TROMBOEMBOLIA PULMONAR

DRA. LINDA SÁNCHEZ PÉREZ
RESIDENTE DE MEDICINA INTERNA
EPIDEMIOLOGÍA

- Tercera causa de enfermedad cardiovascular
- Incidencia anual de 100-200 por 100,000 habitantes / año
- 371 000 muertes
- 34% muerte súbita
- 54% sin diagnóstico
- 7% diagnóstico
- 40 años

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
In this context, it should be borne in mind that cava filter placement is not free of complications, which may include penetration of the caval wall or embolization to the right heart cavities and occasionally require emergency treatment.

Moreover, and importantly, the high success rates of filter retrieval (153 of 164 patients in whom it was attempted) reported in the PREPIC 2 trial will be very difficult to reproduce in the real world, probably increasing the rate of long-term complications.

In conclusion, the evidence derived from trial data does not support the liberalization of cava filter use beyond the strict indications listed previously.
EPIDEMIOLOGÍA

- Aumento de mortalidad a los 3 meses
- 600,000 casos en EU
- 200,000-300,000 muertes al año
- Complicaciones $13.5 a $69.3 billones
- Prevenir $4.5 a $39.3 billones
- 150,000 sin diagnóstico
EPIDEMIOLOGÍA

MÉXICO

- Incidencia
- 60-80 años
- Causa directa de muerte 28%
- 62% indirectamente,
- 10% hallazgo incidental
- 75% mueren
Epidemiología de la enfermedad tromboembólica venosa

- INC
- 1032 autopsias/ 3751
- 231 TEP
- 100 masiva
- Sospecha 18%
- Tercera causa de mortalidad
- 82% TVP

Cuadro I. Riesgo absoluto de TVP en pacientes hospitalizados*

<table>
<thead>
<tr>
<th>Grupo de pacientes</th>
<th>Prevalencia de TVP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padrónamiento médico</td>
<td>10 – 20</td>
</tr>
<tr>
<td>Cirugía general</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Cirugía ginecológica mayor</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Cirugía urológica mayor</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Neurocirugía</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Evento vascular cerebral</td>
<td>20 – 50</td>
</tr>
<tr>
<td>Arthroplastía de cadera o rodilla</td>
<td>40 – 60</td>
</tr>
<tr>
<td>Trauma mayor</td>
<td>40 – 80</td>
</tr>
<tr>
<td>Pacientes de terapia intensiva</td>
<td>10 – 80</td>
</tr>
</tbody>
</table>

*S i n *
It is helpful to divide PE into 3 categories: massive, sub-massive, and low risk. Those with massive PE are at highest risk for death (Table 2).

Definitions

Acquired Risk Factors

- Bed rest
- Travel
- Immobilizer or cast
- Trauma/spinal cord injury
- Major surgery
- Orthopedic surgery
- Malignancy
- Oral contraceptives
- Hormonal replacement therapy
- Antiphospholipid syndrome
- Myeloproliferative disorders
- Polycythemia vera
- Central venous catheters
- Age
- Obesity
- Chemotherapy
- Heparins
- Pregnancy/postpartum period

Hereditary Risk Factors

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V leiden (FVL)
- Prothrombin gene mutation
- Dysfibrinogenemia
- Factor XIII 34val
- Plasminogen deficiency

Mixed/Unknown

- High levels of factor VIII
- High levels of factor IX
- High levels of factor XI
- High levels of factor fibrinogen
- Activated Protein C resistance in absence of FVL
- Hyperhomocysteinemia
- High levels of plasminogen activator
- Elevated levels of lipoprotein (a)
- Low levels of tissue factor pathway inhibitor

Table 1. Risk Factors for VTE

<table>
<thead>
<tr>
<th>Acquired Risk Factors</th>
<th>Hereditary Risk Factors</th>
<th>Mixed/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed rest</td>
<td>Antithrombin deficiency</td>
<td>High levels of factor VIII</td>
</tr>
<tr>
<td>Travel</td>
<td>Protein C deficiency</td>
<td>High levels of factor IX</td>
</tr>
<tr>
<td>Immobilizer or cast</td>
<td>Protein S deficiency</td>
<td>High levels of factor XI</td>
</tr>
<tr>
<td>Trauma/spinal cord injury</td>
<td>Factor V leiden (FVL)</td>
<td>High levels of factor XI</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Prothrombin gene mutation</td>
<td>Activated Protein C resistance in absence of FVL</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Dysfibrinogenemia</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Factor XIII 34val</td>
<td>High levels of plasminogen activator</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Plasminogen deficiency</td>
<td>Elevated levels of lipoprotein (a)</td>
</tr>
<tr>
<td>Hormonal replacement therapy</td>
<td></td>
<td>Low levels of tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy/postpartum period</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SEPSIS

