Systemic Thrombolysis for Pulmonary Embolism: A Review

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INTRODUCTION

Pulmonary embolism (PE) is a common disease, occurring in 60 to 112 of every 100,000 individuals.[1] It is the third most common cause of cardiovascular mortality and is responsible for 100,000 to 180,000 deaths annually.[2,3] The clinical manifestations of acute PE are highly variable, ranging from pulseless electrical activity to mild dyspnea, which can cloud the diagnosis.[4] PE should be a part of the differential diagnosis in patients who present with new or worsening dyspnea, chest pain, or hypotension.[5] Based on the physician's level of suspicion, the diagnostic workup may include a clinical decision rule, biomarkers (e.g., d-dimer), and/or imaging modalities, such as computed tomography angiography or a ventilation-perfusion scan. Additional evaluations may be performed with troponins, B-type natriuretic peptide (BNP), Pro-BNP, and/or echocardiography.[6,7]

PE is commonly classified as massive (high-risk), submassive (intermediate-risk), and low-risk to help determine the required treatment. Risk stratification scores are used to determine the risk of complications and associated mortality.[8] Massive PE is defined as suspected or confirmed PE in the presence of shock, sustained hypotension, the absence of a pulse, or persistent profound bradycardia. Submassive PE is defined as suspected or confirmed PE with right ventricular dysfunction in the absence of shock.[1,4,8]

This review focuses on the evidence behind the use of thrombolytic therapy in patients with massive or submassive PE. Concurrent heparin therapy and the management of bleeding episodes are also discussed.

TREATMENT APPROACHES

Anticoagulation

The treatment of PE begins with the administration of anticoagulants; these agents have been shown to prevent recurrent symptoms and early death in patients with PE.[4,9] The initial pharmacological treatment of acute PE may also include intravenous (IV) unfractionated heparin (UFH), subcutaneous low-molecular-weight heparin, or fonda-parinux (Arixtra, GlaxoSmithKline) for the first five to 10 days.[4,10,11] UFH is initiated at a dose of 80 units/kg followed by 18 units/kg every hour, with dose adjustments based on the activated partial thromboplastin time.[4] Low-molecular-weight heparin and fondaparinux are also dosed based on weight. Both are administered subcutaneously once or twice daily.[9]

After patients with acute PE have been stabilized, parenteral anticoagulation should be supplemented with vitamin K antagonists. Alternatively, a target-specific oral anticoagulant (TSOAC) agent, such as apixaban (Eliquis, Bristol-Myers Squibb/Pfizer), rivaroxaban (Xarelto, Janssen), edoxaban (Savaysa, Daiichi Sankyo), or dabigatran etexilate (Pradaxa, Boehringer Ingelheim) may be initiated.[4,12,13] Patients who are started on warfarin should also receive a parenteral anticoagulant until the international normalized ratio (INR) has been maintained at 2.0 to 3.0 for at least two consecutive days.[4] TSOACs may be started immediately or after one to two days of parenteral anticoagulation.[4] The goal of initial anticoagulant therapy is to inhibit the formation of additional fibrin clots.[14] When choosing between parenteral anticoagulation or TSOACs, clinicians should consider the potential for decompensation, the need for thrombolytic therapy or invasive intervention, the bleeding risk, and the availability of reversal agents.[14] Anticoagulants are administered for a minimum of three months and may be continued indefinitely, depending on the cause of the thrombus.[9,12,13]

Thrombolysis

Hemodynamically unstable PE patients are candidates for treatment with IV thrombolysis or mechanical thrombectomy.[10] Thrombolytic agents convert native plasminogen to plasmin, which in turn hydrolyzes the fibrin of thromboemboli, resulting in clot lysis.[10] Streptokinase, urokinase (also known as urinary plasminogen activator), and alteplase (Activase, Genentech) are the only agents with this indication.[15–19] The third-generation thrombolytics tenecteplase (TNKase, Genentech) and reteplase (Retavase, Chiesi USA) are approved for the treatment of acute coronary syndromes, but they have also been evaluated in subjects with acute PE.[20,21] Alteplase, reteplase, and tenecteplase preferentially activate plasminogen on the clot surface and are classified as fibrin specific. The fibrin-specific agents have longer half-lives, which allow bolus administration. They also alleviate the risk of allergic reactions associated with the first-generation thrombolytics.[22] Streptokinase and urokinase, however, activate systemic plasminogen, which is not part of the clot matrix. Key characteristics of the thrombolytic agents are listed in Table 1.[23–26]

