Treatment and complications of pulmonary embolism

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Introduction

- 200,000 cases of pulmonary embolism diagnosed annually in US
- Acute mortality > 15% in patients with shock or cardiac arrest
- Mortality rates vary widely: approximately 10% of all pt with acute PE die within 3 mo of diagnosis

Complications

- Death
- Bleeding
- Recurrent veno-thrombotic events/PE
- Disability (pulmonary hypertension, CVA)

Treatment options

- Anticoagulation/antithrombotic therapy
- Thrombolysis/Fibrinolysis
- Embolectomy
- Inferior vena cava filter
- Monitoring without intervention

Patient Evaluation

- Risk of death or disability
- Risk of bleeding

Patient Evaluation

- **High risk** (“massive”)
  - SBP < 90 for > 15 minutes
  - Need for vasopressors
  - Clear evidence of shock
- **Intermediate risk** (“submassive”)
  - Lack high risk criteria
  - Signs of RV dysfunction (RV/LV ratio > 1, RV abn on echo, elevated trop)
- **Low risk**
  - None of the above

Treatment of “high risk” PE patients

- Mortality is high
  -studies from the 1960-1970s have a 30-50% mortality at two weeks (pre-anticoagulation?)
  -Currently acute mortality = 15%

- Therefore, rapid systemic thrombolysis is recommended

Treatment of "high risk" PE patients
Evaluate for contraindications to thrombolytic therapy

Absolute

-Prior ICH

-Cerebral aneurysm

-Malig intracranial neoplasm

-Isch CVA within prev 3 mo

-aortic dissection

-active bleeding/diathesis

-closed head/facial trauma prev 3 mo

Relative

-Hx of chronic, severe, poorly controlled HTN

-SBP > 180, DBP > 110

-Isch CVA > 3 mo ago

-Major surgery < 3 week prev

-CPR > 10 min

-Non compressible vasc puncture

-Recent invasive procedure

-Pregnancy

-Active peptic ulcer disease

-Pericarditis/pericardial fluid

-Current use of anticoag (INR > 1.7)

-Age > 75

-Diabetic retinopathy

Treatment of "high risk" PE patients
No contraindication to systemic fibrinolytics

-Support with oxygen/ventilation, IV crystalloid fluids, vasopressors

-Systemic fibrinolytics:

-alteplase (TPA) 100 mg over 2 hours

-tenecteplase 30-50 (TNK) mg (weight based) given over 5 -10 seconds

- Weight based IV heparin can be started immediately after fibrinolytic infusion

Treatment of high risk PE patients
Contraindication to systemic fibrinolytics

-Support with oxygen/ventilation, IV crystalloid fluids, vasopressors

-Catheter based intervention (ultrasound-assisted thrombolysis, Rheolytic embolectomy, rotational embolectomy, suction embolectomy)

- Surgical embolectomy

Treatment of "intermediate risk" PE patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

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Treatment of “intermediate risk” PE patients

- Randomized , double blind trial
- Tenecteplase (TNK) plus heparin versus heparin alone
- n = 1006
- Patients: ≥ 18 yo, confirmed PE within 15 days, normotensive, RV dysfunction, elevated troponin
- Primary outcome: Death or hemodynamic compromise during first 7 days

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

* Plus–minus values are means ±SD. Odds ratios and P values are provided for efficacy outcomes that were prespecified in the trial protocol.

Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N = 506)	Placebo (N = 499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

* Odds ratios and P values are provided for efficacy and safety outcomes that were prespecified in the trial protocol.
† Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis.
‡ Hemorrhagic stroke included hemorrhagic conversion of ischemic stroke.

Treatment of "intermediate risk" PE patients Long-term outcomes

- 709 of 1006 patients participated
- Median f/u was 37.8 mo
- Mortality: TNK 20.3% versus placebo 18.0% *(p = 0.43)
- Dyspnea/functional limitation: TNK 36% vs 30.1% placebo (p = 0.23). Mostly mild dyspnea reported
- Echo: available in 290 patients with no diff in RV function
- CTEPH: TNK 2.1% versus placebo 3.2% (p=0.79)

J Am Coll Card, 2017

Treatment of "intermediate risk" PE patients
Ultrasound-assisted Catheter-directed Thrombolysis

- ULTIMA Trial: Circulation, 2013
- Randomized, controlled trial
- n=59, acute main or LLL PA PE, RV/LV ≥ 1.
- Randomized to USAT 10/20 mg TPA over 15 hr vs hep IV
- Primary outcome: RV/LV ratio baseline to 24 hours
- Safety outcomes at 90 days: death, major and minor bleeding and recurrent VTE events

