

Clinical Practice Guidelines for Anticoagulation for Pulmonary Embolism

Introduction: The Southwest Texas Regional Advisory Council (STRAC), in conjunction with its partner institutions, has developed a pulmonary embolism (PE) guideline to standardize care and referral patterns of patients with acute pulmonary embolism presenting to centers lacking advanced treatment modalities. Anticoagulation is a critical intervention that must be initiated prior to transfer. This whitepaper aims to assess available evidence and make recommendations to guide initial anticoagulant choice in patients with PE who require transfer from an outlying hospital.

Background: Venous thromboembolism guidelines offer four anticoagulation options: direct acting oral anticoagulants (DOAC), unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux. Oral therapies are not appropriate for patients with massive PE or high risk sub-massive PE, which are the populations that would require transfer under this guideline.¹ Fondaparinux has a long half-life, is contraindicated in patients with CrCl < 30 mL/min, may not be available at smaller facilities, and many ED providers may be unfamiliar with its use. Accordingly, the most viable options are LMWH (in this case, enoxaparin) and UFH. While limited evidence suggests LMWH is superior to UFH, either agent would comply with guidelines.²⁻⁴

Low molecular weight heparin: Intermittent dosing with predictable response is a distinct advantage of LMWH over a continuous infusion of UFH during transport. Limitations with real time monitoring, partial reversal by protamine, and long half-life (enoxaparin 4.5 – 7 hrs) may impact follow-on procedures including thrombolysis, ECMO cannulation, catheter-directed therapies (CDTs), and surgical embolectomy. While enoxaparin can be used in renal insufficiency (decreased dosing frequency at CrCl < 30 mL/min), delayed clearance may amplify concerns about its use with the potential for subsequent catheter directed therapies or thrombolysis.⁵ Trials of thrombolysis allowed LMWH use and there is consensus among STRAC partner institutions that it would not substantially impact care after arrival.⁶⁻⁹

Unfractionated heparin: Unfractionated heparin is recommended in patients likely to undergo thrombolysis or CDTs based on short half-life, ease of monitoring with point-of-care assays and complete protamine reversibility. Delivering a continuous infusion of UFH during transport requires a critical care ambulance which can cause transfer delays of several hours. Subcutaneous dosing of UFH has similar efficacy to LMWH.^{1,2,10}

Achieving early administration of anticoagulation and rapid transfer to a higher level of care are paramount in optimizing outcomes in our target patient population.¹¹ The requirement for a critical care ambulance and its associated delays to administer a heparin infusion mandate a single administration of anticoagulant at the transferring hospital.

Recommended Approach:

If the patient is receiving a continuous infusion of UFH at the time referral, discuss anticoagulation strategy with the receiving facility.

If the patient is not receiving a continuous infusion of UFH at the time referral and the time from administration to arrival at receiving facility is estimated to be ≤ 2 hours, administer UFH 80 U/kg (actual body weight) intravenously prior to transfer. Do not initiate a continuous heparin infusion.

If the patient is not receiving a continuous infusion of UFH at the time referral and the time from administration to arrival at receiving facility is estimated to be > 2 hours, administer Enoxaparin 1 mg/kg subcutaneously prior to transfer.

1. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e419S-e496S.
2. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev*. 2017;2(2):CD001100.
3. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. *Ann Intern Med*. 1999;130(10):800-809.
4. Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. *Am J Med*. 1996;100(3):269-277.
5. Lovenox [package insert]. In. Bridgewater, NJ: Sanofi-Aventis; 2009.
6. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *The New England journal of medicine*. 2014;370(15):1402-1411.
7. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12(4):459-468.
8. Piazza G, Hohlfelder B, Jaff MR, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. *JACC Cardiovascular interventions*. 2015;8(10):1382-1392.
9. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M, Investigators M. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol*. 2013;111(2):273-277.
10. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *Jama*. 2006;296(8):935-942.
11. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest*. 2010;137(6):1382-1390.