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Risk management in acute pulmonary embolism

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Abstract
Pulmonary embolism (PE) is a common disease in clinical practice, burdened by high morbidity and mortality. In the last years much evidence has shown that early mortality is related to haemodynamic compromise and/or right heart dysfunction (RHD). About 5-10% of patients with PE presents with shock and should be treated by thrombolysis if not contraindicated and closely monitored. This kind of presentation is commonly known as massive PE; much recently it has been defined as high risk PE according to the most recent European Society of Cardiology (ESC) guidelines based on early mortality risk assessment. In this situation mortality is more than 15%. About 50% of patients with PE are normotensive at the time of presentation and they have neither echocardiographic nor laboratory signs of RHD. This kind of presentation has been defined as non-massive PE or low risk PE by ESC guidelines. Mortality is low, less than 3%, and treatment with low molecular weight heparins or fondaparinux is widely recommended, such as rapid hospital discharge. Between this situations, a window is represented by the patients which are normotensive but with echocardiographic and/or laboratory signs of RHD. This kind of presentation has been defined as sub-massive PE or, much recently, at intermediate risk;

early mortality ranges from 3 to 15%. This not negligible percentage of patients with PE, around 40%, remains the major area of uncertainness in the field of PE treatment. It's uncertain in fact whether this group of patients could receive benefit from thrombolysis or not. Although literature meta-analysis has failed to demonstrate superiority of thrombolysis compared to conventional treatment with heparins, a multicenter trial is ongoing whom results should clarify this hot topic.
Therefore prognostic stratification of acute PE is of utmost importance, since than modern guidelines indicate to customize treatment according to early mortality risk based on clinical findings, echocardiogram, computer tomography pulmonary angiography and laboratory biomarkers, especially represented by cardiac troponins and natriuretic peptides, but which is the best strategies and whether the combination of these parameters improves risk management remain unresolved questions.
In this chapter the Authors review the modern approach to PE treatment based on early risk mortality stratification.

1. Background

Pulmonary embolism (PE) is still one of the leading medical emergencies in clinical practice, burdened by high mortality and morbidity, especially when presentation is associated to cardiac arrest, shock, haemodinamic instability or right heart dysfunction (RHD) (Wood KE 2002). Incidence of PE increases steadily with age both for common population and for hospitalized patients (Silverstein MD et al. 1998, Stein PD et al. 2002, White RH 2003). Population studies reveal that incidence of PE increases from around 30/100.000 inhabitants per year in class of age under 45 years to around 700 cases/100.000 inhabitants per year in 85-years old and older people (Silverstein MD et al. 1998, Spencer FA et al 2006). Based on these data, PE could account for around 150.000-600.000 diagnoses per year in United States with thousands of related deaths (White RH 2003, Wood KE 2002). PE accounts for 0.3-0.4% of all hospital admissions and for 5-10% for all hospital deaths (Stein PD et al 2002, White RH 2003, Aylin P et al 2008). PE hospital incidence increases from 0.04% of admissions for patients under 50 years compared to 0.72% for patients over 50 years (Stein PD et al. 2002). Hospital register demonstrate that elderly people accounts for a great percentage of PE patients; in the ICOPER study around 40% of patients were 70 years old and older (Goldhaber SZ et al 1999).
Acute mortality burden of PE remains severe, two weeks and three months mortality being respectively 11.4% and 17.4% (Goldhaber SZ et al 1999). Acute mortality is strongly influenced by clinical presentation. Patients presented with cardiac arrest die in more than 70% of cases, whereas mortality is more than 30% in patients with shock. In the ICOPER study 58.3% of patients presented with haemodinamic instability died within three months compared to 15.1% of patients without instability (Goldhaber SZ et al 1999). Deaths directly due to PE occur for around 10% in the first hour, for 32.2% in the first 24 hours, for 67.7% in the first week and for 90.3% in the first month (Wood KE 2002, Miniati M et al 2006).
Although PE remains under-suspected and under-diagnosed especially in elderly patients (Leibovitz A et al 2001, Masotti L et al 2008), guidelines on diagnosis have had wide diffusion in the last years with strategies based on pre-test clinical probability, D-Dimers levels, legs ultrasonography, computer tomography pulmonary angiography (CTPA) or scintigraphic lung scan (BTS 2003, ACEP 2003, Cristopher Study Investigators 2006, Stein PD et al 2007,

Righini M et al. 2008, Tapson VF 2008, Torbicki A et al 2008). High clinical suspicion represents the most important step to rule in or out the diagnosis of PE. It derives from combination of history focused on research of risk factor of venous thromboembolism (VTE), clinical examination completed by arterial blood pressure measurement (BP) and results of first levels tools such as 12-leads electrocardiogram (ECG), chest X-ray and arterial blood gas analysis (BGA). If suspect of PE is funded, pre-test clinical probability should be performed by using standardized scores such as Wells or Geneva scores, both revised in the last years (Wells PS et al 1998, Wicky J et al 2001, Cristopher Study Investigators 2006, Le Gal G et al 2006, Klok FA et al 2008). These scores identify three classes of patients with low, moderate or high pre-test probability for PE. Wells score has been recently modified according to criteria used in Cristopher Study and in this formulation it identifies only two classes of patients, one with high (>4 points) and one with non high probability for PE (≤ 4 points) (Cristopher Study Investigators 2006). In low-moderate or non high probability patients, D-Dimer assay by using ELISA or immunoturbidimetric methods, should be performed. In patients with combination of low-moderate or non high probability and D-Dimer negative, PE can be safely excluded, whereas in patients with D-Dimer positive or in patients with high probability, second line tools should be performed for ruling in or ruling out the diagnosis (BTS 2003, Torbicki A et al 2008). Second line tools are represented by multidetector computer tomography pulmonary angiography (CTPA) or scintigraphic lung scan, criteria of this last one have been much recently revised (Sostman HD et al 2008). Pulmonary angiography may represent a third line tool when diagnostic doubts remain after the above mentioned examinations (BTS 2003, Torbicki A et al 2008). In patients with suspected PE and moderate-high pre-test probability, legs ultrasonography positive for proximal deep vein thrombosis permits to rule in the diagnosis of PE and to drop out from diagnostic work-up. Strategy based on legs ultrasonography should be especially encouraged in special subgroups of patients with suspected PE, such as elderly, renal failure and pregnancy (Torbicki A et al 2008). Trans-thoracic echocardiography for diagnosis of PE is fundamental in patients with shock for differential diagnoses, where the absence of RHD could rule out PE (Goldhaber SZ 2002, Torbicki A et al 2008).