Circulation, 2013

Table 2. Echocardiographic Core Laboratory Data

	Baseline		24 h		90 days		Difference: Baseline vs 24 h		Difference: Baseline vs 90 d	
	USAT	Heparin	USAT	Heparin	USAT	Heparin	USAT	Heparin	USAT	Heparin
RV/LV ratio, mean±SD	1.28±0.19	1.20±0.14	0.99±0.17	1.17±0.20	0.92±0.15	0.96±0.16	0.30±0.19	0.03±0.16	0.35±0.22	0.24±0.19
n	26	29	28	28	26	27	25	28	23	27
Between-group comparison	P=0.07		P=0.001		P=0.36		P<0.001		P=0.07	
Within-group comparison	NA		NA		NA		P<0.001	P=0.31	P<0.001	P<0.001
RV systolic dysfunction, n										
None/mild/moderate/severe	0/4/5/16	0/5/11/13	5/10/10/2	1/9/7/11	19/5/0/0	10/15/1/1	1.1±0.8*	0.3±0.4*	2.2±0.9*	1.5±0.9*
Between-group comparison	P=0.37		P=0.01		P=0.003		P<0.001		P=0.01	
Within-group comparison	NA		NA		NA		P<0.001	P=0.02	P<0.001	P<0.001
TAPSE, mean±SD, mm	15.7±3.8	19.9±5.8	18.6±4.3	19.4±5.0	21.4±4.6	23.0±3.6	-3.1±4.4	0.9±4.9	-6.1±4.6	-3.4±5.4
n	20	20	20	23	19	23	16	18	13	18
Between-group comparison	P=0.01		P=0.56		P=0.21		P=0.02		P=0.16	
Within-group comparison	NA		NA		NA		P=0.014	P=0.43	P<0.001	P=0.02
RV/RA pressure gradient, mean±SD, mmHg	42.8±16.6	42.2±16.3	33.9±13.2	40.2±13.3	33.1±13.1	29.9±17.7	9.8±9.9	0.3±10.9	12.3±12.8	11.8±15.1
n	17	22	14	21	12	13	11	17	10	11
Between-group comparison	P=0.91		P=0.18		P=0.62		P=0.03		P=0.91	
Within-group comparison	NA		NA		NA		P=0.01	P=0.91	P=0.01	P=0.03
Minimum IVC diameter, mean±SD, mm	15.5±6.2	14.4±4.3	10.8±3.4	17.4±6.8	9.4±3.6	9.9±5.2	7.2±3.9	0.7±5.0	4.0±9.1	6.1±5.4
n	10	10	8	10	8	13	6	7	4	7
Between-group comparison	P=0.65		P=0.02		P=0.80		P=0.02		P=0.69	
Within-group comparison	NA		NA		NA		P=0.01	P=0.72	P=0.44	P=0.02

IVC indicates inferior vena cava; NA, not applicable; RV/LV, right ventricular to left ventricular; RV/RA, right ventricular to right atrial; TAPSE, tricuspid annular systolic excursion; and USAT, ultrasound-assisted catheter-directed thrombolysis.

*Differences between neighboring categories of right ventricular systolic dysfunction were scored as 1.

Treatment of "intermediate risk" PE patients
Ultrasound-assisted Catheter-directed Thrombolysis

Safety at 90 days:

- No HD decompensation in either group
- No recurrent VTE in either group
- Mortality: USAT 0% vs Hep IV 3% (p =1)
- No major bleeding in either group
- Minor bleeding: USAT 10% vs Hep IV 3% (p=0.6)

Circulation, 2013

Treatment of "intermediate risk" PE patients
Ultrasound-assisted Catheter-directed Thrombolysis

Seattle II study: JACC, 2015

- single arm
- 150 patients (119 int risk, 31 high risk)
- 24mg TPA for 12 or 24 hrs
- At 48 hrs: RV/LV ratio from 1.55 to 1.13 at 48 hr, m PASP 51 to 37 mmHg, mod Miller score 22.5 to 15.8
- One GUSTO severe bleed, 15 moderate bleeds, 0 ICH

Treatment of "intermediate risk" PE patients
Ultrasound-assisted Catheter-directed Thrombolysis

OPTALYSE PE, JACC 2018

-four arms

-n=101

-RV/LV ratio at 48 hrs

-mMiller score

-Bleeding

Cohorts

1: 2hr 4/8 mg TPA

2: 4hr 4/8 mg TPA

3: 6hr 6/12 mg TPA

4: 6hr 12/24 mg TPA

Treatment of "intermediate risk" PE patients
Ultrasound-assisted Catheter-directed Thrombolysis

