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# Submassive Pulmonary Embolism

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## Abstract:

Pulmonary Embolism (PE) presents a spectrum of hemodynamic consequences ranging from being asymptomatic to a life-threatening medical emergency. Management of sub massive and massive PE often involves clinicians from multiple specialties that can potentially delay the development of a unified treatment plan. Additionally, patients with submassive PE can deteriorate after their presentation and require escalation of care. Underlying comorbidities like chronic obstructive pulmonary disease (COPD), cancer, congestive heart failure and interstitial lung disease can impact the patient's hemodynamic ability to tolerate submassive PE. In this review, we will address the definitions, risk stratification (clinical, laboratory & imaging), management approaches and long-term outcomes of submassive PE. We will also discuss the role of the Pulmonary Embolism Response Team (PERT) to manage patients with PE.

**Key words**: Submassive PE, Intermediate PE, PERT, PE risk stratification, catheter directed thrombolysis.

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## Introduction:

PE is the third most common cause of death amongst hospitalized patients.[1] Older age, comorbid cardio-pulmonary diseases and thrombolytic treatment are associated with increased health care cost and worst outcomes.[2] Patients with PE can have mild to moderate functional impairment even after 18 months from the initial event.[3] In one study, impaired quality of life measured by Short Form (SF-36) questionnaire was comparable to acute myocardial infarction.[4] Single episode of VTE itself increases the risk of recurrent VTE.[5,6] The incidence of recurrent VTE is 11.2 % within 2 weeks of the initial presentation despite adequate anticoagulation.[7] Prolonged immobilization, post-operative state, obesity, recent hospitalization and active cancer are risk factors for VTE.[8,9]

## Epidemiology:

The National Hospital Discharge Survey (NHDS) demonstrates increase in VTE occurrence.[10] 246,000 cases of PE were reported in 2006.[11] Similarly, in Europe over one million VTE events or deaths occur each year in 6 large countries.[12] Untreated PE has a mortality rate of 30%.[13] Submassive PE related mortality has been reported to be 3% to 14.2% with a trend towards lower mortality in recently published registries.[8,14-17] The HCUP-NIS 2007 shows an overall PE related mortality of around 3.5%.[18] Recent positive outcomes are attributable to more frequent use of low molecular weight heparin (LMWH) compared to unfractionated heparin, aggressive use of thrombolytic therapy and performance of surgical embolectomy.[16] Isolated DVT has better one year survival than PE or PE with DVT.[5] The incidence rate of VTE has remained constant despite an increase in rate of prophylaxis. The majority of VTE events occurred post-discharge suggesting that in-hospital prophylaxis is not sufficient to prevent VTE.[19]

## Definition and Classification

PE is generally described as an obstruction in the pulmonary artery due to a clot, tumor, air or fat.[20] A saddle pulmonary embolism is described as a clot located in the main pulmonary artery that traverses the right and left pulmonary arteries (Figure 1). Lobar, segmental and sub segmental PEs are clots located in the branches of the pulmonary artery corresponding to the anatomical lung segment. Saddle PE is often associated with a higher clot burden and RV dysfunction, not necessarily increased mortality.[15,21] Most patients with saddle PE are hemodynamically stable and receive heparin (87%).[21]

Terms like acute, sub-acute and chronic PE refer to a time frame from initial event to a confirmation of diagnosis. Signs of chronic PE on a CT angiogram (CTA) are suggested by eccentric thrombus location, calcification within the thrombus, the presence of pulmonary arterial webs or bends, and post-stenotic dilation of the pulmonary artery.[22] Table 1 summarizes definitions of PE from American Heart Association (AHA), American College of Chest Physicians (ACCP) and European Society of Cardiology (ESC) guidelines.[14,23,24] One of the major advantages of ESC classification of PE is the focus on short term PE related mortality (in hospital or 30 day mortality) unlike ACCP or AHA classification.[23,24] To integrate patient's clinical status and comorbidities, ESC guidelines recommend most validated PESI (Pulmonary Embolism Severity Index) or simplified PESI score (sPESI, discussed in detail later). Any patient with a positive sPESI score falls into the intermediate risk PE category (equivalent to submassive PE in AHA/ACCP). ESC guidelines further risk stratifies intermediate PE (submassive PE) into intermediate low risk and intermediate high risk. (Table 1)

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## Pathophysiology of RV failure:

RV is a thin-walled (1-3 mm) structure compared to LV (10 mm). The RV is divided into 3 different regions - RV inflow, apical region and RV outflow. Movement of the interventricular septum that is anterior to RV free wall contributes to 50% of the RV function.[25] The pulmonary circulation is a low-pressure system. Pulmonary vascular resistance (PVR) is regulated by oxygen sensing mechanisms. RV failure can be due to: A) increase in pre-load, B) increase in afterload, or C) a decrease in myocardial contractility due to ischemia.[20] Mechanical obstruction from clot and inflammatory cytokines increase PVR.[26] Inflammation induced neutrophil release contributes to RV dysfunction in murine models.[27] Thrombus occlusion creates a dead space leading to hypoxic vasoconstriction and hypercapnia.[15] Mechanical obstruction, hypoxemia, hypercapnia and cytokine induced hypoxic vasoconstriction increase RV afterload, leading to RV dilation. It ultimately leads to bowing of the interventricular septum into the LV and profound hypotension from obstructive shock.[24]

## Risk Stratification for PE:

Various clinical scores, imaging modalities and biomarkers risk stratify acute PE that have direct implication on short term mortality and therapeutic decisions.

### A) Clinical risk prediction scores

PESI and sPESI scores have been validated to predict 30-day mortality in patients with acute PE.[28] (Table 2) PESI score has a sensitivity of 91% and a negative predictive value of 99% to predict mortality.[29] PESI score identifies patients with PE in low-risk groups I (<65 points) & II (65-85 points) and high-risk groups III (86-105 points), IV (106-125 points) and V (>125

points). Short-term mortality increases from 1% in group I to 24% in group V. The low-risk PESI group had low short-term mortality even with positive troponin and can safely be managed as outpatient.[30] Decrease in PESI score from admission to 48 hours is associated with reduced short-term mortality. sPESI score uses 6 risk factors compared to 11 risk factors in original PESI score.[28,31] Low risk sPESI (score of 0) has short- term mortality risk of 2.5% and a negative predictive value of 97.5% compared to the original PESI score. A meta-analysis of 21 studies that included 50,000 patients demonstrated that both scores (PESI and sPESI) are equally effective in identifying low risk PE patients.[32] PESI and Hestia scores have been validated to predict early home discharge from hospitalization due to PE.[33,34,35]

**B) Biomarkers:**

Brain natriuretic peptide (BNP) and N-terminal (NT) pro BNP are markers of RV pressure overload. Troponin I & troponin T are markers of myocardial ischemia. Elevation of biomarkers carry an independent risk of short term mortality and RV dyfunction.[24,36] Elevated troponin to predict short-term mortality in PE is controversial.[37,38] We recommend against making decisions solely based on elevated biomarkers and pay attention to alternate causes of biomarker elevation.

**C) Imaging**

RV dysfunction on CTA or echocardiogram can risk stratify PE.[24] Even though CTA is usually immediately available, concomitant RV strain on CTA and echocardiogram are better predictive of an adverse outcome.[39] The location of thrombus or clot burden on CTA is not part of the risk stratification.[40] The role of quantitative clot burden indices (Mastora or Qanadli) in immediate risk stratification is limited.[40] On the other hand, RV/LV ratio of >0.9 on CTA or echocardiogram indicate RV dysfunction and associated with adverse clinical outcomes.[41,42,43,44]

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(Figure 2) Interventricular septal flattening, reflux of contrast into the IVC and hepatic veins also implicate RV dysfunction.[40] In experienced hands, bedside echocardiography can identify RV dysfunction.[45] (Figure 3) McConnell sign (decreased RV free wall function with apical sparing) is specific for PE. TAPSE (tricuspid annular plane systolic excursion) ≤ 18 mm and lack of IVC collapsibility and elevated RV systolic pressure (RVSP) have been associated with increased mortality.[44] RV fractional area change, RV myocardial performance (Tei) index, RV longitudinal strain might be useful, but are often time consuming for rapid risk stratification. Comparison to previous echo and RV free wall thickness may help delineate acute vs chronic RV failure.

**D) Combined modalities of biomarkers, lab tests and imaging:**

No single clinical score, imaging modality or laboratory test in isolation predict the prognosis of acute PE. Integrative approach may help drive therapeutic decisions in submassive PE. PROTECT Multi-Marker Index, FAST score, Bova score predict a complicated course (all-cause mortality, need for vasopressors, mechanical ventilation, recurrent PE etc.) in 22%-29.2% of patients with PE.[46-48] (Table 3) PE with DVT has higher mortality than PE alone.[49] We do not recommend using any specific risk stratification model over other, but do emphasize the value of incorporating clinical, radiological, laboratory and other co-morbid illnesses into therapeutic decision-making process.

## Treatment of Submassive (Intermediate risk) PE:

Patients with confirmed PE, or high pretest probability, should be started on anticoagulation as soon as possible unless contraindicated. Decisions for advanced therapies should be individualized. In this section, we will focus on bleeding risk scores and available treatment options for submassive PE.