Concomitantly to diagnostic guidelines, modern concepts about treatment based on early mortality risk have emerged in the last years. Risk assessment can be performed by using many of the diagnostic tools together with other complementary tools. Early mortality risk assessment represents one of the main key points much recently emerged in the field of PE, but which is the best strategy for performing it remains the major challenge.

This chapter focus on early mortality risk based management of PE.

1.1 Haemodynamic and respiratory consequences of acute PE

The understanding of the pathophysiological response to acute PE is of utmost importance for risk assessment and management of PE. Haemodynamic consequences proved by the tromboemboli reflect the (i) size of pulmonary artery blood flow obstruction, (ii) pre-existing cardiopulmonary diseases, and (iii) release of vasoactive humoral factors from clots (Wood KE 2002, Kucher N et al 2006, Tapson VF 2008). The mechanical obstruction induced by the clots, together with the pulmonary artery vasoconstriction stimulated by neuro-humoral substances (such as serotonin from platelets, thrombin from plasma, and histamine from

tissue) and hypoxia due to ventilation/perfusion mismatch (areas of lung ventilated but not perfused with flow re-distribution), determine first of all an increasing of pulmonary vascular resistances. It could prove an acute volume and pressure right ventricle (RV) overload, which in turn can result in RV dilatation. In normal condition the ratio between diameters of RV and left ventricle (LV) is around 0.5-0.7. When pressure and volume RV overload is present, RV/LV ratio could increase until values superior to 1.0. This condition proves the shift toward LV of the interventricular septum, whom mobility could be impaired. Concomitant hypokinesis and ischemic sufferance of myocardial wall of RV and interventricular septum could verify. Pressure overload of RV could lead to tricuspidal valve regurgitation with secondary volume and pressure overload on right atrium. An important parameter of right heart dysfunction, the systolic pulmonary arterial pressure (PAP), is quantified on echocardiography by tricuspidal valve regurgitation. When increased, systolic PAP could be an indirect parameter reflecting the increasing on pulmonary resistances. RHD could determine important consequences on LV. The RV dilatation could prove the collapse of LV, leading to reduction of its pre-load with secondary low LV output and systemic hypotension which in turn could lead to reduction in systemic and coronary perfusion. Shock, cardiac arrest and death could be the dramatic scenario of these extreme consequences (Wood KE 2002, Kucher N et al 2006, Tapson VF 2008).