-Similar decrease in reduction of RV/LV ratio (can get away with shorter time and lower TPA)

-mMiller score all reduced but more so in higher TPA arms

-Major bleeds: 5%

-Major Bleeds by cohort:

1: 0

2: 2 (one ICH)

3: 1

4: 2 (one ICH)

JACC, 2018

Thrombolysis for Acute PE
ACCP Guidelines

- Systemic thrombolysis is indicated for PE patients with hypotension/shock and do not have a high risk of bleeding (Grade 2B)
- Do not use systemic thrombolysis in low or intermediate risk patients (Grade 1B)
- In selected PE patient who deteriorate after anticoagulation, systemic thrombolysis should be given (2C)

Chest, 2016

Thrombolysis for Acute PE
ACCP Guidelines

- In patients with acute PE who are treated with a thrombolytic agent, systemic thrombolysis is preferred (Grade 2C)

- In PE patients with hypotension/shock with: a) high bleed risk, b) failed systemic thrombolysis, c) lifethreatening shock that cannot wait for systemic thrombolysis to work, catheter based therapy is advised if appropriate expertise/resources are available (Grade 2C)

Chest, 2016

Anticoagulation for treatment of PE
Rate of VTE Recurrence w/o anticoagulation

VTE type	First year	Annual rate after first year
First episode of unprovoked	10 %	5 %
Second episode of unprovoked	15 %	7.5%
First episode provoked by surgery	1 %	0.5 %
First episode by non-surgical risk factor	5 %	2.5%

Chest, 2012

Anticoagulation for treatment of PE
Risk factors for Bleeding

- Age >65 y
- Age >75 y
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- Nonsteroidal anti-inflammatory drug

Chest, 2016

Anticoagulation for treatment of PE
Estimate of risk of major bleeding

	Low Risk[e] (0 Risk Factors)	Moderate Risk[e] (1 Risk Factor)	High Risk[e] (≥2 Risk Factors)
Anticoagulation 0-3 mo[f]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[g]	3.2	12.8[h]
Anticoagulation after first 3 mo[f]			
Baseline risk (%/y)	0.3[i]	0.6	≥2.5
Increased risk (%/y)	0.5	1.0	≥4.0
Total risk (%/y)	0.8[j]	1.6[j]	≥6.5

Chest, 2016

Anticoagulation for treatment of PE

Agent selection

- ease of administration
- cost
- pharmokinetics
- effectiveness
- reduced risk of bleeding

Length of treatment

- provoked versus idiopathic
- balance of risk of VTE recurrence versus bleed
- ”long term” (3-6 mo) versus indefinite/extended (forever unless complication)

Anticoagulation for treatment of PE

TABLE 6] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

INR = International Normalized Ratio; NOAC = non-vitamin K oral coagulant. See Table 1 legend for expansion of other abbreviations.

Chest, 2016

Anticoagulation for treatment of PE
Agent selection (ACCP Guidelines)

- For non-cancer patients, DOACs are preferred to vitamin K antagonists (Grade 2B)
- For cancer patients, long term LMWH is recommended over DOACs (Grade 2C) and VKAs (Grade 2B)

Chest, 2016

Anticoagulation for treatment of PE
Length of Treatment (ACCP guidelines)

- All Patients with PE/proximal DVT are recommended to have 3 months of therapy minimum (Grade 1B)
- If surgical or medical reversible risk factor, 3 months is sufficient (Grade 1B)
- If unprovoked PE/proximal DVT, 3 months for high risk bleed patients (Grade 1B) and indefinite/extended for low/medium risk patients (Grade 2B)

Chest, 2016

Anticoagulation for treatment of PE
Length of Treatment (ACCP guidelines)

- All Patients with PE/proximal DVT are recommended to have 3 months of therapy minimum (Grade 1B)
- If surgical or medical reversible risk factor, 3 months is sufficient (Grade 1B)
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Chest, 2016

Aspirin Therapy for Long term prevention of PE

- Less effective than anticoagulants
- Nevertheless, decreases recurrent VTE by approximately 30%
- Major bleed incidence is statistically equal
- ACCP guidelines recommend ASA for patients with a history of unprovoked PE/prox DVT who are not on anticoagulation and can take ASA

Chest, 2016

Summary

- Thrombolysis for PE is reserved for a subset of patients with hypotension/shock
- Systemic thrombolysis is preferred to catheter directed therapy save patients with high risk of catastrophic bleeding
- 3 months anticoagulation is preferred to other limited times frames of treatment but some patients should receive indefinite/extended therapy

Summary

- ASA should be recommended to patients with unprovoked VTE who stop anticoagulation and can take ASA