SÍNDROME NEFRÓTICO

INSUFICIENCIA HEPÁTICA CHILD PUGH C
FISIOPATOLOGÍA

- Interferencia entre la circulación e intercambio de gases
- Sobrecarga del VD
- Falla del VD
- Aumento de la PAP 30-50%
- Vasoconstricción: Liberación de tromboxano A2 y serotonina
- Factor activador de plaquetas, trombina, C3, C5 e histamina
FISIOPATOLOGÍA

- Aumento de la RVP proporcional a la disminución de la compliance arterial

- Aumento de la RVP produce dilatación del VD

- Alteraciones en la contractilidad (Frank-Starling)
Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy

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Summary. I.V. fluid therapy does not result in the extracellular volume distribution expected from Starling’s original model of semi-permeable capillaries subject to hydrostatic and oncotic pressure gradients within the extracellular fluid. Fluid therapy to support the circulation relies on applying a physiological paradigm that better explains clinical and research observations. The revised Starling equation based on recent research considers the contributions of the endothelial glycocalyx layer (EGL), the endothelial basement membrane, and the extracellular matrix. The characteristics of capillaries in various tissues are reviewed and some clinical corollaries considered. The oncotic pressure difference across the EGL opposes, but does not reverse, the filtration rate (the ‘no absorption’ rule) and is an important feature of the revised paradigm and highlights the limitations of attempting to prevent or treat oedema by transfusing colloids. Filtered fluid returns to the circulation as lymph. The EGL excludes larger molecules and occupies a substantial volume of the intravascular space and therefore requires a new interpretation of dilution studies of blood volume and the speculation that protection or restoration of the EGL might be an important therapeutic goal. An explanation for the phenomenon of context sensitivity of fluid volume kinetics is offered, and the proposal that crystalloid resuscitation from low capillary pressures is rational. Any potential advantage of plasma or plasma substitutes over crystalloids for volume expansion only manifests itself at higher capillary pressures.

Keywords: fluid therapy; intensive care
Leading to oedema in clinical practice emerged. Luft revealed 'the fine structure of the capillary and the endocapillary layer' in 1966, and Curry and Michel proposed a theory 'that the molecular sieving properties of the capillary wall reside in a matrix of molecular fibres which covers the endothelial cells and fills the channels through or between them' in 1980. Transvascular exchange depends on a balance between hydrostatic and oncotic pressure gradients. Fluid is filtered to the interstitial space under a dominant hydrostatic pressure gradient ($P_c - P_{is}$) at the arteriolar portion of capillaries, and it was believed that it is absorbed back under a dominant colloid osmotic pressure ($\Delta P_{cop}$) at the venular end. In 2004, Adamson and colleagues showed that the effect of $\Delta P_{is}$ on transvascular fluid exchange is much less than predicted by the standard Starling equation, which therefore has to be revised.

It is now established that non-fenestrated capillaries normally filter fluid to the ISF throughout their length. Absorption through venous capillaries and venules does not occur. $\Delta P_{cop}$ opposes, but does not reverse, filtration. Most of the filtered fluid returns to the circulation as lymph. Levick and Michel now propose that the small pore system of the transvascular semi-permeable membrane is the endothelial glycocalyx layer (EGL) where it covers the endothelial intercellular clefts, separating plasma from a 'protected region' of the subglycocalyx space which is almost protein-free. Subglycocalyx COP ($p_{sg}$) replaces $p_{is}$ as a determinant of transcapillary flow ($J_v$).

Plasma proteins, including albumin, escape to the interstitial space by a relatively small number of large pores, which are responsible for the increased $J_v$ observed in the early stage of inflammation, and may be susceptible to pharmacological intervention. The fact that low protein concentration within the subglycocalyx intercellular spaces accounts for the low $J_v$ and lymph flow in most tissues is a critical insight and the basis of the glycocalyx model.

The endothelial glycocalyx layer

The EGL is a web of membrane-bound glycoproteins and proteoglycans on the luminal side of the endothelial cells, associated with various glycosaminoglycans (GAGs) (mucopolysaccharides) which contribute to the volume of the layer (Fig. 1). It is the active interface between blood and the capillary wall. Visualization of the EGL is technically demanding, but has helped to emphasize its physiological importance.

From indocyanine green dilution studies of patients given a large dose of i.v. colloid, the human EGL volume was estimated to be about 700 ml, and presuming...