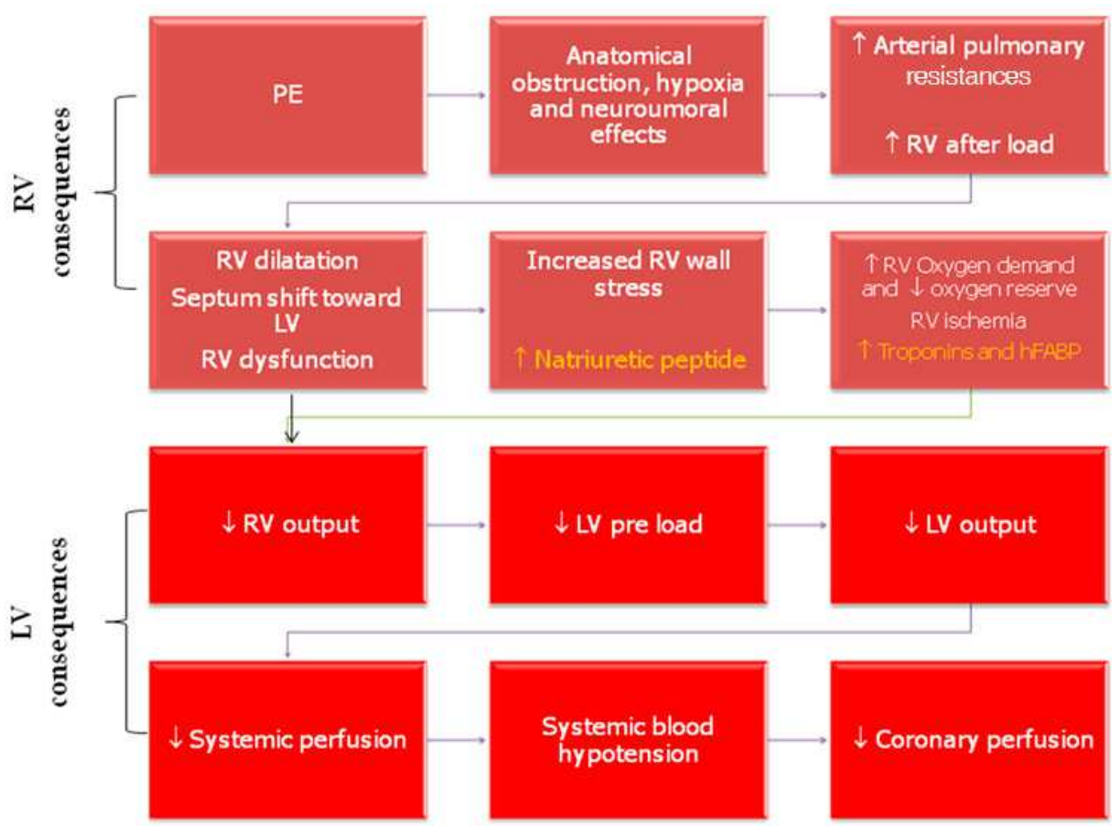


Fig. 1. Pathophysiology of haemodinamic instability in acute PE

Haemodynamic consequences of acute PE could explain the increase of biomarkers used as prognosticators. Cardiac troponins (cTn) and hearty type fatty acid binding protein (hFABP) are released in the bloodstream in presence of myocardial damage secondary to RV microinfarctions (Azzazy H et al 2006, Becattini C et al 2008), whereas natriuretic peptides (NP) reflect the RV volume overload and secondary RV wall stress due to pressure overload (Daniels LB et al 2007). Figure 1 summarizes the haemodynamic picture in acute PE.
The respiratory consequences of acute PE mainly derive from ventilation/perfusion mismatch which lead to hypoxia (Santolicandro A et al 1995). Dyspnoea represents the main symptom; compensatory hyperventilation is viewable and clinical signs are tachypnea and tachycardia. The final picture is represented by acute respiratory failure associated to hypoxemia, hypocarbia and low arterial oxygen saturation (Santolicandro A et al 1995, Tapson VF 2008).

1.2 Clinical presentation of PE and risk assessment

Old classifications divided PE in massive and non-massive, based on burden, shape and distribution of pulmonary thromboemboli (Wood KE 2002). Massive PE, which accounts for 5-10% of total diagnoses, identifies the condition in which pulmonary arterial tree is obstructed bilaterally and for more than 50%. This entity is life-threatening and presentation is generally dramatic and characterized by haemodynamic compromise. Manifestations of massive PE could be represented by sudden death, cardiac arrest, cardiogen shock, collapse, syncope or blood arterial hypotension, defined as arterial blood pressure less than 90 mmHg or a drop of 40 mmHg for at least than 15 minutes (Wood KE 2002, Kucher N et al 2006). In the other side non-massive PE represents the entity with an anatomical burden characterized by flow obstruction inferior to 50% of entire arterial pulmonary vascular tree; the key point of non massive PE is represented by haemodynamic stability with normal arterial blood pressure, which is present in 90-95% of patients with PE (Wood KE 2002). However the demonstration that a not negligible group of normotensive PE patients, accounting for 40-45% of PE, presents echocardiographic RHD and higher mortality ranging from 3% to 15% compared to normotensive patients without RHD (mortality < 3%) (Goldhaber SZ et al 1999), has conducted to classify an intermediate presentation between massive and non massive, this one defined as sub-massive PE, in which anatomical burden could be between 30% and 50% (Tapson VF 1999, ESC 2000, BTS 2003, ACEP 2003). It should be underlined that the cardiopulmonary reserve could influence the response to pulmonary vascular tree obstruction. A vascular obstruction more than 50% in fact could present with haemodynamic stability for example in a young patients with normal cardiopulmonary status, whilst haemodynamic compromise could verify for example in a old patient with anatomical non massive PE but affected by cardiopulmonary diseases (Wood KE 2002).
Since then the old classifications could bring to misleading interpretations, the last guidelines on diagnosis and treatment of PE diffused in 2008 by European Society of Cardiology (ESC) suggest defining PE according to classes of risk for adverse prognosis and early mortality (Torbicki A et al 2008). Therefore ESC suggests to divide PE in high risk when haemodynamic instability is present and therefore previously corresponding to massive PE, and non high risk when haemodynamically stable; within non high risk (normotensive) patients, PE could be divided in intermediate risk (normotensive PE plus signs of RHD and/or signs of myocardial damage) and in low risk (normotensive without signs of RHD and myocardial damage)(Torbicki A et al 2008). While, for definition, high risk

patients require only objective evaluation together with arterial blood pressure measurement and other tools are not necessary, non high risk patients require echocardiogram and biomarkers evaluation for better customizing them. The contemporary absence of echocardiographic or biomarkers signs of RHD and myocardial damage identifies the low risk PE, whereas the presence alone or in combination of echocardiographic and biomarkers signs of RHD and/or myocardial damage identifies intermediate risk PE. Figure 2 shows old and new criteria for defining PE presentation (Torbicki A et al 2008).

Entity	Anatomical burden of flow obstruction	Objective haemodynamic compromise	RHD	Early mortality risk	Clinical presentation
Massive	> 50%	yes	yes	High (> 15%)	Sudden death, cardiac arrest, cardiogen shock, collapse, syncope, hypotension
Sub-massive	30-50%	no	yes	Intermediate (3-15%)	Permanent severe dyspnoea, ischemic chest pain
Non-massive	< 30%	no	no	Low (< 1%)	Mild dyspnoea or tachypnea and tachycardia, pleuritic chest pain

Fig. 2. Synthesis of old and new clinical classification of acute PE

Since then when properly and quickly started, treatment is usually effective in the majority of patients and high risk and non high risk patients should receive different management strategies, the appropriate treatment of acute PE.

2. The risk stratification of acute PE

2.1 Clinical parameters and scores

Although many clinical parameters have been associated to early mortality risk, ***shock*** and/or ***hypotension*** at presentation remains the most important clinical sign of short term poor prognosis in patients with acute PE (Wood KE 2002, Kucher N et al 2006, Becattini C et al 2007, Torbicki A et al 2008). In fact the presence of haemodynamic decompensation or shock is associated to 2.4-15.1 fold increase in early risk mortality (Aujesky D et al 2009). In the ICOPER Study, the 3-months total mortality rate was 17.4%. However mortality rate was 58.3% in patients who were haemodynamically unstable at the time of presentation and 15.1% for those who were haemodynamically stable (Goldhaber SZ et al 1999).