Thrombolytic therapy has been shown to improve pulmonary artery pressure, arteriovenous oxygenation, pulmonary perfusion, and echocardiographic assessment, thereby relieving symptoms, preventing recurrent PE, and reducing mortality.[9,27] However, these benefits may not outweigh an

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Table 1 Key Characteristics of Thrombolytic Agents[23–26]

	Streptokinase	Urokinase	Alteplase	Reteplase	Tenecteplase
Generation	First	First	Second	Third	Third
Clot-specific?	No	No	Yes	Yes	Yes
Half-life (minutes)	12	7–20	4–10	11–19	15–24
FDA-approved for PE?	Yes	Yes	Yes	No	No

PE = pulmonary embolism; FDA = Food and Drug Administration.

Table 2 Contraindications to Systemic Thrombolysis[9,27]

Absolute*	Relative†
• Structural intracranial disease • Previous intracranial hemorrhage • Ischemic stroke within three months • Active bleeding • Recent brain or spinal surgery • Recent head trauma with fracture or brain injury • Bleeding diathesis	• Systolic blood pressure > 180 mm Hg • Diastolic blood pressure > 100 mm Hg • Recent bleeding • Recent surgery or invasive procedure • Ischemic stroke > three months previously • Anticoagulation • Traumatic cardiopulmonary resuscitation • Pericarditis or pericardial fluid • Diabetic retinopathy • Pregnancy • Age > 75 years • Low body weight (e.g., < 60 kg) • Female • African-American

* Thrombolysis could cause a life-threatening situation.
† Caution is required. Thrombolysis is acceptable if the benefits outweigh the risks.

individual patient's risk of major or clinically relevant nonmajor bleeding.[9] Unfortunately, there is no validated tool for predicting the risk of bleeding in patients undergoing thrombolysis, only identified risk factors. Standard assessment tools, such as the Pulmonary Embolism Severity Index (PESI), can help identify patients who may benefit from thrombolytic therapy.[27] Conversely, clinicians may use risk stratification to identify contraindications to thrombolysis (Table 2).[9,27]

A case-control study assessed 62 adults for risk factors that might be associated with bleeding after treatment with alteplase. The investigators found that patients with major bleeding more often had recent major surgery (P = 0.039), an INR greater than 1.7 (P = 0.008), and one or more risk factors for bleeding (P = 0.003) compared with those without major bleeding.[28] Other clinical data have shown that patients with a lower threshold for bleeding during thrombolytic therapy are more likely to have a history of recent major surgery, trauma, pregnancy, cardiopulmonary resuscitation, or an invasive procedure.[27] These findings underscore the importance of considering a patient's bleeding potential before administering thrombolytics.[29]

No head-to-head comparison trials of thrombolytic agents have been conducted. These drugs have been available for decades, however, and several meta-analyses have been performed to determine their risks and benefits in patients with myocardial infarction or stroke. In one meta-analysis that looked at the comparative efficacy of thrombolytics in myocardial infarction, data from 14 clinical trials involving a total of 142,907 patients were evaluated.[30] Of particular interest was a comparison of alteplase and streptokinase. No difference in mortality or reinfarction rates was noted between these agents. However, intracranial hemorrhage occurred at a lower rate in the streptokinase group. When data from the GUSTO-1 study, which looked at accelerated alteplase administration, were removed from the analysis, the streptokinase group continued to show a lower incidence of intracranial hemorrhage, whereas major bleeding was lower in the alteplase group.[30]

Another clinical consideration is the relative merits of systemic versus catheter-directed thrombolysis. Yoo and colleagues compared these two modalities in 72 patients with PE.[31] Forty-four patients were in the systemic group, and 28 were in the catheter group. The patients' mean age was 64 years. There was no significant difference between the two groups with respect to seven-day mortality (13.6% for systemic thrombolysis versus 10.7% for catheter-directed thrombolysis), in-hospital mortality (13.6% versus 14.3%), and major bleeding complications (16.7% versus 16.7%).