Healthy glycocalyx layer which contains glycosaminoglycans

Compressed glycocalyx, shedding or flaking glycosaminoglycans to the plasma

Endothelial cell

Endothelial glycocalyx layer

Glycosaminoglycans

Erythrocyte

Basement membrane/extracellular matrix
**Table 1** Comparison of the original and revised paradigms for prescribing fluid therapy

<table>
<thead>
<tr>
<th>Original Starling principle</th>
<th>Revised Starling equation and glycocalyx model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular volume consists of plasma and cellular elements</td>
<td>Intravascular volume consists of glycocalyx volume, plasma volume, and red cell distribution volume</td>
</tr>
<tr>
<td>Capillaries separate plasma with high protein concentration from ISF with low protein concentration</td>
<td>Sinusoidal tissues (marrow, spleen, and liver) have discontinuous capillaries and their ISF is essentially part of the plasma volume</td>
</tr>
<tr>
<td>Open fenestrated capillaries produce the renal glomerular filtrate</td>
<td>Open fenestrated capillaries produce the renal glomerular filtrate</td>
</tr>
<tr>
<td>Diaphragm fenestrated capillaries in specialized tissues can absorb ISF to plasma</td>
<td>Diaphragm fenestrated capillaries in specialized tissues can absorb ISF to plasma</td>
</tr>
<tr>
<td>Continuous capillaries exhibit ‘no absorption’</td>
<td>Continuous capillaries exhibit ‘no absorption’</td>
</tr>
<tr>
<td>The EGL is semi-permeable to anionic proteins and their concentration in the intercellular clefts below the glycocalyx is very low</td>
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</tr>
<tr>
<td>The important Starling forces are the transendothelial pressure difference and the plasma–interstitial COP difference</td>
<td>The important Starling forces are the transendothelial pressure difference and the plasma–subglycocalyx COP difference. ISF COP is not a direct determinant of $J_v$</td>
</tr>
<tr>
<td>Fluid is filtered from the arterial end of capillaries and absorbed from the venous end. Small proportion returns to the circulation as lymph</td>
<td>$J_v$ is much less than predicted by Starling’s principle, and the major route for return to the circulation is as lymph</td>
</tr>
<tr>
<td>Raising plasma COP enhances absorption and shifts fluid from ISF to plasma</td>
<td>Raising plasma COP reduces $J_v$ but does not cause absorption</td>
</tr>
<tr>
<td>At subnormal capillary pressure, net absorption increases plasma volume</td>
<td>At subnormal capillary pressure, $J_v$ approaches zero. Auto transfusion is acute, transient, and limited to about 500 ml</td>
</tr>
<tr>
<td>At supranormal capillary pressure, net filtration increases ISF volume</td>
<td>At supranormal capillary pressure, when the COP difference is maximal, $J_v$ is proportional to transendothelial pressure difference</td>
</tr>
<tr>
<td>Infused colloid solution is distributed through the plasma volume, and infused ISS through the extracellular volume</td>
<td>Infused colloid solution is initially distributed through the plasma volume, and infused ISS through the intravascular volume</td>
</tr>
<tr>
<td>At supranormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure, and increases $J_v$</td>
<td>At supranormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure, and increases $J_v$</td>
</tr>
<tr>
<td>At supranormal capillary pressure, infusion of ISS also raises capillary pressure, but it lowers COP and so increases $J_v$ more than the same colloid solution volume</td>
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</tr>
<tr>
<td>At subnormal capillary pressure, infusion of colloid solution increases plasma volume and infusion of ISS increases intravascular volume, but $J_v$ remains close to zero in both cases</td>
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</tr>
</tbody>
</table>
Estiramiento de miocitos

Activación neurohumoral: Estimulación inotrópica y cronotrópica

Sistemas compensatorios: Catecolaminas- Taquicardia

Desincronización ventricular

Hipoxia. Aumento del gradiente a-A e hipocapnia
Increased RV afterload

RV dilatation

RV wall tension

Neurohormonal activation

Myocardial inflammation

RV O₂ demand

RV O₂ delivery

RV coronary perfusion

Systemic BP

Low CO

LV pre-load

RV output

RV contractility

Death

Cardiogenic shock

TV insufficiency

RV ischaemia

Increased RV afterload
### CUADRO CLÍNICO

<table>
<thead>
<tr>
<th>Feature</th>
<th>PE confirmed (n = 1880)</th>
<th>PE not confirmed (n = 528)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>50%</td>
<td>51%</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Cough</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Substernal chest pain</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Fever</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Syncope</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Unilateral leg pain</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Signs of DVT (unilateral extremity swelling)</td>
<td>24%</td>
<td>18%</td>
</tr>
</tbody>
</table>
ABORDAJE

- Reglas de predicción estandarizada
- Wells o Ginebra
- Probabilidad clínica de la enfermedad
- 10% baja probabilidad
- 35% probabilidad intermedia
- 65% alta probabilidad
A multicentre, prospective management study evaluated this age-adjusted cut-off in a cohort of 3346 patients. Patients with a normal age-adjusted D-dimer value did not undergo computed tomographic pulmonary angiography and were left untreated and formally followed up for a three-month period. Among the 766 patients who were 75 years or older, 673 had a non-high clinical probability. On the basis of D-dimer, using the age-adjusted cut-off (instead of the ‘standard’ 500 mg/L cut-off) increased the number of patients in whom PE could be excluded from 43 (6.4%; 95% CI 4.8–8.5%) to 200 (29.7%; 95% CI 26.4–33.3%), without any additional false-negative findings.