Other main clinical variables associated to poor prognosis are represented by age over 70 years, history of bed rest over five days, cancer, chronic obstructive pulmonary disease, renal failure, heart failure and cardiovascular diseases, tachycardia and syncope as main

presentation (Aujesky D. et al 2009). Figure 3 reports the risk of early mortality associated to clinical variables.

Variables	Adjusted risk ratio
Age > 70 years	1.6
Male gender	1.2
Heart failure	1.4-2.6
Cancer	2.3-9.5
Chronic obstructive pulmonary disease	1.3-1.8
Previous deep vein thrombosis	2.8
Bed rest over 4 days	2.9
Heart rate ≥ 110 beats for minute	1.8
Respiratory rate ≥ 30 acts for minute	1.5
Systolic blood pressure ≤ 90 mmHg	2.4-15.1
Body temperature ≤ 36°C	1.5
Altered mental status	4.5
Arterial oxygen saturation ≤ 90% or arterial oxygen partial pressure ≤ 60 mmHg	1.8-2.6

From Aujeski D. et.al. 2009

Fig. 3. Odds ratio for adverse outcomes of clinical variables in acute PE

In the last years many of these clinical variables have been enclosed in practical scores aimed to identify early mortality risk and customize treatment in different settings. The Pulmonary Embolism Prognostic Index (***PESI)*** and Geneva Prediction Rule (***GPR***) represent two clinical scores identifying classes of patients with increased risk of adverse outcomes (Wicki J et al 2000, Aujesky D. et al 2007). PESI identifies five classes with increased risk of death; low risk patients (classes I and II) have an early mortality risk ≤ 1.2%, whereas classes III, IV and V have respectively a risk of early death of 4.8%, 13.5% and 25% (Aujesky D et al 2007). GPR encloses six variables; risk of adverse events (death, VTE recurrence, major bleedings) linearly increases with increasing pointing, being 2.2% in patients with GPR ≤ 2, 20.5% for GPR 3-4, 70% for GPR 5-6 (Wicki J et al 2000). Both scores reliably identify low-risk patients with PE who are potential candidates for less costly outpatient treatment. The major strength of these scores is their easy execution in all clinical setting and their reproducibility (Chan CM et al 2010). When these clinical scores are compared between themselves, PESI seems to predict better than GPR the low risk patients candidate to be at home treated (Jimenez D et al 2007). PESI and GPR are shown in Figure 4.

Shock index is an interesting and easily performable clinical parameter for prognostic assessment. It identifies the ratio between heart rate in beats for minute and systolic blood pressure in mmHg (HR/SBP). When its value is over 1, shock index detects high risk for adverse outcome patients. This value in fact has been showed to be related to in-hospital mortality and is highly sensitive although poorly specific to predict poor prognosis alone or in combination with echocardiographic findings (Otero R et al 2007, Toosi MS et al 2008).

• P.E.S.I

• Predictors	Score
• Age	years
• Male sex	+10
• Cancer	+30
• Heart failure	+10
• Chronic obstructive pulmonary disease	+10
• Heart rate ≥ 110 bpm	+20
• Systemic blood pressure < 100 mmHg	+30
• Respiratory Rate ≥ 30	+20
• Body temperature < 36°C	+20
• Delirium	+60
• Arterial oxygen saturation < 90%	+20

Total _____

Low risk
≤ 65 class I
66-85 class II
High risk
86-105 class III
106-125 class IV
> 125 class V

• G.P.R.

Predictors	Points
Cancer	+2
Heart failure	+1
Previous DVT	+1
Hypotension	+2
Hypossemia	+1
DVT	+1

Total_____

Fig. 4. Pulmonary embolism severity index and Geneva prognostic rule

2.2 Imaging

12-leads electrocardiography (ECG) represents a first level diagnostic tool in acute PE. Although ECG does not seem to be a reliable marker of severity of PE, some findings, especially represented by presence and number of T waves inversion in precordial leads and QR in V1, seem to be associated to poor prognosis in patients with acute PE (Jimenez D et al 2005, Toosi MS et al 2007). Much recently it was reported that ECG signs of RV strain represented by complete or incomplete right bundle branch block, S1Q3T3 and negative T waves in V1-V4 precordial leads have adverse outcomes in acute PE independently from echocardiographic signs of RHD with an hazard ratio of 2.58 (95% CI, 1.05-6.36)(Vanni S et al 2009).

Trans-thoracic echocardiography remains the gold standard for showing the RHD. It is non invasive, easily available in many emergency cardiovascular settings and it is inexpensive and repeatable (Vieillard-Baron A. et al 2001, Goldhaber SZ 2002, Kreit JW 2004). Figure 5 shows the main echocardiographic findings of RHD detectable in acute PE.

- **Qualitative**

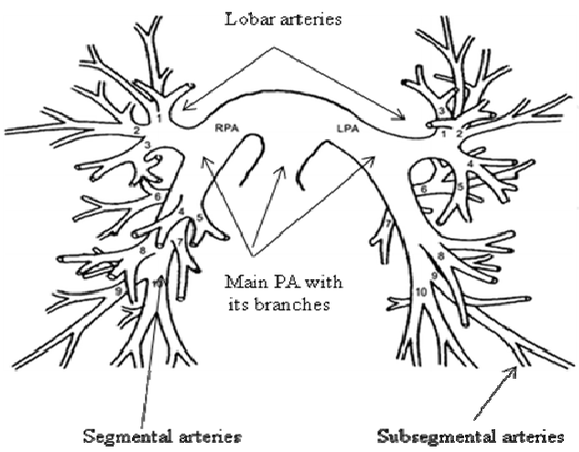
- **RV hypocinesis (mild, moderate, severe)**
- **McConnell sign (RV hypocinesis with normal contractility of apix)**

