

# PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

## International Consensus Statement 2013 Guidelines According to Scientific Evidence

*Developed under the auspices of the:*

Cardiovascular Disease Educational and Research Trust (UK)

European Venous Forum

North American Thrombosis Forum

International Union of Angiology and

Union Internationale du Phlebologie

# Thrombolytic Therapy

## Chapter 15

# General Considerations

## Thrombolysis for PE

- **Strategies to eliminate acute PE are designed to improve survival in patients and reduce the long-standing morbidity of pulmonary hypertension<sup>1</sup>**
- **Although clinical features (age and co-morbidities) influence prognosis of acute PE, they are not sufficiently predictive of outcome in the absence of imaging or biomarkers<sup>2-9</sup>**

1. Jaff MR, et al. *Circulation*. 2011; 123:1788-830.

2. Vogel D, et al. *J Vasc Surg*. 2012; (In press).

3. Goldhaber SZ, et al. *Lancet*. 1999; 353:1386-9.

4. Grifoni S, et al. *Circulation*. 2000; 101:2817-22.

5. Aujesky D, et al. *J Intern Med*. 2007; 261:597-604.

6. Aujesky D, et al. *Eur Heart J*. 2006; 27:476-81.

7. Aujesky D, et al. *Am J Respir Crit Care Med*. 2005; 172:1041-6.

8. Wicki J, et al. *Thromb Haemost*. 2000; 84:548-52.

9. Bova C, et al. *J Thromb Haemost*. 2009; 7:938-44.

# General Considerations

## Thrombolysis for PE - CT Angiography

- **Burden of thrombus by quantitative assessment of a CT angiogram does not predict adverse outcomes<sup>1</sup>**
- **CT scan measurement of right ventricular (RV) dilation is associated with in-hospital mortality, 30-day mortality, and 3-month mortality<sup>2-4</sup>**
  - ▶ RV/LV index  $>0.9$  is associated with adverse outcomes<sup>3,5</sup>
- **Ventricular septal deviation has also been shown to be predictive of short-term mortality<sup>6</sup>**
  - ▶ Meta-analysis (2 studies) in 191 patients showed a sensitivity of 65% (95% CI 35-85%) and specificity of 56% (95% CI 39-71%) for short term mortality<sup>7</sup>

1. Subramaniam RM, et al. JR Am J Roentgenol. 2008; 190:1599-604.

2. Ghuyssen A, et al. Thorax. 2005; 60:956-61.

3. Schoepf UJ, et al. Circulation. 2004; 110:3276-80.

4. van der Meer RW, et al. Radiology. 2005; 235:798-803.

5. Quiroz R, et al. Circulation. 2004; 109:2401-4.

6. Arazo PA, et al. Radiology. 2007; 242:889-97.

7. Sanchez O, et al. Eur Heart J. 2008; 29:1569-77.

# General Considerations

## Thrombolysis for PE - Echocardiography

- **Large PE obstructing the RV outflow can produce RV dysfunction**
  - ▶ Systematic review of RV dysfunction defined by echocardiogram in 5 studies (475 patients) with stable PE demonstrated an odds ratio of 2.53 (95% CI, 1.17-5.50) for short-term mortality<sup>1</sup>
  - ▶ Pooled sensitivity of 70% (95% CI 46-86%) and specificity of 57% (95% CI 47-66%) for short term mortality<sup>1</sup>

# General Considerations

## Thrombolysis for PE - Troponins

- **Troponin-I and troponin-T are markers of myocardial injury released from microinfarction of right ventricular muscle**
  - ▶ Associated with an adverse prognosis in patients with acute PE<sup>1-6</sup>
  - ▶ Meta-analysis of elevated troponin levels in patients with submassive PE demonstrated a mortality rate of 19.7% compared with 3.7% in patients with normal troponins (RR 4.72; 95% CI 3.45 to 6.47)<sup>7</sup>

1. Konstantinides S, et al. *Circulation*. 2002; 106:1263-8.
2. Douketis JD, et al. *Arch Intern Med*. 2002; 162:79-81.
3. Douketis JD, et al. *J Thromb Haemost*. 2005; 3:508-13.
4. Mehta NJ, et al. *Am Heart J*. 2003; 145:821-5.