D-dimer is also more frequently elevated in patients with cancer, in hospitalized patients, and during pregnancy.

### Table 4

<table>
<thead>
<tr>
<th>Items</th>
<th>Clinical decision rule points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wells rule</strong></td>
<td></td>
</tr>
<tr>
<td>Previous PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate ≥100 b.p.m.</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery or immobilization within the past four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td><strong>Clinical probability</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Three-level score</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0–1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2–6</td>
</tr>
<tr>
<td>High</td>
<td>≥7</td>
</tr>
<tr>
<td><strong>Two-level score</strong></td>
<td></td>
</tr>
<tr>
<td>PE unlikely</td>
<td>0–4</td>
</tr>
<tr>
<td>PE likely</td>
<td>≥5</td>
</tr>
</tbody>
</table>

b.p.m. = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism.

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2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
A multicentre, prospective management study evaluated this age-adjusted cut-off in a cohort of 3346 patients. Patients with a normal age-adjusted D-dimer value did not undergo computed tomographic pulmonary angiography and were left untreated and formally followed up for a three-month period. Among the 766 patients who were 75 years or older, 673 had a non-high clinical probability. On the basis of D-dimer, using the age-adjusted cut-off (instead of the ‘standard’ 500 mg/L cut-off) increased the number of patients in whom PE could be excluded from 43 (6.4%; 95% CI 4.8–8.5%) to 200 (29.7%; 95% CI 26.4–33.3%), without any additional false-negative findings.

D-dimer is also more frequently elevated in patients with cancer, in hospitalized patients, and during pregnancy. Thus, the number of patients in whom D-dimer must be measured to exclude one PE (number needed to test)

### Table 4

**Clinical prediction rules for PE**

<table>
<thead>
<tr>
<th>Item</th>
<th>Clinical decision rule points</th>
<th>Original version&lt;sup&gt;93&lt;/sup&gt;</th>
<th>Simplified version&lt;sup&gt;108&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revised Geneva score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous PE or DVT</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>75–94 b.p.m.</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>≥95 b.p.m.</td>
<td></td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Surgery or fracture within the past month</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pain on lower limb deep venous palpation and unilateral oedema</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Clinical probability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-level score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>0–3</td>
<td>0–1</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>4–10</td>
<td>2–4</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>≥11</td>
<td>≥5</td>
</tr>
<tr>
<td>Two-level score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE unlikely</td>
<td></td>
<td>0–5</td>
<td>0–2</td>
</tr>
<tr>
<td>PE likely</td>
<td></td>
<td>≥6</td>
<td>≥3</td>
</tr>
</tbody>
</table>
Suspected acute PE

Shock or hypotension\(^a\)?

Yes

High–risk\(^b\)

No

Not high–risk\(^b\)
Suspected PE without shock or hypotension

Assess clinical probability of PE
Clinical judgment or prediction rule

Low/intermediate clinical probability
or PE unlikely

D-dimer

negative

CT angiography

no PE

No treatment

Treatment

High clinical probability
or PE likely

CT angiography

no PE

PE confirmed

No treatment or investigate further

Treatment
Suspected PE with shock or hypotension

CT angiography immediately available

No

Echocardiography

RV overload

No

Search for other causes of haemodynamic instability

Yes

PE-specific treatment: primary reperfusion

CT angiography available and patient stabilized

No other test available or patient unstable

negative

CT angiography

positive

Search for other causes of haemodynamic instability

CT = computed tomographic; PE = pulmonary embolism; RV = right ventricle.

a Includes the cases in which the patient’s condition is so critical that it only allows bedside diagnostic tests.

b or patient unstable

c Thrombolysis; alternatively, surgical embolectomy or catheter-directed treatment (Section 5).
Risk stratification of patients with acute symptomatic pulmonary embolism

David Jiménez1 · Jose Luis Lobo2 · Deisy Barrios1 · Paolo Prandoni3 · Roger D. Yusen4

Table 1 Pulmonary Embolism Severity Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Years</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
</tr>
<tr>
<td>History of cancer</td>
<td>+30</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>History of chronic lung disease</td>
<td>+10</td>
</tr>
<tr>
<td>Pulse ≥110 beats/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
<td>+30</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt;36 °C</td>
<td>+20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
</tr>
<tr>
<td>Arterial oxyhemoglobin saturation (SaO2) &lt;90 %</td>
<td>+20</td>
</tr>
</tbody>
</table>

A total point score for a given patient is obtained by summing the patients age in years and the points for each predictor when present. The score corresponds with the following risk classes: ≤65, class I; 66–85, class II; 86–105, class III; 106–125, class IV; and >125, class V. Patients in risk classes I and II are defined as low risk.