- **Quantitative**

- **RV dilatation**
  - **Four chambers end-diastolic RV/LV diameters ratio > 1.0**
  - **Four chambers end-diastolic RV diameters > 30 mm**
- **Pulmonary hypertension**
  - **Systolic pulmonary arterial pressure > 30 mmHg**
  - **Tricuspidal regurgitation peak velocity > 2.8 m/sec**
  - **Mean pulmonary arterial pressure > 20 mmHg**

Fig. 5. Echocardiographic findings demonstrating RHD in acute PE

The presence of RHD is related to poor prognosis in acute PE both in patients with haemodynamic instability (Goldhaber SZ et al 1999, Kreit JW 2004) and in normotensive patients (Kucher N et al 2005). In normotensive patients RHD is detected in around 40% of patients (Goldhaber SZ et al 1999, Kreit JW 2004, Kucher N et al 2005). In normotensive patients without RHD hospital mortality ranges from 0% to 9.6% while in stable patients with RHD the hospital mortality range is 11.8-23% (Gibson N et al 2006). Normotensive patients without RHD have 30-days mortality relative risk reduction of 17% compared to patients with RHD (Kucher N et al 2005). In a monocentric study enrolling more than 1400 patients a RV/LV diameter ratio > 0.9 was found as independent risk factor for hospital mortality in normotensive patients with PE (Frèmont B et al 2008). Much recently it has been published a meta-analysis of prognostic value of echocardiography in haemodynamically stable patients with PE. The pooled data of five echocardiographic studies demonstrate a 2.5 fold increased predicting death risk in normotensive patients with RHD (Sanchez O et al 2008). Moreover it should be remarked that echocardiography at presentation could predict long term prognosis of patients suffered of first episode of PE. Echocardiographic RHD at presentation in fact seems to be related with poor resolution of pulmonary clots after six months from PE and with higher incidence of VTE recurrence (Kaczynska A et al 2008) and persistence of RHD at hospital discharge predicts VTE recurrence (Grifoni S et al 2006). More recently it has been demonstrated that shortening of pulmonary artery acceleration time and impairment of LV systolic function as related to long term poor prognosis in patients with acute PE (Kjaergaard J. et al 2009).
However echocardiography examination has some limitations, mainly due to operator-dependence and lack of definitely established criteria of RHD.



- **CPTE index:** $\Sigma\ (n \cdot d) / 40 \times 100$
  (n= number of segments dependent from the obstructed pulmonary artery involved [min1;max20];
  d= obstruction severity [complete=2; >50% <100% =1; <50% =0]

- **Ghanima score:**
  4=main pulmonary artery and its branches
  3=lobar arteries
  2=segmental arteries
  1=sub-segmental arteries

- **RV/LV diameter ratio >1**

Fig. 6. CTPA proposed prognostic parameters

Up to now, ***CTPA*** represents the diagnostic gold standard for PE, and is widely integrated in validated diagnostic strategies (Perrier A et al 2005, Cristopher Study Investigators 2006, Stein PD et al 2006, Righini M et al 2008, Torbicki A et al 2008). In the last years, evidence has been reported about the prognostic role of CTPA in acute PE, especially for detecting of RHD (Schoepf UJ et al 2004, Schoepf UJ et al 2004, Ghuysen A. et al 2005, van der Meer RW et al 2005, Mansencal N. et al 2005, van der Meer RW et al 2005, Araoz PA et al 2007). Some tomographic findings have been suggested for risk stratification in patients with confirmed PE (see Figure 6) (Qanadli SD et al 2001, Wu AS et al 2004, Ghanima W. et al 2007). The CTPE index (Computer Tomography Pulmonary Embolism index) combines distribution and severity of pulmonary vascular tree obstruction proven by clots and it could be used for burden detection. CTPE index values seem to be linearly related to clinical severity of PE (Qanadli SD et al 2001). Since then proximal clots could be burdened by more sever PE presentation, it has been suggested to divide the pulmonary vascular tree in four group of arteries (sub-segmental, segmental, lobar arteries and main pulmonary artery with its left and right branches, respectively named 1, 2, 3, 4) for identifying clots from distal to central localization (Ghanima W et al 2007). It was observed that this pulmonary artery obstruction index, derived from sum of arteries involved, is correlated to biomarkers levels, CTPA and echocardiographic RV/LV diameter ratios, hypoxemia (Ghanima W et al 2007, Masotti L et al 2007). Also the RV/LV diameter ratio detected by multidetector CTPA has been evaluated as prognosticator in acute PE (Wu AS et al 2004). Up to now concerns exist about this prognostic parameter. Nevertheless several studies enrolling small size series have found association between CTPA RV/LV > 0.9 or > 1.0 and short term mortality (Wu AS et al 2004, Ghuysen A. et al 2005, van der Meer RW et al 2005, Sanchez O et al 2008), the PIOPED II enrolling around seven hundreds patients, failed to find relation between CTPA RV enlargement and poor prognosis (Stein PD et al 2008).

2.3 Laboratory biomarkers

The most studied biomarkers as prognosticator in acute PE are represented by cardiac troponins (cTnI and cTnT) and natriuretic peptides (brain natriuretic peptide, BNP, and/or its N-terminal portion, NT-proBNP).

The troponin complex comprises three proteins (troponin I, T and C) that control and determine the contraction of cardiac and skeletal muscle (Becattini C et al 2008). Most of troponin I and T are related to the myofilaments, while a small fraction is free in the cytosol of muscle cells. When myocytes are irreversibly damaged as in myocardial necrosis resulting from ischemic attack, the cytosolic component of troponin is released (Becattini C. et al 2008). The increase of cTn is correlated with echocardiographic and CTPA findings of RHD (Binder L et al 2005, Ghanima W et al 2007). A meta-analysis of the studies considering the relation between troponins and poor adverse events in acute PE demonstrates that the increase of cTnI or cTnT is related with a fourfold risk of mortality both in haemodynamic instability and in normotensive patients; (17.9% in patients with elevated cTn levels vs 2.3% in patients with normal cTn levels)(Becattini C. et al 2007, Becattini C. et al 2008). After publication of this meta-analysis, a large prospective study has confirmed that in normotensive PE patients, increased cTnI values predict fatal PE (Jimenez D et al 2008).