5. La Vecchia L, et al. *Heart*. 2004; 90:633-7.
6. Post F, et al. *Clin Res Cardiol*. 2009; 98:401-8.
7. Becattini C, et al. *Circulation*. 2007; 116:427-33.

# General Considerations

## Thrombolysis for PE - Natriuretic Peptides

- **The natriuretic peptides include brain natriuretic peptides (BNP) and N-terminal pro-BNP**
  - ▶ Reviews demonstrate mortality is increased 5 to 9.5 fold depending upon whether BNP or N-terminal pro-BNP was studied<sup>1-3</sup>
  - ▶ Meta-analysis (2 studies) in 170 patients showed a pooled sensitivity of 93% (95% CI 14-100%) and specificity of 59% (95% CI 14-92%) for short term mortality<sup>4</sup>

1. Tulevski II, et al. *Thromb Haemost.* 2001; 86:1193-6.
2. Cavallazzi R, et al. *Intensive Care Med.* 2008; 34:2147-56.
3. Klok FA, et al. *Am J Respir Crit Care Med.* 2008; 178:425-30.
4. Sanchez O, et al. *Eur Heart J.* 2008; 29:1569-77.

# General Considerations

## Thrombolysis for PE - Electrocardiography

- **PE large enough to cause abnormalities in the conducting system that reveal right heart strain is indicative of worsening prognosis<sup>1-11</sup>**
  - ▶ Electrical abnormalities include sinus tachycardia, atrial arrhythmias, right bundle branch block, S1Q3T3 pattern and ST-segment changes in V1-V4

1. Kosuge M, et al. *Circ J.* 2006; 70:750-5.
2. Kucher N, et al. *Eur Heart J.* 2003; 24:1651-6.
3. Vanni S, et al. *Am J Med.* 2009; 122:257-64.
4. Geibel A, et al. *Eur Respir J.* 2005; 25:843-8.
5. Ferrari E, et al. *Chest.* 1997; 111:537-43.
6. Kanbay A, et al. *Respir Med.* 2007; 101:1171-6.

7. Nielsen TT, et al. *Cardiology.* 1989; 76:274-84.
8. Toosi MS, et al. *Am J Cardiol.* 2007; 100:1172-6.
9. Escobar C, et al. *Rev Esp Cardiol.* 2008; 61:244-50.
10. Kucher N, et al. *Eur Heart J.* 2003; 24:1113-9.
11. Daniel KR, et al. *Chest.* 2001; 120:474-81.



# General Considerations

## Thrombolysis for PE – Risk Stratification

- **Low-risk PE refers to patients with the lowest mortality of acute PE**
  - ▶ Normotensive with no RV dysfunction and normal biomarkers
  - ▶ Prognosis in these patients is good, with a short-term mortality rate of approximately 1%<sup>1-3</sup>
- **Submassive PE refers to patients that are hemodynamically stable but with acute PE large enough to cause tachycardia, electrical disturbances on EKG, RV dysfunction, or an increase in cardiac biomarkers**

1. Bova C, et al. J Thromb Haemost. 2009; 7:938-44.
2. Post F, et al. Clin Res Cardiol. 2009; 98:401-8.
3. Palmieri V, et al. Intern Emerg Med. 2008; 3:131-8.

# General Considerations

## Thrombolysis for PE – Risk Stratification

- **Massive PE is defined as acute PE causing sustained hypotension (>15 min)**
  - ▶ The MAPPET registry demonstrated in-hospital mortality of 25% for patients presenting with cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation compared with 8.1% in those who were hemodynamically stable<sup>1</sup>
  - ▶ Systolic blood pressure of <100 mmHg is a predictor of adverse outcomes<sup>2,3</sup>
- **ICOPER registry showed the 90-day mortality rate for patients with acute PE and systolic blood pressure <90 mmHg was 52.4% versus 14.7%<sup>4</sup>**