### *A) Bleeding Risk Scores:*

Bleeding risk should be considered in selecting advance treatment options. Definitions of major bleeding vary in literature. International Society on Thrombosis & Hemostasis (ISTH) defines major bleeding as a fall in Hgb >2.0 gm/dl, >2 units of PRBC transfusion, or a critical bleeding site like intracranial, intraarticular, retroperitoneal, intraspinal, pericardial or intramuscular with compartment syndrome.[50] Various bleeding risk scores have been described in literature, mainly for potential bleeding on Vitamin K antagonist (VKA) therapy. One of the most well described bleeding risk score is Registro Informatizado de Enfermedad Thrombo Embólica (RIETE) score.[51] RIETE score includes age >75 years (1 point), recent bleeding (2 points), cancer (1 point), creatinine levels >1.2 mg/dl (1.5 points), anemia (1.5 points), or pulmonary embolism at baseline (1 point).[51] (Table 4) Recently published trial showed that at least four VKA related bleeding predicting scores held its relevance when tested for rivaroxaban. RIETE score performed the best at predicting bleeding on rivoraxaban.[52] There is growing evidence to support that DOACs have better safety profile for bleeding compared to VKA.[53] We recommend DOACs as a first line therapy for VTE over VKAs unless in special situations like cancer, advance renal failure, anti-phospholipid antibody syndrome, etc.

Age >65 and kidney disease increase the intracranial hemorrhage risk with thrombolysis.[54] PE-CH score (**P**eripheral arterial disease: 1-point, **E**lderly age>65: 1-point, prior **C**VA with residual effect: 1-point, history of **H**eart attack: 5-point) is one of the novel bleeding risk score to predict the risk of intracranial hemorrhage with thrombolytics therapy.[55] (Table 4)

Bleeding risk score prediction is only modest because of several reasons. Bleeding risk scores were derived from patients who were already deemed appropriate to be on anticoagulation by the

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treating physicians. This bias could have excluded high bleeding risk patients at first place. The safety data for DOACs appears to come from the clinical trial settings, which excluded majority of the high bleeding risk patients.

***B) Systemic thrombolysis:***

The role of systemic thrombolysis in submassive PE is controversial. Submassive PE patients with clinical deterioration are the potential candidates of thrombolysis.[23] Alteplase is given as 100 mg infusion over 2 hours; tenecteplase is given as push dose injection. A double-blind randomized trial demonstrated mortality benefit with alteplase when compared to heparin only in submassive PE without additional bleeding risk.[56] Pulmonary Embolism Thrombolysis (PEITHO) trial compared tenecteplase plus heparin vs placebo plus heparin in 1006 patients with submassive PE.[57] Tenecteplase group had reduced hemodynamic decompensation and all-cause mortality but increased ICH (2%) and major bleeding (6.3%). Three-year follow-up data from the PEITHO study showed no long-term mortality benefit or difference in incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in either group.[58] Chatterjee et al, in a meta-analysis of 1775 patients showed mortality benefit with thrombolysis with increased risk of major bleeding (9.24%) and ICH (1.46%).[59] In another meta-analysis by Riera-Mestre A et al, that included 1833 showed no mortality benefit but an increased risk of major bleeding (5.9%) and ICH (1.74%).[60] It was interesting to note that the risk of ICH and major bleeding is higher with tenecteplase than alteplase.[60] There have been several systemic reviews since release of PEITHO trial with varying results of mortality benefit and bleeding risk. Riva et al, performed an extensive review of 12 meta-analysis and found that systemic reviews were largely concordant in finding of reduced all-cause mortality but with increased bleeding risk.[61] ACCP 2016 guidelines suggest considering systemic thrombolysis in submassive patients with clinical decline and low

bleeding risk. Low dose t-PA (50 mg/2hrs or 0.6mg/kg) has a potential role in submassive PE. It has dual advantage of rapid clot resolution like full dose thrombolytic and bleeding risk profile comparable to heparin.[62] The upcoming PEITHO-3 trial plans to address the role of half dose thrombolytics in submassive PE in larger clinical trial.

### *C) Catheter Based Treatment (CBT):*

Catheter-based treatment (CBT) has an emerging role in the management of PE. CBT includes catheter directed thrombolysis (CDT), mechanical fragmentation or combination of both. CDT includes positioning catheters directly into thrombosed pulmonary artery (PA) and infusing thrombolytic drugs in it. CDT catheters can be positioned unilaterally or bilaterally into the pulmonary artery. Main PA or lobar branches with heavy clot burden are the ideal locations. CDT can be performed with standard 5-F multi-side hole catheters or EkoSonic catheter (EKOS/BTG, West Conshohocken, PA). EkoSonic catheter (Figure 4) adds high frequency low power ultrasound waves that induce reversible disaggregation of uncross-linked fibrin fibers which create additional binding sites for thrombolytic agents. Ultrasound waves may increase thrombus penetration of thrombolytic drugs by acoustic streaming. Catheter directed mechanical fragmentation techniques include either clot fragmentation or clot extraction without thrombolytics.

