Submitted August 2017; Accepted August 2017

EDITORIAL

Management of submassive pulmonary embolism

M. Coppens

Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands

Correspondence

m.coppens@amc.nl

Keywords - (submassive) pulmonary embolism; low-molecular weight heparin; unfractionated heparin.

Venous thromboembolism (VTE) is the third most common cause of death from cardiovascular diseases after myocardial infarction and ischaemic stroke.[1] The case fatality rate at 30 days after pulmonary embolism (PE) is reported to be around 10%.[1] The majority of VTE related deaths, however, occur in patients who were never diagnosed as having PE. From an epidemiological model it was estimated that each year 370,000 deaths related to VTE occur in six European Union countries with a total population of 454 million.[2] Of these deaths, 34% are caused by sudden fatal PE, in 59% of deaths PE remained undiagnosed during life and only 7% of cases were correctly diagnosed as PE before death. The risk of recurrence or progression of VTE on anticoagulant therapy is highest during the first 14 days and declines thereafter.[1]

In patients with acute severe PE, right ventricular failure is considered the primary cause of death due to the acute increase in pulmonary vascular resistance, which only occurs when more than 30-50% of the cross-sectional area of pulmonary arteries is obstructed by emboli. Secondary PE-induced vasoconstriction, mediated by thromboxane A2 and serotonin release, adds to the right ventricular pressure overload.[1] In the International Cooperative Pulmonary Embolism Registry (ICOPER) risk factors for early death by PE were age >70 years, systolic blood pressure <90 mmHg, respiratory rate >20 breaths/min, cancer, chronic heart failure and chronic obstructive pulmonary disease.[3] The Pulmonary Embolism Severity Index (PESI) is the best validated prognostic model for patients with acute PE and consists of these and other risk factors.[4] With points assigned to individual risk factors, a total score is calculated that puts patients into any of five risk categories. The main strength of the PESI score is that it reliably identifies patients at low risk of death for which home treatment of PE is likely to be safe (PESI classes I and II, corresponding to a 30-day mortality of 0-3.5%). Patients in PESI classes III-V have a higher risk of death at 30 days of 3.2-24.5%.[4] In PE patients with shock or hypotension, defined as a systolic blood pressure <90 mmHg or a systolic pressure drop of ≥40 mmHg for >15 min (not caused by new-onset arrhythmia, hypovolaemia, or sepsis), the European Society of Cardiology (ESC) guideline on acute PE recommends reperfusion therapy by systemic fibrinolysis, usually with recombinant tissue plasminogen activator (rt-PA).[1] For all other patients, treatment with anticoagulation with either unfractionated or low-molecular-weight heparin (LMWH) or with a direct oral anticoagulant is the mainstay of therapy. The recommendation is based on a meta-analysis of randomised trials in which fibrinolysis added to routine anticoagulation reduced the risk of death or recurrent early PE by 55% only in patients with haemodynamically unstable PE but not in haemodynamically stable patients.[5] Still, many haemodynamically stable patients fall into PESI classes III-V and have significant short-term mortality, including patients with tachycardia, severe hypoxia, as well as patients with signs of right ventricular overload and patients with elevated biomarkers such as troponin-T and or N-terminal pro-brain natriuretic peptide. This group of patients are usually referred to as patients with submassive PE. The question remains whether anticoagulation alone is sufficient or that more aggressive therapy is warranted to reduce mortality.

In this edition of the Netherlands Journal of Critical Care De Pont and Brandjes present two cases with submassive PE.[6] Both patients were initially treated with LMWH and developed a major thrombotic complication three and nine days after initiation of therapy. One patient died in spite of attempted rescue fibrinolysis, the other stabilised after a switch from LMWH to intravenous unfractionated heparin (UFH).[6] The authors highlight the importance of prognostic risk stratification in PE patients by using the PESI score and imaging and laboratory markers of right ventricular strain. They further argue that patients with submassive PE admitted to the intensive care unit (ICU) need 'aggressive anticoagulation' and suggest that continuous intravenous UFH might be preferred over intermittent subcutaneous LMWH.

In spite of the cases presented, there is no evidence to support that UFH is a more aggressive form of anticoagulation than LMWH. In fact, the Cochrane systemic review of randomised trials that compared LMWH with UFH suggests the opposite.[7] In patients with non-massive PE, LMWH, compared with UFH for initial anticoagulation of acute VTE, reduced the risk of thrombotic complications by 30%, the risk of major bleeding by 42%, and the risk of death by 23%.[7] It is presumed that the superiority of LMWH in these patients is explained by the inherent difficulty of achieving and maintaining the target activated partial thromboplastin time (APTT) in patients treated with UFH. For example, in an observational study in patients treated with UFH who were admitted to the ICU, only 56% of patients achieved a therapeutic APTT within the first 24 hours.[8] Whether UFH would be superior to LMWH in patients with submassive PE admitted to the ICU is speculative and based on pharmacokinetic arguments and some low-quality evidence from observational data. No randomised studies in this subgroup of PE patients have compared the effects of UFH with LMWH.