Thrombolytic Management of Massive PE

Massive or high-risk PE is defined as sustained hypotension (i.e., systolic blood pressure of less than 90 mm Hg for more than 15 minutes), with the patient showing symptoms of shock or hemodynamic compromise in addition to other symptoms of PE.[4,8,29] Thrombolytic therapy is a key treatment option for patients presenting with these clinical findings. The European Society of Cardiology (ESC), for example, classifies thrombolytic administration in patients with acute high-risk PE as a 1B recommendation, and the 2016 updated CHEST guidelines list it as a grade 2B recommendation.[9,23,29]

In the setting of massive PE, the benefits of systemic thrombolysis generally outweigh the risks. Although contraindications exist for the administration of thrombolytic agents, their use should be avoided only in the presence of active, uncontrollable bleeding.[5,32]

Varying doses and infusion durations have been studied. ESC guidelines recommend accelerated regimens of alteplase 100 mg infused peripherally over two hours in place of first-generation thrombolytics, which require prolonged infusion.[4,9] Thrombolytics provide the greatest benefit if they are administered within 48 hours of symptom onset.[4] PE patients with transient, less-severe signs of hypotension or shock, but who later experience sudden clinical deterioration, may still be considered for systemic thrombolytics.[4,29] In patients with contraindications to thrombolytic therapy, mechanical thrombectomy or other procedures may be considered.[29] Patients who receive systemic thrombolytic therapy and remain hypotensive with a high mortality risk before experiencing the full effect of the thrombolytic are candidates for catheter-assisted thrombus removal or other mechanical interventions.[4,29]

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Thrombolytic Management of Submassive PE

Intermediate-risk, submassive PE is characterized by right ventricular dysfunction (RVD) and/or myocardial necrosis, as indicated by elevated biomarkers, in the absence of persistent hypotension or shock.[33] The use of prognostic measures, such as the PESI model, may help clinicians with decisions on the overall management of these patients.[34]

The role of thrombolysis in hemodynamically stable patients with submassive PE continues to be an area of debate. Patients with submassive PE require case-by-case analysis with shared decision-making regarding the risks and benefits of thrombolytic therapy.[35] A thorough understanding of the literature is essential in making these determinations.

The MAPPET-3 trial, conducted in 2002, was one of the earliest studies to evaluate the use of thrombolytic agents in patients with submassive PE. This study compared heparin plus alteplase 100 mg with heparin plus placebo, both administered over a period of two hours. The primary endpoint was in-hospital death or clinical deterioration requiring an escalation of treatment. The incidence of the primary endpoint was significantly higher in the heparin-plus-placebo group than in the heparin-plus-alteplase group ($P = 0.006$), and the probability of 30-day event-free survival was higher in the heparin-plus-alteplase group ($P = 0.005$). No difference was observed, however, in in-hospital deaths ($P = 0.71$).[36]

In the MOPETT trial, 121 patients with moderate PE received low-dose heparin plus alteplase 50 mg or alteplase 50 mg alone. The coprimary endpoints were pulmonary hypertension and a composite endpoint of pulmonary hypertension and recurrent PE at 28 months. Pulmonary hypertension occurred in 16% (nine of 58) of the heparin/alteplase group compared with 57% (32 of 56) of the alteplase group ($P < 0.001$). Similarly, the composite endpoint occurred in 16% (nine of 58) of the heparin/alteplase group compared with 63% (35 of 56) of the alteplase group ($P < 0.001$). The average duration of hospitalization was 2.2 days for heparin/alteplase versus 4.9 days for alteplase ($P < 0.001$). The rate of death plus recurrent PE was 1.6% for the heparin/alteplase group compared with 10.0% for the alteplase group ($P = 0.0489$). No bleeding occurred in either group.[37]

The randomized, double-blind PEITHO trial compared tenecteplase plus heparin with placebo plus heparin in 1,005 patients with intermediate-risk PE. All of the patients had RVD. The study's primary outcome was death or hemodynamic decompensation (or collapse) within seven days after randomization. The primary endpoint occurred in 13 of 506 patients (2.6%) in the tenecteplase group compared with 28 of 499 patients (5.6%) in the placebo group ($P = 0.02$). Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and in six patients (1.2%) in the placebo group ($P < 0.001$). Stroke occurred in 12 patients (2.4%) in the tenecteplase group and was hemorrhagic in 10 patients; one patient (0.2%) in the placebo group had a stroke, which was hemorrhagic ($P = 0.003$). Thus, thrombolytic therapy was shown to prevent hemodynamic decompensation, but at an increased risk of major hemorrhage and stroke.[21]