Multi-center trial involving 59 submassive PE patients demonstrated that ultrasound facilitated catheter directed thrombolysis (USCDT) when compared to heparin, reduced RV/LV ratio at 24 hours.[63] There was no incidence of ICH or major hemorrhage in USCDT group. The SEATTLE II trial included 31 massive and 119 submassive PE (n=119) patients.[64] USCDT group had statistically significant reduction in RV/LV ratio, mean pulmonary artery systolic pressure

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(mPAP) and modified miller obstructive score without any ICH. A retrospective study involving 14 massive and 38 submassive PE patients showed significant improvement in cardiac index, RV/LV ratio and pulmonary artery pressure post USCDT. Two deaths occurred in 3-month follow up period and 2 episodes of non-fatal major bleeding were noted in the study.[65] Recently published multi center registry involving 101 patients support effectiveness and safety profile of CBT in massive (n=28) and submassive PE (n=73).[66] OPTALYSE-PE trial compared efficacy of reduced dosing and duration of USCDT in 101 patients dividing into 4 cohorts.[67] All 4 cohorts had similar reduction in RV/LV ratio at 48 hours with one case of ICH (Cohort D: 2 mg/hr for 6 hours) and 3 major bleeding. Even though role of CBT is evolving, effectiveness of USCDT Vs Standard CDT has been questioned in recent meta-analysis involving 700 patients.[68] Table 5 summarizes all major CBT trials.

Catheter directed embolus fragmentation can be achieved via simple rotational pigtail catheters or balloon angioplasty catheters. Potential disadvantage of such technique is distal embolization.[69] High pressure saline jet injection via Angiojet (Possis) device, has received black box warning due to serious adverse events like bradycardia, massive hemoptysis and renal failure. Amplatz thrombectomy device that uses hydrodynamic vortex to dissolve emboli and aspirex spiral rotating catheters are studied in a small series of patients with PE. The Flow Triever device (Inari Medical) is another mechanical clot retrieval device being studied in submassive PE patients in a large prospective trial.[70] AngioVac Cannula (Angiodynamics) is a FDA approved device that requires venous drainage cannula (26 Fr), reperfusion cannula (18 Fr), centrifugal pump and perfusionist support to remove emboli from IVC or clot in transit.[71] The Penumbra device (Penumbra Inc.) is approved for peripheral arterial or venous thrombus removal and only requires small size venous access (6-8 Fr).[72]

Risk of ICH appear to be as low as 0.5% with CDT.[73,74] Given the lack of randomized trials, different clinical endpoints and lack of long-term follow-up data about safety and efficacy of CBT therapy, we do not recommend routine use of CBT in all patients with submassive PE. Patients with intermediate high-risk PE with high bleeding risk should be considered for CBT over systemic thrombolysis.

D) ***IVC filter:***

IVC filter is reserved for patients who cannot be anticoagulated or are progressively thrombosing despite anticoagulation.[23,75] The American College of Radiology-Society of Interventional Radiology (ACR-SIR) guidelines extend their recommendation for IVC filter in patients with free floating iliocaval thrombus, massive PE with DVT and in patients with severe cardiopulmonary disease.[76] PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) and PREPIC2 trials showed no role of IVC filter in acute PE or DVTs to prevent recurrent VTE events. IVC filter itself can serve as a trigger for DVTs.[77,78] The Angel Catheter (Bio2 Medical) is a triple lumen central venous catheter with an IVC filter at the tip that has recently been FDA approved. It can be placed at bedside via femoral vein in critically ill patients. The device must be removed prior to discharge.[79]

***E) Surgical Embolectomy:***

Surgical embolectomy should be reserved for patients with absolute contraindication or failed thrombolysis, clot in transit, clot traversing patent foramen ovale. Surgical embolectomy for submassive PE has a very good survival rate (86.7%) except in older age group (>80 years).[80] It has a low incidence of major bleeding compared to systemic thrombolysis.[81] Surgical embolectomy requires median sternotomy and potential cardiopulmonary bypass. Surgical

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candidates must be able to tolerate anticoagulation. Patient may need VA ECMO as a bridge to surgery or post operatively. We recommend surgical embolectomy reserved for special situations in submassive PE at expert centers. Table 6 summarizes all available treatment options for pulmonary embolism.