Table 2 Simplified Pulmonary Embolism Severity Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80 years</td>
<td>1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1</td>
</tr>
<tr>
<td>History of chronic cardiopulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Pulse ≥110 beats/min</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mmHg</td>
<td>1</td>
</tr>
<tr>
<td>Arterial oxyhemoglobin saturation (SaO2) &lt;90 %</td>
<td>1</td>
</tr>
</tbody>
</table>

A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥1, high risk.
Table 3  Hestia criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamically unstable? (^a)</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis or embolectomy necessary?</td>
<td></td>
</tr>
<tr>
<td>Active bleeding or high risk of bleeding? (^b)</td>
<td></td>
</tr>
<tr>
<td>Oxygen supply to maintain oxygen saturation &gt; 90 % &gt; 24 h?</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism diagnosed during anticoagulant treatment?</td>
<td></td>
</tr>
<tr>
<td>Intravenous pain medication &gt;24 h?</td>
<td></td>
</tr>
<tr>
<td>Medical or social reason for treatment in the hospital &gt;24 h?</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance of less than 30 mL/min? (^c)</td>
<td></td>
</tr>
<tr>
<td>Severe liver impairment? (^d)</td>
<td></td>
</tr>
<tr>
<td>Pregnant?</td>
<td></td>
</tr>
<tr>
<td>Documented history of heparin-induced thrombocytopenia?</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1  Pulmonary embolism markers of severity

| Clinical variables               | PESI\(^\text{37}\)  
|                                | Simplified PESI\(^\text{18}\)  
| Right ventricular dysfunction   | Echocardiogram\(^\text{7}\)  
|                                | Computed tomography\(^\text{11}\)  
|                                | BNP or NT-proBNP\(^\text{41}\)  
| Clot burden                    | Concomitant deep vein thrombosis\(^\text{42}\)  
|                                | D-dimer\(^\text{43}\)  
|                                | Computed tomography\(^\text{44}\)  
| Myocardial injury              | cTnl or cTnT\(^\text{12}\)  
|                                | hsTnT\(^\text{45}\)  
|                                | H-FABP\(^\text{46}\)  

Current Controversies and Areas of Ongoing Research.

Phase 3 trials investigating the new, non-vitamin K-dependent oral anticoagulant agents (NOACs) apixaban (30), dabigatran (31,32), edoxaban (33), and rivaroxaban (34,35) in the treatment of VTE have been completed and published. A meta-analysis showed that these agents are noninferior to the standard heparin/VKA regimen, in terms of prevention of VTE recurrence (relative risk [RR]: 0.90; 95% confidence interval [CI]: 0.77 to 1.06), and that they are probably safer in terms of major bleeding (RR: 0.61; 95% CI: 0.45 to 0.83), particularly intracranial (RR: 0.37; 95% CI: 0.21 to 0.68) and fatal hemorrhage (36). A result, NOACs are recommended in the 2014 ESC Guidelines as an alternative to the standard heparin/VKA treatment (4). All 4 NOACs mentioned earlier are now licensed for treatment of VTE in the United States and the European Union (edoxaban still awaits approval in Canada); the approved regimens are summarized in Table 1.

Post-marketing experience with these drugs in clinical practice (under "real-world" conditions) appears reassuring in the setting of stroke prevention in atrial fibrillation, and has also begun to accumulate in VTE. In a prospective German registry of patients treated with rivaroxaban, rates of major bleeding for patients with VTE were 4.1% per year (95% CI: 2.5% to 6.4% per year), and case fatality rates were low (approximately 5% at 30 days) (37). Importantly, available data suggest that the first reversal agent against a NOAC, the monoclonal antibody idarucizumab, which binds the thrombin inhibitor dabigatran, is effective in emergency situations (38); this is expected to obtain U.S. Food and Drug Administration approval soon. In parallel, phase 3 clinical trials are currently being conducted with andexanet, a modified recombinant form of factor Xa, which is catalytically inactive (39) and may serve as a reversal agent for rivaroxaban, apixaban, and edoxaban.

Single oral drug regimens for PE might be expected to improve (reduce) patients’ perceived burden of treatment.