The randomized, double-blind, placebo-controlled TIPES trial evaluated the effect of tenecteplase on RVD in hemodynamically stable patients with PE. Fifty-eight patients were randomly assigned to receive weight-adjusted single-bolus tenecteplase (n = 23) or placebo (n = 28) along with UFH.

The study's primary endpoint was the reduction in RVD at 24 hours. The reduction of the right-to-left ventricle end-diastolic dimension ratio at 24 hours was 0.31 in patients treated with tenecteplase compared with 0.10 in patients given placebo ($P = 0.04$). One patient treated with tenecteplase experienced a clinical event (recurrent pulmonary embolism) compared with three patients in the placebo group. Two nonfatal major bleeds occurred with tenecteplase (one intracranial) and one with placebo. The authors concluded that treatment with single-bolus tenecteplase is feasible at the same dosages used for acute myocardial infarction and can reduce RVD at 24 hours in hemodynamically stable patients with PE.[38]

In the TOPCOAT trial, 83 normotensive patients with submassive PE and right ventricular strain received low-molecular-weight heparin followed by random assignment to either a single weight-based bolus of tenecteplase (n = 40) or placebo (n = 43) administered in a double-blind fashion. The authors hypothesized that a larger proportion of patients who received tenecteplase would have a favorable composite outcome. Three patients treated with placebo experienced an adverse outcome within five days, including one who died from a cardiac arrest that was directly attributed to PE. One patient treated with tenecteplase died from an intracranial hemorrhage that occurred five hours after drug administration. No patients died in the period between hospital discharge and 90 days. At follow-up, 16 of the 43 patients (37%) treated with placebo and six of the 40 patients (15%) treated with tenecteplase had at least one adverse outcome (two-sided $P = 0.017$).[39]

Meta-analyses of thrombolytic therapies have been conducted in an attempt to develop treatment recommendations based on the current literature. In one such study, Chatterjee and colleagues conducted a literature review to evaluate the survival benefit of thrombolysis compared with that of anticoagulation in patients with acute PE.[19] The analysis included 16 studies, which enrolled a total of 2,115 patients. Eight of these trials involved 1,775 patients with intermediate-risk PE. Thrombolytic agents were found to be associated with lower all-cause mortality compared with anticoagulants (2.17% versus 3.89%, respectively), but they increased the risk of major bleeding (9.24% versus 3.42%) and intracranial hemorrhage (1.46% versus 0.19%). Major bleeding was not significantly increased in patients 65 years of age or younger.[19] It should be noted that the results of this analysis have been challenged because of purported flaws in the statistical methods.[40]

In another meta-analysis, Xu and colleagues analyzed data from seven studies involving a total of 1,631 patients with intermediate-risk PE treated with thrombolytics or anticoagulants. The two treatment groups were not significantly different with regard to 30-day, all-cause mortality ($P = 0.08$). The patients treated with thrombolytic agents, however, had significantly lower rates of clinical deterioration ($P < 0.01$) and recurrent PE ($P = 0.01$). There was no difference in the rates of major bleeding events between the two groups ($P = 0.25$).[2]

Meyer and colleagues recently reviewed the main advances or recommendations in the care of patients with PE, including recent data on the use of thrombolytic treatment. The authors concluded that, given at the current dosage, thrombolytics are associated with a reduction in the combined endpoint of mortality and hemodynamic decompensation in patients with intermediate-