**Long term outcomes of acute PE**

CTEPH is a well known entity, but chronic thromboembolic disease (CTED) and post PE syndrome are relatively new terms.[82,83] Incidence rate of CTEPH is around 0.56 % in all comers with PE and 3% in PE survivors at 2 years.[84] Recurrent VTE and unprovoked PE are the strongest predictors for CTEPH. CTEPH is defined as mPAP >25 mm HG, PCWP <15 mm HG and at least one (segmental) perfusion defect detected by V/Q scan, CTA or pulmonary angiography after 3 months of effective anticoagulation. CTED is defined as pulmonary vascular obstruction with mPAP at rest of <25 mm HG. Patients with CTED and CTEPH showed reduction in oxygen update and work rate compared to control on cardiopulmonary exercise testing in a recent study.[83] There is no standardized treatment for CTED, even though patients are functionally impaired. There has been a growing interest in the role of pulmonary endarterectomy in management of CTED. Other overlapping term described in literature is 'Post PE syndrome' that can be described as follows: 'It is the time line following an acute episode of PE where patient initially experiences functional impairment (reduce QOL) that may progress and lead to CTEPH.[82] Persistent mPAP, RV dysfunction and thrombotic burden appear to play a role in the development of Post PE syndrome. It is hard to say at this point whether CTED leads to Post PE syndrome or falls under the spectrum of post PE syndrome. Nonetheless, it is important to know that following an acute episode, patients can have functional limitation and impaired quality of life prior to occurrence of CTEPH. True prevalence, mechanism of post PE

syndrome or CTED largely remain unknown. Recently published results of ELOPE prospective cohort demonstrated that almost half of patients with acute PE (mostly low risk) have exercise limitation at 1 year that adversely influences health related quality of life (HRQoL), dyspnea and walking distance.[85] Female sex, higher BMI and exercise limitation at one-month cardiopulmonary test were the independent predictors of functional impairment. High pulmonary artery pressure on day 10 echocardiogram and increased pulmonary artery diameter were associated with adverse quality of life measured by Survey form-36 and pulmonary embolism quality of life measures (PEmb-QoL) in the same cohort.[85]

**Role of Pulmonary Embolism Response Team (PERT)**

The concept of PERT is based on the rapid response team that leverages input from clinical specialists from varied disciplines to provide time sensitive comprehensive management plan for acute PE.[86] (Figure 5) It represents a formal pathway to evaluate all possible treatment modalities in real time. (Table 6) It can also incorporate a process to identify the low risk patient for early home discharge. Being a multidisciplinary model, the PERT can make team-based decisions rather than individualized decisions that take longer time and may at times are feared to be driven by proceduralists. PERT team members can follow patients closely in outpatient setting following an acute episode. Out-patient follow-up also allows the opportunity to investigate etiology of PE, decide on the type and duration of anticoagulation, and consider the removal of an IVC filter if present. Patients with persistent symptoms after an initial event can be screened for Post PE syndrome, CTED or CTEPH.

**Conclusion**

Authors would like to summarize following important points from this review as follows.

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A) There is a high incidence of VTE post hospital discharge even after adequate VTE prophylaxis.

B) ESC guidelines focus on short term PE related mortality by integration of PESI or sPESI score into classification of Intermediate PE (submassive PE). It further re classifies Intermediate PE into low and high risk.

C) Clot burden on CTA should not have any direct implication on treatment decision.

D) Clinical, radiological, laboratory and bleeding risks should be used in conjunction to drive therapeutic decision-making process.

E) Bleeding risk scores at best have modest predictability and there are numerous scores described in literature.

F) DOACs are preferred over VKA. Safety profile of DOACs come from clinical trials only, real world data from DOACs related bleeding is at best limited.

G) Full dose systemic thrombolysis should only be reserved for patients with signs of clinical deterioration with low risk of bleeding and younger age in submassive PE. Half dose tPA appear to be relatively a safer option.

H) CDT appears safe in terms of risk of ICH (0.5%) and major bleeding compared to full dose systemic thrombolysis. Ideal patient selection should be done in multi-disciplinary setting. There is no evidence to suggest USCDT is superior to standard CDT.

I) IVC filter should be only be used when anticoagulation is absolutely contraindicated. It should be removed as soon as possible when no longer indicated.

J) Recurrent VTE and unprovoked PE remain the most common risk factors for development of CTEPH.

M) Recent evidence suggests that incidence of CTEPH is close to 3% in PE survivors. Post PE syndrome or CTED patient have functional limitation without CTEPH.

**N)** Multi-disciplinary PERT team should become standard of care to provide a comprehensive care for PE.

**Future Direction**

It is an exciting time in the field of pulmonary embolism with availability of new diagnostic and therapeutic techniques along with involvement of multiple disciplines working together to improve short term and long-term outcomes in patients with submassive PE. It also comes with the responsibility to identify the most immediate research targets to support and justify the use of new technology which ultimately should be targeted towards nothing but the patient care. We propose following targets for future research or quality improvement initiatives.