The natriuretic peptides are neurohormones released from the heart as a result of pressure and volume overload (Daniels LB et al 2007). Three types of natriuretic peptides have been identified: the atrial natriuretic peptide (ANP), released mainly from the atria, the B-type natriuretic peptide (BNP), which is mainly synthesized by the ventricles and the C-type natriuretic peptide (CNP), synthesized by endothelial cells. The atrial natriuretic peptides have a common amino acid structure of 17 amino acids. Among these three natriuretic peptides, BNP and its amino terminal portion NT-proBNP have been useful in diagnosis in patients with dyspnoea. When ventricle wall is exposed to volume or pressure overload, the pre-proBNP is released by myocytes. Subsequently, the pre-proBNP is firstly cleaved in proBNP consisting of 108 amino acids, from whom derive BNP (32 amino acids) and its terminal portion (NT-proBNP). While the terminal portion is inactive, the BNP is functionally active causing vasodilatation, increased diuresis and natriuresis and inhibition of the activation of the renin-angiotensin-aldosterone system (Daniels LB et al 2007). NP reflects the RH overload and secondary RV wall stress and therefore are indirectly the expression of RHD (Daniels LB et al 2007). Several studies, pooled in meta-analyses, have reported the relation between high values of NP and short term poor prognosis in acute PE (Cavallazzi R et al 2008, Coutance G et al 2008, Klok FA et al 2008, Lega JC et al 2009). However although the increase of the BNP and NTpro-BNP is highly sensitive, it is poorly specific for detect RHD and patients at risk of severe adverse events such as cardiac arrest, shock, needing to use thrombolysis or vasopressors or mechanical ventilation or needing of intensive care units; in the other hand NP have high negative predictive value for detect low risk patients (Cavallazzi R. et al 2008, Coutance G. et al 2008, Klok FA et al 2008, Lega JC et al 2009).

Much recently hearty type fatty acid binding protein (hFABP), a small cytosolic protein released earlier than troponins into circulation when the myocardium is injured, has been evaluated as a prognostic tool in acute PE. At least two studies have demonstrated that, when increased, hFABP values identify the patients with poor outcomes (Kaczyñska A. et al 2006, Puls M. et al 2007).

Other cardiac biomarkers have been studied as prognosticators in acute PE. Of interest but up to now with few evidences the negative prognostic role of myoglobin and growth-differentiation factor-15 (gdf-15) in acute PE (Pruszczyk P. et al 2003, Lankeit M. et al 2008).
D-Dimer, a product of fibrin degradation, is widely used in diagnostic work-up of acute PE. However some literature evidence seem to demonstrate that D-Dimer values could be linearly related to the burden and prognosis of acute PE Studies of limited size highlight in fact that D-Dimer values higher than 3000 or 4000 microg/L FEU are associated to proximal localization of thromboemboli, RHD, mortality, 6-months poor recanalization of pulmonary vascular three, VTE recurrence, while values less than 1500 microg/L FEU seem to be related to low risk of adverse events (De Monyè W et al 2002, Aujesky D et al 2006, Ghanima W. et al 2007, Masotti L. et al 2007, Kline et al 2008, Vuilleumier N. et al 2009, Klok FA et al 2010). Prospective, multicenter study are warranted to confirm these evidence.
Arterial blood gas analysis represents a first level tool; its values have been studied as prognostic indexes, but only invasive and not widely diffuse determinations could be associated to outcomes (Te Hsu J. et al 2007). Much recently a prospective multicenter cohort study has demonstrated that hypoxemia (arterial oxygen partial pressure, paO2, values ≤ 60 mmHg) predicts in hospital and 3-months all-cause mortality in haemodynamically stable patients with acute PE (Bova C. et al 2009)

Sensitivity, specificity, negative and positive predictive values of echocardiography, CTPA and main biomarkers are shown in Figure 7.

	Echo-cardiography	CTPA	Troponins	BNP	NT-proBNP
Sensitivity (%)(95% CI)	70 (46-86)	65 (35-85)	81 (23-100)	88 (65-96)	93 (14-100)
Specificity (%)(95% CI)	57 (47-66)	56 (39-71)	84 (77-90)	70 (64-75)	58 (14-92)
Negative predictive value (%)(95% CI)	60 (55-65)	58 (51-65)	73 (68-78)	76 (73-79)	81 (65-97)
Positive predictive value (%)(95% CI)	58 (53-63)	57 (49-64)	75 (69-80)	67 (64-70)	63 (50-76)

From Sanchez O. et.al. 2008

Fig. 7. Summary of prognostic indexes for detect RHD

Figure 8 summarizes the strongest clinical, instrumental and laboratory indexes of adverse outcomes in acute PE.

- **Clinical variable and scores**

-	- Shock/Hypotension	Systolic blood pressure ≤ 90 mmHg
-	- Shock index	> 1
-	- P.E.S.I.	class III, IV, V
-	- GPR	≥ 3

- **Imaging**

-	- Echocardiography	RHD findings
-	- CTPA	CTPE index, proximal clot RV/RV diameter ratio > 1

- **Biomarkers**

-	- Increased levels of	cTnI or cTnT BNP or NT-proBNP D-Dimer?

Fig. 8. Summary of main negative prognostic variables in acute PE

2.4 Combinations of clinical, instrumental or biomarker parameters and comparison between them

Although many tools have been proposed for risk stratification, some questions remain unresolved: (i) which is the best strategies for risk assessment? (ii) combination of single strategies could improve risk assessment?

