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[1]**
- **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[2-9]**

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[1]**
- **CT scan measurement of right ventricular (RV) dilation is associated with in-hospital mortality, 30-day mortality, and 3-month mortality[2-4]**
  - RV/LV index >0.9 is associated with adverse outcomes[3,5]
- **Ventricular septal deviation has also been shown to be predictive of short-term mortality[6]**
  - 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[7]

1. Subramaniam RM, et al. JR Am J Roentgenol. 2008; 190:1599-604.
2. Ghuysen 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. Araoz 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[1]
  - Pooled sensitivity of 70% (95% CI 46-86%) and specificity of 57% (95% CI 47-66%) for short term mortality[1]

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

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[1-6]
  - 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)[7]

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[1-3]
  - 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[4]

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[1-11]**
  - 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%[1-3]
- **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[1]
  - Systolic blood pressure of <100 mmHg is a predictor of adverse outcomes[2,3]
- **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%[4]**

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[1,2]**
  - Systemic thrombolysis with a lytic agent was 3.7 times more effective than heparin alone[3]
  - Pooled analysis of 13 studies demonstrated that only 4% treated with heparin had successful lysis compared with 45% receiving systemic thrombolysis[4]
  - Prolonged streptokinase infusions were often associated with allergic reactions and a hemorrhagic rate three-fold higher than patients managed with heparin anticoagulation alone[3]

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[1]**
  - 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)[1-3]**

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[1-9]
  - Results in fewer major bleeding complications[1-9]
  - Associated with improved efficacy[1-9]
  - Successful CDT in 80-90% of patients if treated within 14 days [1-10]
  - May result in improved QoL[10,11]
  - Frequency and severity of PTS is directly related to degree of residual thrombus following CDT[12]

1. Elsharawy M, et al. E. 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[1]**
  - 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[2]
- **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[1]**
  - 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

1. Elsharawy M, Elzayat E. Eur J Vasc Endovasc Surg. 2002; 24:209-14.

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[1-3]
  - Clot manipulation in the absence of concomitant thrombolytic therapy has been associated with increased risk of symptomatic PE[1-3]

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[1,2]**
  - At one year follow-up, lytic patients had better oxygen diffusing capacity and pulmonary capillary blood volume[3]

1. Urokinase-streptokinase embolism trial. JAMA. 1974; 229:1606-13.
2. The urokinase pulmonary embolism trial. Circulation. 1973; 47:II1-108.
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[1]**
- **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)[2]**

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[1]**
  - Not widely adopted secondary to technical and physiologic difficulties
- **Advances in catheter-based technology has demonstrated thrombus fragmentation can be performed[2-8]**

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[1]**
  - 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[2]**

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[1]
- **Reports of operative mortality of 25-30% have reduced enthusiasm for operative approaches[2]**
- **Contemporary series are associated with substantially improved outcomes[3,4]**

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