A) There is a high risk of VTE post hospital discharge. Establish the role of post hospital VTE prophylaxis.

B) It is very important to have uniform definitions of PE that is endorsed by all societies (ESC/ACCP/AHA) to reduce practice variations.

C) Definitions of major bleeding should be more precise and clinically relevant when comparing major adverse outcomes with different modalities of treatment. i.e. ISTH defines drop in Hgb >2 gm/dl as major bleeding event. Patients often have a drop-in

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hemoglobin without obvious clinically relevant bleeding. i.e. intravenous fluid administration, repeated blood draws etc.

D) Develop and validate standardized patient selection criteria for CBT in submassive PE.

E) Determine an ideal time for CDT after diagnosis of submassive PE. Does time to intervention predict short term (i.e. hemodynamic decompensation) and long-term outcomes (i.e. Post PE syndrome or CTED)?

F) Establish the role of ideal dosing and duration for CDT.

G) What is the best way to determine effectiveness of CBT: a) clinical improvement Vs b) right heart catheterization (RHC) pre-and post CBT treatment Vs c) CTA before and after Vs d) cardiac biomarkers before and after. This may have a direct impact on length of stay in ICU, hospitalization cost, resource allocation and utilization.

H) Effect of catheter-based treatment in prevention of CTED/Post PE syndrome or CTEPH.

I) Effect of weight reduction program, structured post PE exercise or rehab program on improving functional limitation following acute PE.

J) Compare effectiveness of half dose thrombolytics with catheter-based treatments in a) prevention of hemodynamic decompensation in submassive PE b) risk of major and minor bleeding c) reduction in long term functional outcomes

K) Role of upfront surgical embolectomy to improve long term functional outcomes in recurrent VTE.

**Table 1.** Definition of Pulmonary Embolism based on severity from ACCP, AHA, ESC guidelines.

| | | **sPESI (Simplified PE severity index) score** | **Shock** | **RV dysfunction on imaging (CTA or Echo) OR Biomarker elevation (BNP/troponin)** |
|---|---|---|---|---|
| **ACCP** | Low risk | N/A | No | No |
| | Intermediate Risk | N/A | No | Either one present |
| | High Risk | N/A | SBP<90mm Hg for 15 min. | N/A |
| **AHA** | Submassive without RV Strain | N/A | No | No |
| | Submassive with RV strain | N/A | No | Either one present |
| | Massive | N/A | SBP<90mm Hg for 15 min or needing inotropic support, pulselessness or profound bradycardia (HR<40 bpm with shock) | N/A |
| **ESC** | Low risk | 0 | No | No |

AJRCCM Articles in Press. Published on 19-April-2018 as 10.1164/rccm.201711-2302CI

| | | | | |
|---|---|---|---|---|
| | Intermediate risk- low risk | 1 or more | No | Either one positive |
| | Intermediate- High | 1 or more | No | Both positive |
| | High Risk | 1 or more | Yes | N/A |

**Table 2.** Original and simplified pulmonary embolism severity score.

| **Parameter** | **Original PESI point** | **sPESI point** |
|---|---|---|
| **Age** | Age in years | 1 point (if age>80 years) |
| **Male sex** | +10 points | N/A |
| **Hx of Cancer** | +30 points | 1 point |
| **Hx of Chronic lung disease** | +10 points | 1 point |
| **Hx of Heart Failure** | +10 points | |
| **HR ≥110** | +20 points | 1 point |
| **SBP < 100** | +30 points | 1 point |
| **Resp. Rate >30** | +20 points | N/A |
| **Temp <36 C** | +20 points | N/A |
| **Altered mental status** | +60 points | N/A |
| **Oxygen Sat < 90%** | + 20 points | 1 point |

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**Table 3.** Multi-marker short term mortality prediction scoring system for PE.

| **PROTECT multi-marker index** | **FAST score** | **BOVA score** |
|---|---|---|
| Troponin I<br>BNP<br>sPESI<br>DVT | H-FABP >6 ng/ml (1.5 points)<br>HR>100 bpm (2 points)<br>Syncope (1.5 points) | SBP 90-100 mg Hg (2 points)<br>HR >110 bpm (1 points)<br>RV dysfunction (2 points)<br>Troponin I (2 points) |

PROTECT multi-marker model (all four variables present), FAST score (>3) and BOVA score (>4) predict a complicated course (all-cause mortality, need for vasopressors, mechanical ventilation or cardiopulmonary resuscitation, recurrent PE etc.) in 22%-29.2% of patients with PE.[46-48]