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**CENTRAL ILLUSTRATION** Acute PE: Current Risk Stratification

<table>
<thead>
<tr>
<th>Early Mortality Risk</th>
<th>Risk Parameters and Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or Hypotension</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate-high</td>
</tr>
<tr>
<td></td>
<td>Intermediate-low</td>
</tr>
<tr>
<td>Low</td>
<td>−</td>
</tr>
</tbody>
</table>

*Markers of myocardial injury (e.g., elevated cardiac troponin or heart type-fatty acid-binding [H-FABP] plasma concentrations), or of right ventricular dysfunction (elevated natriuretic peptide plasma concentrations). Adapted with permission from the 2014 European Society of Cardiology Guidelines on the Diagnosis and Management of Pulmonary Embolism (4). PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index.
OTROS MARCADORES DE RIESGO EN RIESGO INTERMEDIO

- Taquicardia
- Taquipnea
- Hipoxia
ABORDAJE

- sPESI
- BNP
- CCUS

Combinación de variables:
  - Daño miocardio
  - Disfunción de VD
  - Presencia de TVP concomitante
for those patients who received an IVC filter (relative risk with filter, 2.00; 95% CI, 0.51–7.89; \( p = 0.5 \)).

In summary, although some observational data suggest that IVC filter placement in addition to anticoagulation might improve survival in patients with unstable PE or after thrombolytic therapy, controlled data do not support its routine use in patients at high risk of death unless there is a contraindication to anticoagulant therapy.

Clinical Algorithm

Management algorithms need to incorporate the probability of PE-related complications, the accuracy of the available prognostic tests, the potential benefits and harms of aggressive treatments, the risk of bleeding, and patient preferences. Based on information from prospective studies and on the authors’ clinical experience, we propose a treatment strategy according to risk stratification of patients with acute PE (►Fig. 1). This algorithm will change as the evidence base evolves. The authors propose that this decision algorithm should supplement and not replace clinical judgment.

Hemodynamic status remains the most important short-term prognostic factor for patients with acute PE. Guidelines recommend the use of thrombolytic therapy for patients with acute symptomatic PE and hemodynamic instability (i.e., high-risk PE) that do not have major contraindications owing to bleeding risk. Alternatively, if expertise is available, thrombus removal may be achieved by infusion of lower doses of thrombolytic drug directly into the thrombus, by catheter-based fragmentation and aspiration of thrombus, by use of these two modalities together, or by surgical embolectomy.

These techniques may be preferred if there is a high risk of bleeding or a poor response to systemic thrombolysis. Bolus systemic thrombolytic therapy could be considered in urgent situations with hemodynamic instability, although fewer data have been published with this approach.

Intravenous unfractionated heparin should be administered to high-risk PE patients as the preferred mode of initial anticoagulation.

For hemodynamically stable patients with PE, the categorization of risk for subgroups may assist with decision making regarding PE therapy. Clinical models (e.g., Pulmonary Embolism Severity Index [PESI] or sPESI) may accurately identify those at low risk of short-term death, and such patients might benefit from abbreviated hospital stay or outpatient therapy.

It has been suggested that only patients that have tachycardia or borderline low blood pressure should proceed to further testing with cardiac biomarkers (e.g., troponin) or RV imaging to identify those at intermediate risk of PE-related complications.

Careful monitoring and rescue fibrinolysis for intermediate-risk PE patients who experience hemodynamic compromise or deterioration while receiving standard anticoagulant therapy can minimize...
Hemodynamic management in the ICU

Although data are lacking from clinical trials in humans, recent guidelines of the European Society of Cardiology recommended the following support:

1. Use volume expansion with caution.
2. Use norepinephrine infusion to improve RV function if necessary when blood pressure is low.
3. Ventilate patients, when required, with a low tidal volume and plateau pressure.

A proposal for hemodynamic management is presented in Fig. 1.

Historically, dobutamine was considered as the reference drug in case of hypotension/shock, although without strong evidence. Jardin et al. reported in a very small series of 10 patients spontaneously breathing that a 30-min dobutamine infusion (8.3 ± 2.7 µg/kg/min) significantly increases cardiac index and also reduces pulmonary vascular resistance [21].

Probably that the main interest of dobutamine compared to norepinephrine is that its infusion can easily done through a peripheral venous catheter.

One study performed in humans with intermediate-risk PE has reported that increase in cardiac output was inversely correlated with RV dilatation before fluid expansion [22]. The larger the right ventricle, the lower the positive effect on cardiac output and hemodynamics.

Moreover, an experimental study in PE has shown that volume expansion could be deleterious by increasing RV stress and then decreasing cardiac output and blood pressure by its deleterious consequences on the left ventricle [23]. Conversely, rather than increasing RV overload by fluids, norepinephrine infusion has been reported as very efficient to support the right ventricle and to increase the cardiac output when the blood pressure is low [23, 24]. It especially acts by restoring the coronary perfusion pressure [25]. A study performed in a canine model of PE with shock has also reported that all dogs treated with norepinephrine were resuscitated and remained hemodynamically stable for 1 h, whereas all dogs treated with volume or isoproterenol died [26].