Few studies have directly compared single strategies between them. Studies which have compared biomarkers seem to demonstrate that low levels of NP stratify better than cTn and D-Dimer the low risk PE (Binder L. et al 2005, Maziere F. et al 2007, Kline JA et al 2008, Klok FA 2008, Vuilleumier N. et al 2009, Klok FA et al 2010).

Nevertheless only two studies have investigated the role of hFABP as prognosticators, both seem to demonstrate that hFABP predict better prognosis compared to cTn and natriuretic peptides (Kaczyñska A. et al 2006, Puls M. et al 2007).

Much recently literature reports aimed to compare clinical score or instrumetal tools with biomarkers have been published. Again, natriuretic peptides seem to identify low risk patients better than PESI and CTPA RV/LV diameters ratio >1 (Klok FA et al 2010, Vuilleumier N et al 2009), while PESI seems to be superior on cTn in predicting low risk patients (Moores L. et al 2009). Finally when compared to pulse oximetry values over than 92.5% oxygen, PESI seems to have not significative differences in predicting low risk patients (negative predictive values, NPV, 98% vs 99%)(Nordhenolz R. et al 2009)

Only few studies have investigated the role of instrumental and biomarkers tools combined together for risk stratification of acute PE. Results of them demonstrate that the combination of values of NT-proBNP > 1000 pg/mL or cTnI elevation plus echocardiographic RHD increase 12-fold the risk of adverse outcomes in acute PE (Binder L. et al 2005). Much recently combination of clinical variables with imaging and biomarkers has been studied, demonstrating that this strategy could improve the risk stratification for adverse outcomes

(Sanchez O et al 2010). Variables identified in this potential bedside adverse outcomes score were alterated mental status, shock at hospital admission, cancer, increased BNP and RV/LV ratio > 1.0. Validation studies are warranted.

2.5 The risk based management of acute PE

Acute treatment of PE is actually customized on early mortality risk. Last version of ESC and American College of Chest Physicians (ACCP) guidelines in fact suggest a based-risk approach for PE treatment (Kearon C. et al 2008, Torbicki A. et al 2008).

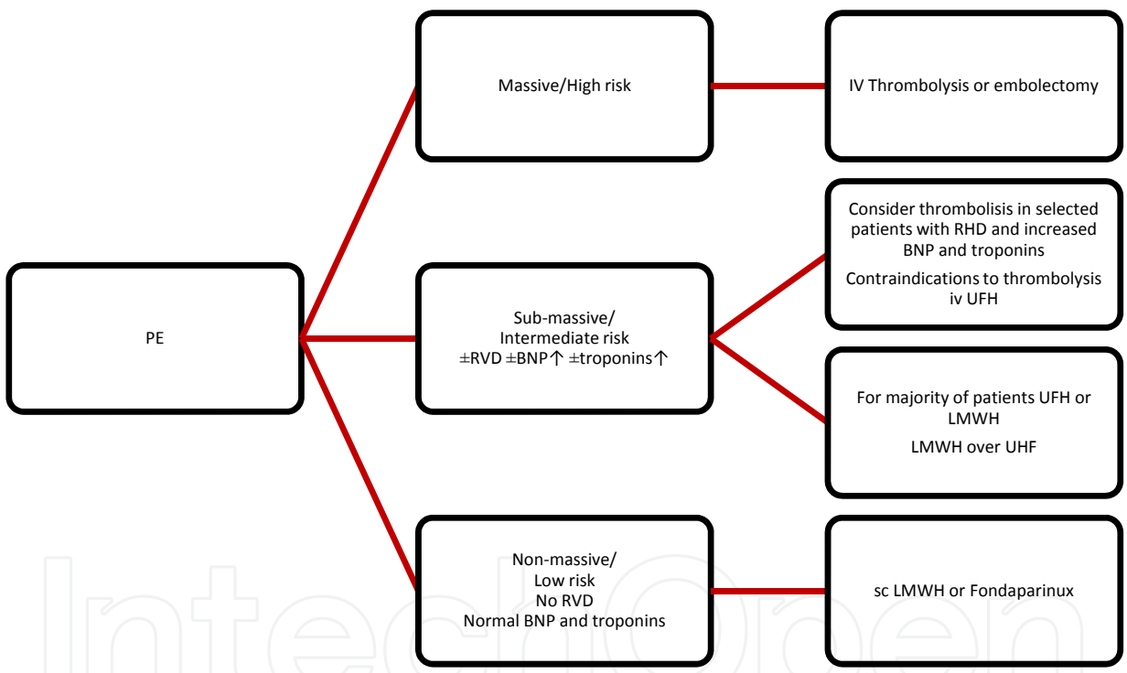
In *massive-high risk PE*, thrombolysis with alteplase (rtPA) is the choice therapy other than haemodinamic and respiratory support (Kearon C. et al 2008, Torbicki A. et al 2008). Although all trials have failed to demonstrate the superiority of thrombolysis compared to unfractioned heparin (UFH) in term of prognosis in acute PE, thrombolysis seems to improve more quickly the haemodynamic decompensation compared to UFH (Wan S et al 2004). Other approved thrombolytic drugs for acute PE are represented by streptokinase and urokinase (Kearon C. et al 2008, Torbicki A. et al 2008). It should be remembered that in the last years literature reports cases of acute PE treated by tenecteplase which has the advantage of bolus injection (Melzer C. et al 2004, Becattini C. et al 2010). This thrombolytic agent has been approved for a multicenter trial aimed to evaluate thrombolysis in submassive/intermediate risk PE (www.clinicaltrials.gov, NCT00639743). However, up to now, the use of tenecteplase in acute PE is off-label. UFH should be administered in patients undergoing to thrombolysis and continued after it. UFH should represent the first choice of treatment in patients with contraindications to thrombolysis (Kearon C et al 2008, Torbicki A et al 2008).