**Table 4.** Major bleeding risk predicting scores in PE treatment.

| **RIETE score for Major bleeding**[51]<br><br>(VKA related bleeding score) | **% of predicted major bleed** |
|---|---|
| Low risk (0 points) | 0.3% |
| Intermediate risk (1-4 points) | 2.6% |
| High Risk (>4%) | 7.3 |
| **PE-CH Score for ICH**[55]<br><br>(Systemic thrombolytics related bleeding risk score) | **% of predicted ICH** |
| 0 | 1.2% |
| 1 | 2.9% |
| 2 | 3.4% |
| >5 | 17.8% |

AJRCCM Articles in Press. Published on 19-April-2018 as 10.1164/rccm.201711-2302CI

**Table 5.** Characteristics of major clinical trials of catheter-based interventions in PE.

| Trial | Primary end-point | Adverse events | Thrombolytic Dose |
|---|---|---|---|
| **Kucher et al,[63](ULTIMA)**<br>**(N=59)**<br>**Multi center randomized trial** | Reduction of RV/LV ratio at 24 hours from baseline<br>Safety Outcome: Major bleeding, minor bleeding, ICH and recurrent VTE at 90 days | Major bleeding: None<br>ICH: None<br>Minor bleeding: 3 in USCDT, one in heparin group<br>Death: One in heparin arm | 1 mg/hr. for 5 hours followed by 0.5mg/hr. for next 10 hours. Total dose of rtPA 10 mg for unilateral and 20 mg for bilateral catheters |
| **Piazza et al,[64](SEATTLE II)**<br>**(N=150, 31 massive PE, 119 submassive PE)**<br>**Multi center, single arm prospective study** | Reduction CTA measured RV/LV ration, reduction in mean pulmonary artery systolic pressure, and miller obstruction index at 48 hours | Severe Bleeding: n=1<br>ICH: None<br>Moderate Bleeding: n= 16 | 1 mg/hr. for 24 hours for unilateral catheters and 1/mg for 12 hours for bilateral catheters. Total fixed dose of 24 mg irrespective of one or two catheters. |

| | | | |
|---|---|---|---|
| **Engelberger et al**[65]<br><br>**(N=52, 14 high risk PE, 38 Intermediate risk PE**<br><br>**Retrospective series** | Reduction in pulmonary artery pressure and improvement in cardiac index | Major bleeding: n=2<br><br>Death in follow up 3 months, n =2<br><br>ICH: none | 1 mg/hr. for 5 hours followed by 0.5mg/hr. for next 10 hours. Total dose of tPA 10 mg for unilateral and 20 mg for bilateral catheters |
| **Kuo et al**[66]<br><br>**(PERFECT registry)**<br><br>**(N=101, 28 massive and 73 submassive)**<br><br>**Prospective multi-center registry** | Stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge | Major Bleeding: None<br><br>ICH: None | tPA dose was 28+/-11 mg of tPA (n=76) and urokinase dose of 2.7+/-1 million IU of urokinase (n =23) |

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**Table 6.** Treatment options based on PE risk category.

| Types of PE | Definitions | Treatment options |
|---|---|---|
| **Low risk PE** | Hemodynamically stable, and no imaging or biomarker signs of right ventricular strain. | Systemic anti-coagulation<br>Low molecular weight heparin<br>Oral Anti-coagulant<br>IVC filter* |
| **Intermediate risk (Submassive) PE[$]** | Hemodynamically stable but with imaging and/or biomarkers evidence of right ventricular strain | Systemic anti-coagulation<br>Low molecular weight heparin<br>Oral anti-coagulant<br>Catheter Directed Thrombolysis<br>Half dose (50 mg tPA) thrombolysis<br>IVC filter* |
| **High risk (massive) PE[$]** | Hemodynamically unstable patient irrespective of clot location. | Systemic anti-coagulation<br>Full dose thrombolysis (100 mg tPA)<br>Catheter directed thrombolysis<br>Catheter based thrombus fragmentation<br>Percutaneous mechanical thrombectomy<br>Mechanical circulatory support devices (e.g. VA ECMO)<br>Surgical Embolectomy<br>Inotropic and vasopressor support<br>Inhaled Nitric Oxide/prostacyclins<br>IVC filter*<br>Oral anti-coagulation |

- * IVC filter should be considered only in cases where anti-coagulation is absolutely contraindicated.
- $ All listed treatment options for Intermediate and High-risk PE are best taken in the multi-disciplinary setting and should be individualized after taking bleeding risk into consideration.

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Figure 1: CTA showing saddle pulmonary embolism

Figure 2: CTA evidence of RV dysfunction with RV/LV ratio > 1

Figure 3: Short axis view of 2D echocardiogram showing evidence of RV dysfunction with Septal bowing towards left

Figure 4: Chest CXR showing bilateral USAT (ultrasound assisted thrombolysis) catheters placed in lower lobe pulmonary arteries.

