CLINICAL DECISIONS
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Treatment of Intermediate-Risk Pulmonary Embolism

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Woman with a Pulmonary Embolism

Robert Smyth, M.D.

A 33-year-old woman presents to her local rural health center with acute-onset dyspnea and chest pain. She has no relevant medical history and takes a combined oral contraceptive for birth control. On examination, she has no fever, and her respiratory rate is 26 breaths per minute, heart rate 122 beats per minute, blood pressure 116/80 mm Hg, and oxygen saturation 92% while she is breathing ambient air. Her right leg is swollen from the upper thigh to below the knee. An electrocardiogram shows sinus tachycardia with an incomplete right bundle-branch block. Laboratory tests show a high-sensitivity troponin I level of 92 ng per liter (reference value, <35) and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 2150 pg per milliliter (reference range, 0 to 130). A computed tomographic pulmonary angiogram shows a saddle pulmonary embolism with a clot in the proximal right and left main pulmonary arteries, patchy parenchymal infiltrates, and flattening of the cardiac interventricular septum, with a ratio of right ventricular diameter to left ventricular diameter of 1.0. An echocardiogram shows moderate right ventricular dilatation with a reduced ejection fraction. The patient's vital signs remain unchanged over the course of 30 minutes. You have heard that catheter-directed therapy is being studied in some patients with pulmonary embolism at the nearest referral center, but transferring your patient would involve a 5-hour ground transport.

You must decide whether this 33-year-old woman with an acute pulmonary embolism should be treated with standard parenteral heparin alone or whether heparin should be administered in conjunction with a reduced-dose thrombolytic agent.

TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the literature, your own experience, published guidelines, and other information.

1. **Recommend thrombolysis in addition to heparin therapy.**
2. **Recommend parenteral heparin therapy only.**

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

OPTION 1

Recommend Thrombolysis in Addition to Heparin Therapy

Christopher Kabrhel, M.D., M.P.H.

After a diagnosis of pulmonary embolism is made, clinicians must estimate the patient's likelihood of death, clinical deterioration, recurrent pulmonary embolism, and bleeding, because such risk stratification guides both treatment and disposition. In particular, the decision to use advanced therapies, such as thrombolysis, should be based on the clinicians' assessments of whether these treatments maximize benefit and minimize risk.

Several factors influence the assessment of risk after a pulmonary embolism has been diag-

nosed. Among these variables, the most immediate one to consider is the patient's hemodynamic condition — particularly whether the patient is in shock. Other considerations include age and coexisting conditions, the extent and proximity of the clot, and the effects of the clot on right ventricular function. Finally, when considering treatment options, clinicians must estimate the risk of bleeding, especially intracranial hemorrhage.[1] Although multiple scoring systems are available to guide this process, the risk stratification of any given patient is more nuanced than one score can capture and is best addressed by a multidisciplinary team.

The patient in the vignette is young and has no relevant medical history or risk factors for bleeding. However, she has a clot obstructing her entire pulmonary arterial system with evidence of both right ventricular dysfunction and myocardial necrosis. The presence of a saddle pulmonary embolism and the leg swelling consistent with residual deep-vein thrombosis are worrisome, and further embolization of either could be fatal. Although she does not yet have hypotension, her heart rate is greater than her systolic blood pressure (shock index >1), and healthy young patients often maintain a normal blood pressure for a time despite substantial right ventricular dysfunction.

According to the European Society of Cardiology guidelines, this patient is at least at high-intermediate risk and may be at high risk.[1] The Bova Score is a validated prognostic model for intermediate-risk pulmonary embolism that is based on clinical variables, an assessment of right ventricular function, and myocardial injury. The score for the patient in the vignette is 5, which is stage III (the highest stage). This indicates a risk of pulmonary embolism–related complications of 42% and a risk of pulmonary embolism–related death of 10% within 30 days.[2] Conversely, because she is young with no history of stroke or myocardial infarction, her predicted risk of intracranial hemorrhage from systemic thrombolysis, on the basis of a predictive model derived from a retrospective study involving more than 9000 patients undergoing thrombolysis for pulmonary embolism, is low (1.2%).[3]

Although a large, randomized trial comparing a fibrinolytic agent (tenecteplase) plus heparin with heparin alone showed no overall benefit among intermediate-risk patients with pulmonary embolism,[4] in a prespecified subgroup analysis limited to patients 75 years of age or younger, thrombolytic therapy was associated with a lower incidence of clinical deterioration than heparin alone (1.7% vs. 5.1%). There was no increased risk of intracranial hemorrhage among these patients. In fact, no patient younger than 65 years of age had intracranial hemorrhage. A subsequent meta-analysis showed that among patients 65 years of age or younger, the number needed for thrombolytic therapy to prevent death was 51, whereas the number needed to cause harm from major bleeding was 176.[5]

Clinicians should use the lowest effective dose of a thrombolytic drug. Current evidence suggests that using a full dose of a thrombolytic drug is no more effective, and may be riskier, than using a reduced dose. A meta-analysis of five randomized trials including a total of 440 patients showed that reductions in clot burden and pulmonary artery pressure with a full dose of a tissue plasminogen activator were similar to those with a reduced dose of a tissue plasminogen activator, whereas bleeding with the reduced-dose treatment was one third as common as bleeding with the full-dose treatment.[6] In fact, the risk of major bleeding with reduced-dose thrombolytic therapy was similar to that with anticoagulant therapy alone.

