in hospital</td>
<td>LMWH and switch to (N)OAC*, or single oral drug regimen with rivaroxaban/apixaban.</td>
</tr>
<tr>
<td><strong>Low-risk PE and ambulatory DVT</strong> treatment</td>
<td>Single oral drug (apixaban, rivaroxaban) may be more attractive.</td>
</tr>
</tbody>
</table>

* 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.
If no contraindications for switch from parenteral to oral therapy at 72 hrs:

- Enrolment after eligibility criteria verified and informed consent
- Confirm intermediate-risk PE within 24 hours of diagnosis (chest CT, echocardiogram, lab biomarkers)
- Continue LMWH for a total of 72 hrs
- If no contraindications for switch from parenteral to oral therapy at 72 hrs:
  - First dosage of dabigatran

30-day, 6-month follow-up

Initial heparin followed by NOAC for intermediate-risk PE

EudraCT Nr. 2015-001830-12
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

++ Absence of RV dilatation/dysfunction
Absence of RA or RV thrombi

CUS, compression ultrasound

EudraCT Nr. 2013-001657-28
Specific subgroups: Recent Hokusai VTE Cancer trial

Recurrent VTE (mITT, n=1046)

Major bleeding (mITT, n=1046)

**Rationale:** To assess the efficacy and safety of rivaroxaban versus dalteparin for the treatment of VTE in patients with cancer not currently receiving chemotherapy.

**Indication:** VTEx patients with cancer

**FPFV:** Q4-13

**LPLV:** 16/17

**Short design:** Prospective, randomized, open-label, multicentre pilot phase III study

---

*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
1) Defining low, intermediate and intermediate-high risk
2) Risk-adapted acute-phase treatment
3) Optimal duration (and dose) of anticoagulation
4) How to follow patients after acute PE?
Recommendations | Class | Level
--- | --- | ---
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months. | I | B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months. | I | A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk. | IIa | B
In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals. | I | C
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis. | IIb | B

Recommendations | Class | Level
--- | --- | ---
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months. | I | B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months. | I | A
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In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis. | IIb | B

High risk of VTE recurrence – highly effective prevention by VKA

Cumulative incidence of VTE recurrence over time

- Treatment period
- Posttreatment follow-up


So, why not VKA indefinitely after index VTE?

**The New England Journal of Medicine**

**Recurrence rate reduced by 90%**

**Major bleeding:** 3.8% / year

Bleeding is frequent under 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%

Duration of anticoagulation after VTE in real world
RIETE Registry (N=6944)

Extended prophylaxis with *half-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
- **Primary EP:** 8.8% in placebo vs. 1.7% in EACH apixaban dose

**Major / CRNM bleeding:**

2.7% vs. 3.2% (2.5 mg) vs. 4.3% (5 mg)

Extended prophylaxis with *half-dose* NOAC: EINSTEIN Choice

**Efficacy**

![Graph showing cumulative incidence of events over days for Rivaroxaban 20 mg od vs ASA, Rivaroxaban 10 mg od vs ASA.](image)

- 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**

![Graph showing cumulative incidence of events over days for Rivaroxaban 20 mg od vs ASA, Rivaroxaban 10 mg od vs ASA.](image)

- 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 0.39–6.94), p=0.50

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

Remaining challenge: For whom half dose, for whom full dose?

**Early recurrence**
- Poor quality of anticoagulation (failure to achieve therapeutic aPTT and INR)
- Cancer

**Late recurrence**

**Strong established factors**
- Unprovoked (vs provoked) VTE
- More than one VTE event
- On-going hormonal therapy
- Elevated D-dimer levels after/during VKA treatment

**Weaker/controversial factors**
- Male sex
- Location: PE/proximal DVT vs distal DVT
- Age
- Family history of VTE
- Obesity (increased BMI)
- Cancer
- Antiphospholipid syndrome
- Hereditary thrombophilia

---

aPTT, activated partial thromboplastin time; BMI, body mass index; INR, international normalized ratio.

Continue anticoagulants, except if ‘safely low’ recurrence risk!

### Early recurrence¹

- Poor quality of anticoagulation (failure to achieve therapeutic aPTT and INR)
- Cancer

### Late recurrence²,³

#### Strong established factors

- Unprovoked (vs provoked) VTE
- More than one VTE event
- On-going hormonal therapy
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#### Weaker/controversial factors

- Male sex
- Location: PE/proximal DVT vs distal DVT
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aPTT, activated partial thromboplastin time; BMI, body mass index; INR, international normalized ratio.


1) Defining low, intermediate and intermediate-high risk
2) Risk-adapted acute-phase treatment
3) Optimal duration (and dose) of anticoagulation
4) How to follow patients after acute PE?
Selecting candidates for regular FU, CTEPH workup: Where do we stand today?

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In PE survivors with persistent dyspnoea, diagnostic evaluation for CTEPH should be considered</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Screening for CTEPH in asymptomatic survivors of PE is currently not recommended</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

*Eur Heart J 2014:35:3145–3146*
<table>
<thead>
<tr>
<th>Findings at baseline (index PE event)</th>
<th>Conditions other than index PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo: Elevated sPAP, &gt;60 mmHg</td>
<td>☐ Myeloproliferative disorders ☐</td>
</tr>
<tr>
<td>Echo/CT: RV pressure overload</td>
<td>☐ History of malignancy</td>
</tr>
<tr>
<td>CT: Central thrombi</td>
<td>☐ Splenectomy</td>
</tr>
<tr>
<td>CT: signs of pre-existing CTEPH*</td>
<td>☐ Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Chronic osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Ventriculo-atrial shunts</td>
</tr>
<tr>
<td></td>
<td>Chronic central venous lines</td>
</tr>
<tr>
<td></td>
<td>Pacemakers</td>
</tr>
</tbody>
</table>

2014 -> 2017 -> 2019

› Check for CTEPH risk factors at 3-6-month FU
2014 -> 2017 -> 2019
How could a ‘CTEPH search’ algorithm look like?

**Acute PE**

Follow-up at 3-6 months, ON A/C
“Are you asymptomatic? Has your functional status returned to ‘pre-PE’ levels?”

- NO, I have symptoms / functional limitation
- YES, I am fine

- Echo +/- BNP/NT-proBNP
- Both normal
- ≥1 abnormal

- Diagnostic work-up
  - V/Q scan, MRA, [catheterization]
- Proceed to echo /biomarker test
  OR follow at 6-12-month intervals
- Focus on anticoagulation; advise to return if symptoms develop

'Risk factors’ for CTEPH?

- YES
- NO
Areas for advances in VTE management

- Distinguish PE severity from overall risk related to comorbidity
- Put clinical scores such as the (s)PESI into the right perspective!
- Better define candidates for reperfusion treatment
- Investigate safer regimens of systemic or local thrombolysis
- Dissect strategies of risk-adjusted initial anticoagulation
- Define when indefinite anticoagulation (and at what dose) is recommended, when it should be considered, when it may be considered
- Propose follow-up strategies for patients after acute VTE.
Pulmonary Circulation & Right Ventricular Function
ESC Working Group