1. Kasper W, et al. J Am Coll Cardiol. 1997; 30:1165-71.

2. Aujesky D, et al. Am J Respir Crit Care Med. 2005; 172:1041-6.

3. Wicki J, et al. Thromb Haemost. 2000; 84:548-52.

4. Kucher N, et al. Circulation. 2006; 113:577-82.

# Review of Evidence

## Systemic Thrombolysis

- **Analysis of selected trials of systemic streptokinase demonstrate venous valve function may be preserved compared with standard anticoagulation therapy<sup>1,2</sup>**
  - ▶ Systemic thrombolysis with a lytic agent was 3.7 times more effective than heparin alone<sup>3</sup>
  - ▶ Pooled analysis of 13 studies demonstrated that only 4% treated with heparin had successful lysis compared with 45% receiving systemic thrombolysis<sup>4</sup>
  - ▶ Prolonged streptokinase infusions were often associated with allergic reactions and a hemorrhagic rate three-fold higher than patients managed with heparin anticoagulation alone<sup>3</sup>

1. Arnesen H, et al. Acta Med Scand. 1978; 203:457-63.

2. Jeffery P, et al. Paper presented at: Proceedings of the 2nd International vascular Symposium, 1986; London.

3. Goldhaber SZ, et al. Am J Med. 1984; 76:393-7.

4. Comerota AJ, et al. Can J Surg. 1993; 36:359-64.

# Review of Evidence

## Systemic Thrombolysis

- **RCT comparing recombinant tissue plasminogen activator (rt-PA) versus anticoagulation<sup>1</sup>**
  - ▶ rt-PA achieved >50% greater clot lysis than anticoagulation alone (58% vs 0%,  $P=0.002$ )
  - ▶ rt-PA-treated patients tended to have reduced PTS (25% vs 56%,  $P=0.07$ )
- **However, major bleeding was significantly higher with lytics compared to anticoagulation alone ( $P<0.04$ )<sup>1-3</sup>**

1. Turpie AG, et al. Chest. 1990; 97:172S-5S.  
2. Goldhaber SZ, et al. Am J Med. 1984; 76:393-7.  
3. Goldhaber SZ, et al. Am J Med. 1990; 88:235-40.

# Review of Evidence

## Catheter-Directed Thrombolysis

- **Catheter-directed thrombolysis**

- ▶ Infusion of plasminogen activator directly into the thrombus using ultrasound-guided access and fluoroscopic positioning of catheter into the thrombus<sup>1-9</sup>
- ▶ Results in fewer major bleeding complications<sup>1-9</sup>
- ▶ Associated with improved efficacy<sup>1-9</sup>
- ▶ Successful CDT in 80-90% of patients if treated within 14 days<sup>1-10</sup>
- ▶ May result in improved QoL<sup>10,11</sup>
- ▶ Frequency and severity of PTS is directly related to degree of residual thrombus following CDT<sup>12</sup>

1. Elsharawy M, et al. *Eur J Vasc Endovasc Surg.* 2002; 24:209-14.
2. Enden T, et al. *J Thromb Haemost.* 2009; 7:1268-75.
3. Baekgaard N, et al. *Eur J Vasc Endovasc Surg.* 2010; 39:112-7.
4. Semba CP, Dake MD. *Radiology.* 1994; 191:487-94.
5. Bjarnason H, et al. *J Vasc Interv Radiol.* 1997; 8:405-18.
6. Mewissen MW, et al. *Radiology.* 1999; 211:39-49.

6. Sillesen H, et al. *Eur J Vasc Endovasc Surg.* 2005; 30:556-62.
8. Comerota AJ, Kagan SA. *Phlebology* 2000; 15:149-55.
9. Martinez Trabal JL, et al. *J Vasc Surg.* 2008; 48:1532-7.
10. Comerota AJ, et al. *J Vasc Surg.* 2000; 32:130-7.
11. Grewal NK, et al. *J Vasc Surg.* 2010; 51:1209-14.
12. Comerota AJ, et al. *J Vasc Surg.* 2012; 55:768-73.