It is very unusual to have patients with PE under mechanical ventilation. It mainly occurs after cardiac arrest or for refractory shock. Positive pressure ventilation may be avoided when possible because it is deleterious by more increasing the RV afterload. If needed, it is recommended to limit the tidal volume and the plateau pressure.

A few treatments have been proposed but cannot be currently recommended due to the lack of data. In a few

---

**Fig. 1.** Proposal for hemodynamic management in high-risk PE:

- *in the absence of contraindication; **may improve the coupling between the right ventricle and the pulmonary circulation by increasing the RV contraction and decreasing the pulmonary vascular resistance.

- RV right ventricle, LV left ventricle, CTPA computed tomography pulmonary angiography, CO cardiac output, MV mechanical ventilation, NO nitric oxide inhalation, VA ECMO veno-arterial extracorporeal membrane oxygenation.
Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*
Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-analysis

Saurav Chatterjee, MD; Anasua Chakraborty, MD; Ido Weinberg, MD; Mitul Kadakia, MD; Robert L. Wilensky, MD; Partha Sardar, MD; Dharam J. Kumbhani, MD, SM, MRCP; Debabrata Mukherjee, MD, MS; Michael R. Jaff, DO; Jay Giri, MD, MPH

2115 pacientes
Hemodinámicamente estables, disfunción del VD (riesgo intermedio)
2115 pacientes
Mortalidad y hemorragia mayor
Disminución de mortalidad, incremento de hemorragia mayor
NO pacientes estables sin datos de disfunción de VD
Thrombolysis for acute intermediate-risk pulmonary embolism: A meta-analysis

Guang-yuan Gao, Ping Yang, Miao Liu, Mei Ding, Guo-hui Liu, Ya-liang Tong, Chun-yan Yang, Fan-bo Meng *

Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun, China

- Evaluación de mortalidad, hemorragia, recurrencia
- 1755 pacientes
- Disminución de la mortalidad, así como el riesgo a pesar del riesgo de hemorragia mayor y menor
Regular Article

Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: A meta-analysis

Antoni Riera-Mestre a, *, Cecilia Becattini b, Michela Giustozzi b, Giancarlo Agnelli b

a Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat Barcelona Spain
b Internal and Cardiovascular Medicine, Stroke Unit, University of Perugia, Perugia Italy

1833 pacientes

No existe evidencia de reducción de mortalidad

Incremento del riesgo de HIC y hemorragia mayor
Further considering the risks and benefits, simplifying the existence of variable contraindications. The degree of hemodynamic compromise posed. A sample algorithm to help in triaging patients by discussion with the patient and family members, including the presenting history, vital signs, CT, echocardiogram, and lab data. The most important data include the presenting history, with a focus on symptoms and signs of hemodynamic instability, the level of risk and optimal therapy for each individual patient.

Once the PERT has been activated, members typically do not require "do not resuscitate" orders. Anticoagulation initiated, unless contraindicated. Acute PE confirmed by Computed Tomography (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
of all fibrinolysis trials, including patients with catheter-directed fibrinolysis (CDF), demonstrated a statistically significant mortality benefit from fibrinolysis in patients with intermediate-risk PE. There was a significantly increased risk of hemorrhage, but the benefits appeared to outweigh the risks when the analysis excluded patients older than 65 years of age. Importantly, subanalyses of patients younger than 65 years of age were performed post hoc in the trials included in the meta-analysis.

Taken together, these studies show that the use of IV fibrinolytic therapy in patients with massive or submassive PE leads to improved hemodynamic stabilization and, possibly, a lower risk of recurrent PE and PE-attributed death. However, this benefit comes with an increased risk of severe bleeding and intracranial hemorrhage.

**CATHETER-BASED THERAPIES**

Catheter-based therapies aim to relieve obstruction quickly and restore pulmonary blood flow, thus improving cardiac output and converting a hemodynamically unstable situation into a stable one. This is accomplished with reduced or no doses of fibrinolytic agents. Catheter-directed therapies (CDT) might include clot fragmentation, aspiration, and low-dose fibrinolytic injection. The American Heart Association and American College of Chest Physicians guidelines address catheter-based management of PE.