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Table 3 Key Clinical Trials of Systemic Thrombolysis in Patients With Submassive PE				
Year	Design	Comparators	Primary Endpoint	Key Results
MAPPET-3[36]				
2002	Prospective, randomized, double-blind, placebo-controlled	Heparin + alteplase (n = 118) vs. heparin + placebo (n = 138)	In-hospital death or clinical deterioration requiring escalation of treatment at end of hospital stay or on day 30 after randomization, whichever occurred first	• Rate of primary endpoint significantly lower with heparin + alteplase than with heparin + placebo (11% vs. 25%, respectively; *P* = 0.006) • Rate of recurrent PE low in both groups • Bleeding incidence similar in both groups
TIPES[38]				
2010	Randomized, double-blind, placebo-controlled	Weight-adjusted, single-bolus tenecteplase (n = 23) or placebo (n = 28), both with heparin	Reduction of RVD at 24 hours	• Reduction of right-to-left ventricle EDD ratio at 24 hours was 0.31 for tenecteplase vs. 0.10 for placebo (*P* = 0.04) • Recurrent PE in one tenecteplase patient and in three placebo patients • Two major nonfatal bleeds with tenecteplase vs. one with placebo
MOPETT[37]				
2012	Prospective, randomized	Low-dose alteplase (10-mg bolus followed by 40 mg over two hours) + heparin vs. placebo + heparin	PHTN at 28 months	• Rate of primary endpoint significantly lower with alteplase + heparin vs. placebo + heparin (16% vs. 57%, respectively; *P* < 0.001) • No bleeding in either group
TOPCOAT[39]				
2014	Randomized, double-blind, placebo-controlled	Weight-adjusted, single-bolus tenecteplase (n = 40) or placebo (n = 43), both with heparin	Composite outcome: 1) death, circulatory shock, intubation, or major bleeding within five days, or 2) recurrent PE, poor functional capacity, or SF36 PCS score of less than 30 at 90-day follow-up	• Adverse outcome rate significantly lower with tenecteplase + heparin vs. placebo + heparin (15% vs. 37%, respectively; *P* = 0.017)
PEITHO[21]				
2014	Randomized, double-blind, placebo-controlled	Tenecteplase + heparin (n = 506) vs. placebo + heparin (n = 499)	Death or hemodynamic decompensation (collapse) within seven days after randomization	• Six patients in the tenecteplase group died vs. nine patients in the placebo group (1.2% vs. 1.8%, respectively; *P* = 0.42) • Extracranial bleeding occurred in 32 patients in the tenecteplase group vs. six patients in the placebo group (6.3% vs. 1.2%; *P* < 0.001) • Stroke occurred in 12 patients in the tenecteplase group vs. one patient in the placebo group (2.4% vs. 0.2%, *P* = 0.003)

EDD = end-diastolic dimension; PE = pulmonary embolism; PHTN = pulmonary hypertension; RVD = right ventricular dysfunction; SF36 PCS = Short Form Health Survey (36 Items) Physical Component Summary.

risk PE, but this benefit is obtained without a decrease in overall mortality and with a significant increase in major extracranial and intracranial bleeding. In the authors' opinion, thrombolytic therapy should be given in cases of hemodynamic worsening in patients with "high-intermediate risk" PE.[32]

Because of the equivocal nature of the clinical data related to systemic thombolytic therapy in patients with submassive PE (summarized in Table 3), the decision to treat these individuals requires careful consideration of the risks and benefits involved. It should be noted that the 2016 CHEST guidelines recommend against the administration of thrombolytics in patients with acute PE in the absence of hypotension (grade 1B). The European guidelines also recommend against the routine use of thrombolysis in these patients (class III, level B).[4,29] With regard to patients with intermediate-risk PE, studies have indicated the importance of appropriately stratifying each patient based on his or her comorbidities and mortality risk before administering thrombolytics.[27,34]

Management of Low-Risk PE

PE patients without shock, hypotension, or signs of cardiac dysfunction are considered to have a low 30-day mortality risk.[41] Thrombolytic therapy is not recommended for these patients.[4] A PESI class of I or II (Table 4) should prompt clinicians to consider outpatient treatment.[30,41]