# Review of Evidence

## Catheter-Directed Thrombolysis

- **Bleeding complications exceeded 10%, in early studies but have been reduced in contemporary reports<sup>1</sup>**
  - ▶ CaVenT investigators reported that patients randomized to CDT plus anticoagulation had a major bleeding event rate of 3% versus 0% of patients randomized to anticoagulation alone<sup>2</sup>
- **Reduction in bleeding events is multifactorial**
  - ▶ Lower concentrations and overall dose of plasminogen activators
  - ▶ Routine incorporation of ultrasound-guided vein puncture
  - ▶ Lower doses of heparin during lytic infusion

1. Mewissen MW, et al. Radiology. 1999; 211:39-49.

2. Enden T, et al. Lancet. 2012; 379:31-8.

# Review of Evidence

## Catheter-Directed Thrombolysis

- **RCT (209 patients) compared CDT followed by anticoagulation with anticoagulation alone for iliofemoral DVT<sup>1</sup>**
  - ▶ Incidence of PTS was reduced from 55.6% in the control group to 41.1% in the CDT group ( $P=0.047$ ) at 24 months
  - ▶ Iliofemoral patency was found in 65.9% of patients in the CDT group and 47.4% in the control group ( $P=0.012$ ) at 6 months
  - ▶ 20 bleeding complications related to CDT included 3 major and 5 clinically relevant bleeds

# Review of Evidence

## Pharmacomechanical Thrombolysis

- **Pharmacomechanical thrombolysis refers to percutaneous catheter-based techniques that integrate mechanical clot disruption in conjunction with intra-thrombus infusion of plasminogen activator**
  - ▶ Catheter-based mechanical thrombectomy alone, which includes aspiration, maceration, and/or fragmentation, has not been successful<sup>1-3</sup>
  - ▶ Clot manipulation in the absence of concomitant thrombolytic therapy has been associated with increased risk of symptomatic PE<sup>1-3</sup>

1. Kasirajan K, et al. Vasc Interv Radiol. 2001; 12:179-85.
2. Delomez M, et al. Cardiovasc Intervent Radiol. 2001; 24:42-8.
3. Vedantham S, et al. J Vasc Interv Radiol. 2002; 13:1001-8.



# Review of Evidence

- **NIH-sponsored trials comparing lytic therapy versus heparin demonstrated more rapid and complete clearing of PE with lysis but without reduction of mortality and an increased risk of bleeding<sup>1,2</sup>**
  - ▶ At one year follow-up, lytic patients had better oxygen diffusing capacity and pulmonary capillary blood volume<sup>3</sup>

1. Urokinase-streptokinase embolism trial. JAMA. 1974; 229:1606-13.  
2. The urokinase pulmonary embolism trial. Circulation. 1973; 47:111-108.  
3. Sharma GV, et al. N Engl J Med. 1980; 303:842-5.

# Review of Evidence

- **RCT of thrombolytic therapy plus heparin versus heparin alone for submassive PE demonstrated improved outcomes with lysis with significantly fewer patients requiring salvage lysis or aggressive clinical support<sup>1</sup>**
- **Patients with massive PE demonstrated a meaningful reduction in recurrent PE or death with thrombolytic therapy (9.4%) versus anticoagulation (19.0%) (OR 0.45, 95% CI 0.22-0.90)<sup>2</sup>**

1. Konstantinides S, et al. N Engl J Med. 2002; 347:1143-50.

2. Wan S, et al. Circulation. 2004; 110:744-9.

# Catheter-Based Interventions for PE

- **Early technique of aspiration thrombectomy (Greenfield suction) and embolectomy catheter is currently the only FDA-approved device<sup>1</sup>**
  - ▶ Not widely adopted secondary to technical and physiologic difficulties
- **Advances in catheter-based technology has demonstrated thrombus fragmentation can be performed<sup>2-8</sup>**