Figure 5: Pulmonary Embolism Response Team flow chart.

**Figure 1**

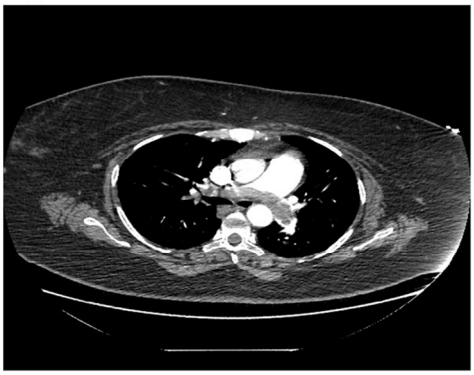

Figure 1: CTA showing saddle pulmonary embolism

338x190mm (96 x 96 DPI)

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**Figure 2**

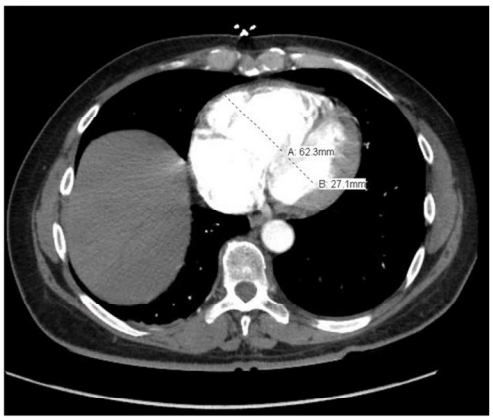


Figure 2: CTA evidence of RV dysfunction with RV/LV ratio > 1

338x190mm (96 x 96 DPI)

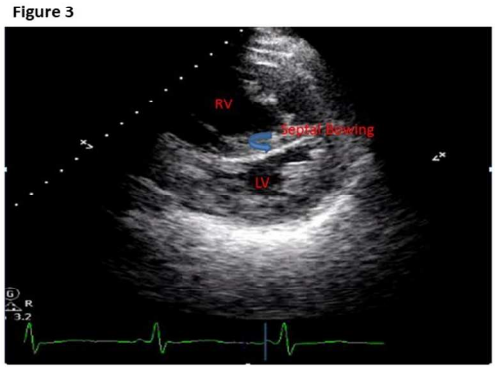


Figure 3: Short axis view of 2D echocardiogram showing evidence of RV dysfunction with Septal bowing towards left

338x190mm (96 x 96 DPI)

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Figure 4

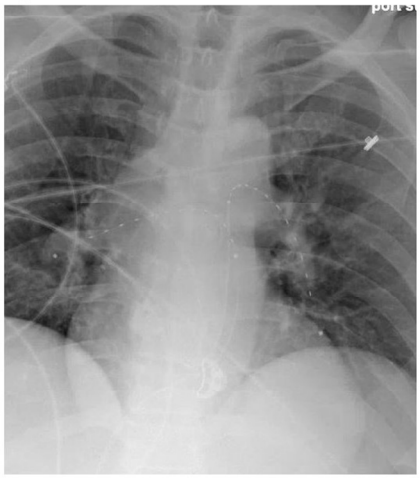

Figure 4: Chest CXR showing bilateral USAT (ultrasound assisted thrombolysis) catheters placed in lower lobe pulmonary arteries.

338x190mm (96 x 96 DPI)

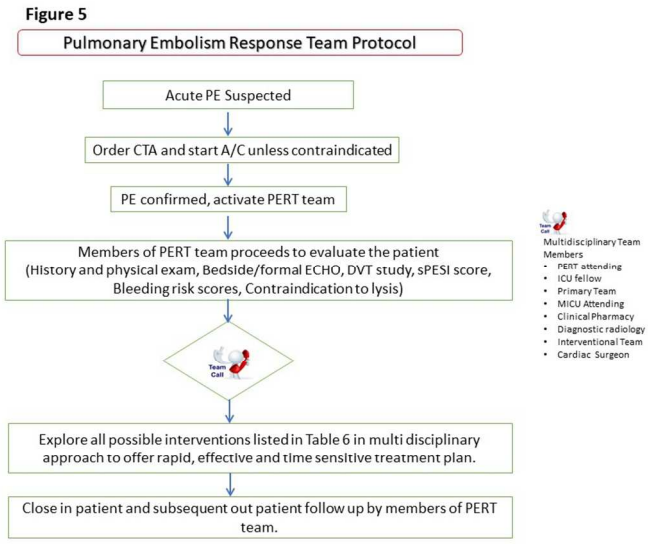


Figure 5: Pulmonary Embolism Response Team flow chart.

338x190mm (96 x 96 DPI)