Thus, although guidelines recommend against routine thrombolysis for intermediate-risk pulmonary embolism,[1] the selective use of a reduced dose of a thrombolytic agent for our young, previously healthy patient with a life-threatening pulmonary embolism will maximize her chances of survival while minimizing her risk of hemodynamic decompensation and bleeding.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend Parenteral Heparin Therapy Only

Timothy Morris, M.D.

This young woman with an acute pulmonary embolism is in a hemodynamically stable condition but presents with clinical, chemical, and

radiographic evidence of right ventricular strain that reflects a small but actual risk of subsequent deterioration. Although the mechanisms of such deterioration are not entirely clear (and may differ among patients), the apparent coexisting deep venous thrombosis in her right leg entails a short-term risk for recurrent embolization that would add to the already substantial clot burden in her pulmonary arteries. Unfortunately, intravenous plasminogen activator (fibrinolytic) treatment is unlikely to provide additional benefits with respect to her risk of death or her long-term cardiopulmonary function beyond treatment with an anticoagulant alone.

Early trials that investigated intravenous fibrinolytic agents showed reductions in pulmonary vascular resistance and lung perfusion defects during the first day of treatment for pulmonary embolism when compared with heparin alone.[7] However, the difference had diminished by nearly half by the second day, presumably owing to the patients' own intrinsic plasminogen activation. By the fifth day, the degree of resolution was identical to that with heparin alone, a finding that persisted at 1 year. It is important to note that fibrinolytic treatment provided no mortality benefit but led to substantial complications. The fibrinolysis group had nearly twice the rate of spontaneous major bleeding as the heparin-alone group.

Subsequent trials over the next five decades disclosed a disappointing effect of fibrinolysis, as compared with anticoagulation alone, on clinical outcomes in patients with pulmonary embolism whose condition was hemodynamically stable. In one of the largest trials, treatment with fibrinolytic agents in patients with pulmonary embolism and evidence of right ventricular dysfunction did not reduce the risk of death, shock, or respiratory failure.[8] A meta-analysis similarly found no survival benefit with fibrinolytics.[9]

In a large, randomized trial involving patients with pulmonary embolism and right ventricular dysfunction, there was no significant difference between patients who received fibrinolytic therapy and those who received anticoagulants alone with respect to 7-day mortality, prolonged hospitalization, rehospitalization, or 30-day mortality.[4] Hemodynamic decompensation did occur less often in the group that received fibrinolytic therapy than in the group that received heparin only (1.6% vs. 5.0%), although death from hemodynamic decompensation was rare in both groups (0.2% and 0.6%, respectively; note that no statistical comparison of deaths from hemodynamic compromise was performed). On the other hand, the odds of major bleeding were nearly 5 times as high in the fibrinolysis group (11.5% vs. 2.4%), and the odds of stroke (predominantly hemorrhagic) were more than 12 times as high (2.4% vs. 0.2%). Death from extracranial bleeding or stroke occurred in 1.0% of the patients in the fibrinolysis group but in none of those in the heparin-alone group. Finally, a subsequent analysis revealed no benefit of fibrinolytic therapy on 3-year survival either.[10] Thus, in our patient, fibrinolytic treatment would not be expected to provide an advantage with respect to pulmonary embolism–related mortality but would increase her risk of serious bleeding.

Long-term problems after acute pulmonary embolism include a small risk of chronic thromboembolic pulmonary hypertension as well as the much more common complication of chronic dyspnea due to demonstrable cardiopulmonary dysfunction.[11] Unfortunately, fibrinolytic treatment would not reduce our patient's risk of these long-term complications. A large, randomized trial showed no beneficial effect of fibrinolysis, as compared with anticoagulation alone, on the long-term risk of chronic dyspnea, pulmonary hypertension, right ventricular dysfunction, or chronic thromboembolic pulmonary hypertension.[10]

Thus, fibrinolytic therapy will not provide tangible benefits to our patient with respect to short-term or long-term survival or the risk of long-term complications. That therapy will, however, expose her to an increased risk of catastrophic bleeding.

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