1. Greenfield LJ, et al. J Vasc Surg. 1993; 18:450-7

2. Kucher N, et al. Radiology. 2005; 236:852-8.

3. Handa K, et al. Angiology. 1988; 39:775-8.

4. Schmitz-Rode T, et al. J Am Coll Cardiol. 2000; 36:375-80.

5. Fava M, Loyola S. Tech Vasc Interv Radiol. 2003; 6:53-8.

6. Cho KJ, Dasika NL. Semin Vasc Surg. 2000; 13:221-35.

7. Skaf E, et al. Am J Cardiol. 2007; 99:415-20.

8. Chechi T, et al. Catheter Cardiovasc Interv. 2009; 73:506-13.

# Catheter-Based Interventions for PE

- **A systematic review of percutaneous therapy alone for patients with massive PE found<sup>1</sup>**
  - ▶ 81% success rate with mechanical therapy
  - ▶ 95% success rate when combined with the addition of infusion of a thrombolytic agent
  - ▶ It appears that incorporating both the pharmacologic and mechanical advantage when catheter techniques are used for massive PE is reasonable
- **The risk of pulmonary artery perforation increases when arteries smaller than 6 mm in diameter are treated<sup>2</sup>**

1. Skaf E, et al. Am J Cardiol. 2007; 99:415-20.

2. Biederer J, et al. J Endovasc Ther. 2006; 13:549-60.

# Surgical Embolectomy

- **Operative embolectomy for acute massive PE remains a viable treatment option**
  - ▶ Effective in rescue of patients with failed systemic thrombolysis<sup>1</sup>
- **Reports of operative mortality of 25-30% have reduced enthusiasm for operative approaches<sup>2</sup>**
- **Contemporary series are associated with substantially improved outcomes<sup>3,4</sup>**

1. Meneveau N, et al. Chest. 2006; 129:1043-50.

2. Skaf E, et al. Am J Cardiol. 2007; 99:415-20.

3. Leacche M, et al. J Thorac Cardiovasc Surg. 2005; 129:1018-23.

4. Sukhija R, et al. Am J Cardiol. 2005; 95:695-6.

# Recommendations

## Thrombolysis for DVT

- **Systemic thrombolysis for proximal DVT patients is not recommended due to low efficacy and increased risk of bleeding complications**
  - ▶ Level of evidence: High
- **Catheter-directed thrombolysis is recommended for patients with acute iliofemoral DVT**
  - ▶ Level of evidence: Moderate
- **Physicians puncturing deep veins should use ultrasound guidance for access**
  - ▶ Level of evidence: Low

# Recommendations

## Thrombolysis for DVT

- **In centers where expertise is available, pharmacomechanical thrombolysis is recommended as initial therapy for patients with iliofemoral DVT**
  - ▶ Level of evidence: Low
- **Pharmacomechanical thrombolysis is recommended in preference to CDT for iliofemoral DVT in centers where appropriate expertise is available**
  - ▶ Level of evidence: Low

# Recommendations

## Thrombolysis for DVT

- **Percutaneous mechanical thrombectomy alone (in the absence of thrombolytic therapy) is not recommended for the management of patients with acute DVT**
  - ▶ Level of evidence: Low
- **Patients treated with CDT or pharmacomechanical thrombolysis should receive the same intensity and duration of anticoagulation**
  - ▶ Level of evidence: Low



# Recommendations

## Thrombolysis for PE

- **All patients with PE should undergo risk stratification**
  - ▶ Level of evidence: High
- **Patients with massive PE should undergo thrombolytic therapy in the absence of risk factors for bleeding complications**
  - ▶ Level of evidence: High
- **Thrombolytic therapy should be considered in patients with submassive acute PE if they are not at high risk for bleeding complications**
  - ▶ Level of evidence: Moderate

# Recommendations

## Thrombolysis for PE

- **Thrombolytic therapy is not recommended for patients with low risk PE**
  - ▶ Level of evidence: Moderate
- **The same intensity and duration of anticoagulation should be offered to patients treated with thrombolytic therapy for PE**
  - ▶ Level of evidence: Low
- **In patients with massive PE, catheter-based intervention or surgical embolectomy are reasonable alternatives**
  - ▶ Level of evidence: Low

# Recommendations

## Thrombolysis for PE

- **Catheter-based embolectomy or surgical embolectomy is recommended following unsuccessful thrombolysis for PE**
  - ▶ Level of evidence: Low
- **Catheter-based intervention or operative surgical embolectomy can be considered for patients with submassive PE who are at increased risk for bleeding from systemic thrombolytic therapy**
  - ▶ Level of evidence: Low
- **Patients with acute PE who are at low risk are best treated with anticoagulation alone**
  - ▶ Level of evidence: Moderate