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CLINICAL CONSIDERATIONS

Use of Low-Dose Thrombolytics

The bleeding complications associated with alteplase are dose dependent and have raised questions as to whether the standard dosage of 100 mg administered over two hours is appropriate for all PE patients.[42] As mentioned earlier, both the PEITHO and MOPETT trials used lower doses of thrombolytics and adjusted the doses according to weight. Specifically, the PEITHO study dosed tenecteplase as high as 50 mg in patients weighing more than 90 kg and as low as 30 mg in patients weighing less than 60 kg.[21] In the MOPETT trial, intermediate-risk PE patients weighing less than 50 kg received a weight-based dosing regimen of 0.5 mg/kg (10-mg bolus administered over one minute, with the remainder of the dose administered over two hours).[37] A meta-analysis of trials using low-dose recombinant tissue plasminogen activator (rt-PA) in patients with acute PE found that a low dose (50-mg infusion over two hours) was as effective as the standard dose (100-mg infusion over two hours), with fewer major bleeding events.[43] In patients with massive PE, lower doses of thrombolytic agents may benefit patients at high risk of bleeding, such as those weighing less than 65 kg. Lower doses of thrombolytics may also help prevent bleeding complications in elderly, pregnant, and surgical patients.[42]

Concurrent Heparin

When there is a high clinical suspicion of PE, anticoagulation with UFH should be initiated while the diagnostic workup is being completed. If the decision is made to administer a thrombolytic agent, the clinician must consider how best to handle the IV heparin infusion. According to the American Heart Association, the decision to coadminister thrombolytic agents with heparin anticoagulation requires a strict risk–benefit assessment.[8] When a thrombolytic and heparin are used concomitantly, there is a greater likelihood that the symptoms will be alleviated and that the patient's cardiac and respiratory parameters will be stabilized.[8] The ESC recommends withholding parenteral anticoagulation when first-generation thrombolytics are administered, but UFH may be given in conjunction with rt-PA infusions.[30] The 2016 CHEST guidelines do not go into detail with regard to the coadministration of anticoagulants and thrombolytics, but they do state that patients with acute PE whose condition worsens after parenteral anticoagulation may receive systemic thrombolytic therapy (grade 2C recommendation).[29]

Management of Bleeding

If a patient shows signs or symptoms of severe bleeding, the first step is to discontinue both the thrombolytic and anticoagulation infusions. The next step is to institute supportive therapy, which may include the application of pressure to bleeding sites, volume repletion with blood products and fluids, and emergency surgery.[44] Protamine sulfate is an antidote to heparin overdose. The dose required for heparin reversal is 1 mg of protamine for every 100 units of heparin, for a maximum of 50 mg.[45] It is likely that the patient will be receiving a continuous infusion of UFH. If so, clinicians should consider heparin's half-life (60 to 90 minutes) when calculating the protamine dose.[46] Aminocaproic acid (Amicar, Xanodyne Pharmaceuticals) may be used to enhance hemostasis when thrombolysis contributes to bleeding. Doses of 4 g to 5 g should be injected into a 250-mL bag of diluent and administered over one hour. A continuous infusion of the same concentration is then given at a dosage of 1 g per hour for eight hours or until the bleeding is resolved.[47] Cryoprecipitate may be indicated in patients with massive bleeding to replenish fibrin stores, but this treatment should be reserved for life-threatening situations.[48] Intravenous tranexamic acid has also been used in patients with post-tPA bleeding. In a case report, a patient received 1.676 g within three hours.[49]

CONCLUSION

PE is a major cause of morbidity and mortality. With careful risk stratification, clinicians should be able to perform systemic thrombolysis safely and effectively in most of these patients. Systemic thrombolytic agents are a viable option in patients with hemodynamically unstable PE, as their potential benefits will almost certainly outweigh the risk of a life-threatening bleed. Patients with submassive PE are more challenging, and clinicians must carefully evaluate their clinical trajectory, comorbidities, and bleeding risk before administering thrombolytic therapy.

Table 4 Pulmonary Embolism Severity Index (PESI) Scoring System[30,41]	
Parameter	**Points**
Age	Age in years
Altered mental status	60
Cancer	30
Systolic blood pressure < 100 mm Hg	30
Pulse rate ≥ 100 beats per minute	20
Respiratory rate > 30 breaths per minute	20
Temperature < 36° C	20
Arterial oxygen saturation < 90%	20
Male gender	10
Chronic heart failure	10
Chronic pulmonary disease	10
PESI Class	**Score**
Class I (very low 30-day mortality risk)	≤ 65 points
Class II (low mortality risk)	66–85 points
Class III (moderate mortality risk)	86–105 points
Class IV (high mortality risk)	106–125 points
Class V (very high mortality risk)	> 125 points

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