The cases presented by De Pont and Brandjes also raise an important point with respect to dosing of LMWH in specific patient groups, such as patients with severe renal impairment and (severely) obese patients. UFH is enzymatically degraded while LMWHs are mainly cleared renally. In patients with eGFR <30 ml/min, impaired LMWH clearance may lead to accumulation and increased bleeding risk. In patients with severe obesity, the optimal LMWH dose is similarly challenging due to differences in drug absorption, distribution and elimination in obese versus non-obese patients. The nadroparin product monograph recommends a dose of 86 IU/kg twice daily (bid) and suggests to cap the dose at a maximum of 8550 IU bid in patients weighing 90 kg or over.[9] The rationale for a cap/maximum dose would be that the volume of distribution of LMWH does not further increase with increasing body weight in severely obese patients and consequently, dosing per kg in these patients would lead to over-anticoagulation. However, in a pharmacokinetic study comparing obese (body mass index (BMI) 30-48 kg/m^2, weight 78-144 kg) with non-obese volunteers (BMI 19-26 kg/m^2) treated with enoxaparin, no indication of over-anticoagulation was observed in obese patients.[10] A similar anti-Xa activity was achieved in both groups using weight-based dosing without a maximum dose. In the light of this uncertainty of LMWH dosing in the severely obese, the ESC guideline suggests monitored UFH over unmonitored LMWH in patients with severe obesity, defined as a BMI of 35 kg/m^2 or higher.[1]

Two randomised studies have compared anticoagulation with UFH with or without systemic fibrinolysis in patients with submassive PE.[11;12] The first trial included 256 patients with acute PE without shock or hypotension but with signs of right ventricular overload on imaging or electrocardiography.[11] The second trial included a more severe subgroup of 1006 patients with submassive PE with a combination of imaging signs of right ventricular overload and elevated cardiac biomarkers.[12] In both studies, additional fibrinolysis failed to demonstrate a survival benefit over UFH only. While fibrinolytic therapy did reduce the risk of further haemodynamic decompensation, this benefit was offset by a significant increase in major bleeding in the patients treated with fibrinolysis (11.5% vs. 2.4%, OR 5.6, 95% CI 2.3-13.4), including a 2.0% risk of intracranial bleeding.[12] This suggests that systemic fibrinolysis may be too aggressive, in spite of the increased risk of death in patients with submassive PE. An interesting alternative is the use of lower dosages of fibrinolytics, either systemically or delivered locally by a pulmonary artery catheter.[13;14] Both approaches have demonstrated a reduction in right ventricular overload without an apparent increase in bleeding compared with routine anticoagulation, although neither study was adequately powered to show a difference in clinical endpoints such as thrombotic complications, bleeding or mortality. Alternatively, DS-1040 is an inhibitor of activated thrombin-activatable fibrinolysis inhibitor (TAFI) currently undergoing phase I/II testing in patients with acute PE (clinicaltrials.gov; NCT02923115).[15] TAFI inhibits fibrinolysis in the presence of high thrombin concentrations, i.e. in patients with acute submassive PE. Theoretically, TAFI inhibition could promote fibrinolysis without the increase in bleeding risk induced by systemic fibrinolysis.

In summary, studies in patients with submassive PE have thus far failed to show survival benefit from more aggressive strategies than routine anticoagulation. However, the significant risk of adverse events including death in these patients presents an unmet clinical need, for which more aggressive strategies may be justified. The question which strategy should be used is as yet unsolved and needs to be answered by robust randomised clinical trials.

Disclosures

The author has received research support, consulting and lecturing fees or travel support outside the present work from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, Pfizer, Portola, Sanquin Blood Supply.

References

1. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014 ;35:3033-9k.
2. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98:756-64.
3. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-9.
4. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172:1041-6.

5. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110:744-9.
6. De Pont AC, Brandjes D. Treating pulmonary embolism in the intensive care unit: are the guidelines helpful? Neth J Crit Care. 2017;25:xx-xx
7. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD001100.
8. Aarab R, van Es J, de Pont AC, Vroom MB, Middeldorp S. Monitoring of unfractionated heparin in critically ill patients. Neth J Med. 2013;71:466-71.
9. Aspen Pharmacare Canada Inc. Product monograph Fraxiparine nadroparin calcium injection (9,500 anti-Xa IU/mL). 11-7-2017. https://pdf.hres.ca/dpd_pm/00040204.PDF. [For users in the Netherlands, see: https://db.cbg-meb.nl/IB-teksten/h11878.pdf]
10. Sanderink GJ, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther. 2002;72:308-18.
11. Konstantinides SV, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347:1143-50.
12. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370:1402-11.
13. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-86.
14. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol. 2013;111:273-7.
15. Zhou J, Kochan J, Yin O, et al. A first-in-human study of DS-1040, an inhibitor of the activated form of thrombin-activatable fibrinolysis inhibitor, in healthy subjects. J Thromb Haemost. 2017;15:961-71.