**FIGURE 1**

**ER PE Protocol Utilizing PERT**

**PE confirmed: Anticoagulate**

**Stable patient**

- Low risk PE pt sPESI* 0
- Submassive PE suspected sPESI ≥ 1

**Unstable patient**

- Massive PE (SBP < 90)
  - PERT consult
  - 1. Discuss IV lytics/catheter/surgery with PERT leader
  - 2. If lytics, consider initiation in ER

**Stable patient**

- Echo + Troponin
  - Echo and troponin (-) for RV dysfunction
  - Echo or troponin (+) for RV dysfunction

**Anticoagulate, admit to medicine floor**

**Admit to critical care unit**

*Simplified pulmonary embolism severity index (sPESI) score = 1 point for age > 80 years, cancer, chronic heart failure or chronic pulmonary disease, heart rate > 110 beats/min, SBP < 100 mm Hg, or O₂ saturation < 90%.

Adapted with permission from Bloomer et al. (6). Echo = echocardiography; ER = emergency room; IV = intravenous; PE = pulmonary embolism; PERT = pulmonary embolism response team; RV = right ventricular; SBP = systolic blood pressure.
DOSIS DE FIBRONOLÍTICOS ¿50 O 100 MG ALTEPLASE?
Pulmonary Embolism

Figure 2

A filter canister, allowing clot capture utilizing a centrifugal pump canister, cannula used in cardiopulmonary bypass (ing the centrifugal pump and venous reinfusion venous catheter that can remove soft thrombi utilizing the AngioVac thrombectomy device.

Figure 3

Diagram of AngioVac insertion and reinfusion circuit. The cannula

Saline Bag

Circuit

AngioVac Cannula

Centrifugal Pump Console

Filter

Reinfusion Cannula

AngioVac Circuit

FIGURE 3 FlowTriever Device

A

B

AGC

FRC

RAD
wires may be inserted into the catheter and utilized in a gentle back-and-forth motion to
...The 6- to 8-F straight or angled aspiration catheter (CAT6 or CAT8, respectively)
...et al
...Pulmonary Embolism
...Penumbra Indigo Aspiration System
...ev3 Endovascular Inc.), the Fountain catheter (Merit
...Commonly available infusion catheters used off-
...thromboplastin time on the low end of the ther-
...between 12 and 24 mg, delivered over 6 to 24 h. Low-
...to potentially reduce bleeding risk is to hold the hep-
...Maintenance of anticoagulation post-intervention is
...tomy as a...
...FIGURE 6 EkoSonic Endovascular Device
...FIGURE 6
...}

### FIGURE 1  PE: Risk-Adjusted Management in the Acute Phase and Over the Long Term

<table>
<thead>
<tr>
<th>Pre-test</th>
<th>Diagnosis</th>
<th>ACUTE RISK STRATIFICATION</th>
<th>Treatment</th>
<th>Long-term Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Assessment</td>
<td>(Age-adjusted) D-dimers</td>
<td>PESI and sPESI</td>
<td>Parenteral anticoagulants</td>
<td>Assess bleeding risk</td>
</tr>
<tr>
<td></td>
<td>CTPA</td>
<td>Biochemical markers*</td>
<td>Oral anticoagulants</td>
<td>Predict VTE recurrence</td>
</tr>
<tr>
<td></td>
<td>V/Q scan</td>
<td>RV dysfunction (echocardiography)</td>
<td>Fibrinolytics</td>
<td>Focused screening for CTEPH in symptomatic patients</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td>RV enlargement (CTPA)</td>
<td>Catheter-directed techniques</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CUS</td>
<td></td>
<td>Surgical embolectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vena cava filters</td>
<td></td>
</tr>
</tbody>
</table>

#### ALGORITHM FOR HIGH-RISK PE

- CTPA
- Echocardiography (if CTPA not readily available or uncontrolled hypotension)

#### ALGORITHM FOR NON HIGH-RISK PE

- CTPA
- V/Q scan

**HIGH RISK**

- Hemodynamic instability

**INTERMEDIATE RISK**

- INTERMEDIATE-HIGH
- INTERMEDIATE-LOW

**LOW RISK**

**PRIORITY REPERFUSION**

- ANTICOAGULANT THERAPY

**ANTICOAGULANT THERAPY**

- (Rescue reperfusion)
- (Early discharge)

**IMMobilization**

- Trauma or fracture
- Hormonal contraception
- Hormonal replacement treatment
- Surgery
- Pregnancy and postpartum

**Thrombophilia†**

- Inflammatory bowel disease
- Obesity
- Cancer chemotherapy
- D-dimers
- First unprovoked VTE event

**Prior VTE**

- Active cancer
- Male sex

**Risk Factors for Recurrent VTE**

- Age
- Chronic heart failure
- Chronic lung disease
- Active cancer
- Hypoxemia
- RV dysfunction (CT/ECHO)
- Biochemical markers*

**Predictors of Early Adverse Outcome**

- Vitalsigns
- Hypoxemia
- Biochemical markers*
CONCLUSIONES

- Alta sospecha diagnóstica
- Prevención
- Elevada mortalidad
- Toma de decisiones oportuna
- Intervencionismo, probable futuro