Embolectomy could represent an alternative therapy in acute setting of patients with haemodynamic compromise when thrombolysis is contraindicated or it has failed (Kearon C. et al 2008, Torbicki A. et al 2008, Goldhaber SZ 2010).

Major concern exists whether *sub-massive/intermediate risk PE* should be treated with thrombolysis since than conventional treatment has failed to reduce mortality in this group of patients which could evolve toward haemodynamic instability (Lankeit M. et al 2010). Mortality in normotensive PE with RHD could reach the not neglegible percentage of 10-15%; therefore more aggressive treatment has been postulated and studied. Meta-analysis of a five studies involving a total of 464 normotensive patients with PE, 100 of them undergoing to echocardiogram, comparing thrombolysis with UFH has failed to demonstrate superiority of thrombolysis in terms of mortality and VTE recurrence with non significant differences in major bleedings (Tardy B et al 2009). Up to now modern guidelines reserve thrombolysis in selected patients with submassive-intermediate risk PE, when the risk for adverse prognosis is very high and there is lack of contraindications to it (grade IIB of ESC and ACCP guidelines VIII Edition)(Kearon C. et al 2008, Torbicki A. et al 2008). For the majority of submassive/intermediate risk PE, UFH or low molecular weight heparins (LMWH) represent the first treatment choice. Both ESC and ACCP suggest LMWH over UFH in this setting (Kearon C. et al 2008, Torbicki A. et al 2008). Meta-analyses have in fact demonstrated the non inferiority of LMWH compared to UFH in non high risk PE (Quinlan DJ et al 2004). Thrombolysis should be the rescue treatment in patients initially treated with UFH or LMWH and secondary onset of clinical instability as demonstrated by the MAPPET III Study (Management Strategies And Prognosis of Pulmonary Embolism Trial-3)(Konstantidnes S. et al 2002). In this study in fact it was observed that although rtPA

reduced mortality in a non-significant way (3.4% in patients treated with UFH vs 2.2% in patients treated with rtPA, p = ns), rtPA added in patients initially treated with UFH with subsequent evolution toward haemodynamic instability clearly and significantly reduced mortality compared to patients not undergoing it in the event of deteriorating haemodynamics (mortality 10.2 vs. 24.6% respectively, $p<0.05$)(Konstantidines S et al 2002)
Wide and strong consensus is given to treatment of *non-massive-low risk PE* by using LMWH or fondaparinux (grade IA ESC and ACCP VIII Edition)(Kearon C. et al 2008, Torbicki A. et al 2008). Rapid hospital discharge could be safe and cost-effectiveness (Janjua M. et al 2008)
Vitamin K antagonists (VKA) should be started in the first day and should be overlapped to UFH and LMWH or fondaparinux for at least five days (grade I A ESC and ACCP VIII Edition)(Kearon C. et al 2008, Torbicki A. et al 2008). LMWH should be continued in cancer patients for at least six months (Kearon C. et al 2008, Torbicki A. et al 2008).

Figure 9 summarizes the actual choice treatment based on early mortality risk.



Legend: RHD = right heart dysfunction; BNP = Brain natriuretic peptide; IV = intravenous; sc = subcutaneous

Fig. 9. PE treatment according to modern guidelines

3. Ongoing trials

There is much attendance for the results of two much important multicenter ongoing trials which could give fundamental answers for risk management of PE. These are represented by Pulmonary Embolism Thrombolysis Study (PEITHO) and Outpatients Treatment for Pulmonary Embolism (OTPE) trials (www.clinicaltrials.gov, NCT00639743, NCT00425542).

The first one (PEITHO) compares thrombolysis by using single intravenous bolus of tenecteplase with conventional pharmacological treatment represented by UFH or LMWH in sub-massive (intermediate risk) PE, defined as echocardiographic evidence of RHD associated to increased cTn. The aim of this study is to demonstrate the superiority of thrombolysis compared to conventional strategy without increasing of haemorrhagic side effects. Patients in the investigational group will receive i.v. bolus of tenecteplase as a single body-weight administered over 5 - 10 seconds not later than 30 minutes after randomization, and not later than 2 hours after the diagnosis of RHD and concomitant UFH as an intravenous bolus followed by an infusion weight adjusted to be administered immediately after randomization in all patients for at least 48 hours following randomization. Beyond this period, intravenous UFH may be substituted with subcutaneous LMWH. Patients in the control group will receive i.v. bolus of placebo as a single body-weight administered over 5 - 10 seconds not later than 30 minutes after randomization, and not later than 2 hours after the diagnosis of RHD and concomitant therapy with UFH (www.clinicaltrials.gov, NCT00639743).
The purpose of OTPE is to demonstrate the non inferiority in terms of effectiveness and safety of outpatients treatment compared to inpatients treatment in low risk patients with PE, identifying by using PESI score (≤ 85 points). In this trial patients randomized to the outpatient arm are discharged from the emergency department within 24 hours after randomization, whereas patients randomized to the inpatient arm are admitted to the hospital and are discharged based on the decision of the managing physician at the hospital (www.clinicaltrials.gov, NCT00425542).
Results of PEITHO are waited within 2012, while 2010 could see the final results of OTPE.

4. Conclusions

Risk assessment represents one of the major key point emerged in the last years for acute management of acute PE. Clinical, instrumental and laboratory parameters are now fundamental for identifying different early mortality risk and customizing the antithrombotic treatment of acute PE in each patient. Although many strategies have been proposed for risk stratification, which is the best one remain unclear since then there is lack of evidence about the superiority of one over others. Therefore next studies aimed to discover this unresolved issue are warranted.
Up to now certainness seem to be represented by close monitoring and thrombolysis, when not contraindicated, in high risk patients and LMWH or fondaparinux and rapid hospital discharge in low risk patients. Whether intermediate risk patients should be treated by thrombolysis and low risk patients should be treated as outpatients remained opened challenges. The results of the above mentioned ongoing trials could give us what we are looking for.

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