Unraveling the Gordian Knot: Stratifying Risk and Individualizing Care for Each Patient

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Once an acute pulmonary embolism (PE) has been diagnosed, risk stratification is important to tailor treatments for an individual patient. Risk stratification allows physicians to identify low-risk patients to promote early discharge on novel oral anticoagulant therapy and high-risk patients who may benefit from escalation of care beyond simple anticoagulation alone. Determining who these higher-risk patients are requires an efficient strategy utilizing available resources to allow escalation of care with a cohesive approach aimed at optimizing outcomes. The most important immediate step in risk stratification is to assess the right ventricle's ability to overcome the afterload caused by the pulmonary thrombus obstruction, which is evaluated using a variety of clinical, imaging, and/or laboratory data. Regardless of which assessment tools are used, the ultimate goal is to categorize patients into one of the following categories shortly after diagnosis: (1) high-risk or massive PE, (2) intermediate-risk or submassive PE, or (3) low-risk/minor PE.[1] Treatments can range from anticoagulation alone, catheter-directed thrombolysis, full-dose systemic thrombolysis, reduced-dose systemic thrombolysis, catheter embolectomy, surgical embolectomy, and/or mechanical circulatory support such as extracorporeal membrane oxygenation.

HIGH-RISK (MASSIVE) PE

Patients with acute PE presenting in cardiogenic shock (systolic blood pressure < 90 mm Hg for longer than 15 minutes or requiring inotropic support) and/or cardiac arrest are defined as high-risk (massive) PE. Patients with high-risk PE have a 3-month mortality up to 50% and represent only 5% of all acute PE.[1] Given this high risk of early death, identification of shock and early thrombolysis is critical to relieve the obstruction and improve cardiac output.

Although systemic thrombolysis is the standard of care for many patients with high-risk PE, studies suggest up to 30% to 70% of patients with massive PE fail to receive this potentially life-saving therapy due to absolute or relative contraindications.[2] For patients with contraindications to and/or failure of thrombolysis, it is important to consider alternative options such as catheter-directed thrombolysis, reduced-dose systemic thrombolysis, surgical or catheter embolectomy, and/or hemodynamic support as discussed later in this issue.

INTERMEDIATE-RISK (SUBMASSIVE) PE

Patients with evidence of right ventricular (RV) dysfunction but normal blood pressure on admission are classified as intermediate-risk (submassive) PE. About 40% of patients are classified as intermediate risk and are at higher risk for in-hospital adverse events and mortality than patients with normal RV function.[1] In a systematic review of 12 trials, patients with RV dysfunction by CTA or echocardiography but normal blood pressure are associated with a higher risk for in-hospital mortality (hazard ratio, 2.43; 95% confidence interval [CI], 1.33–4.45).[3] RV dysfunction can be identified on CTA as an increased RV-to-left ventricle ratio. On echocardiography, RV dysfunction is noted by RV dilation, RV hypokinesis, or presence of McConnell's sign (regional pattern of RV free wall dysfunction with sparing of the apex).[4,5] Whenever possible, comparison against prior imaging studies is important in assessing the acuity of the RV findings seen on CT or echocardiography. Many patients experience chronic pulmonary hypertension and RV dysfunction from a variety of causes and may arrive with acute PE. Assuming that all findings of a dilated RV are due to acute PE can be erroneous. Comparison with prior echocardiograms or, if available, CT imaging and medical records is important.

The European Society of Cardiology (ESC) guidelines further subdivide this intermediate-risk group based on the results of serum cardiac biomarker testing.[6] Patients with RV dysfunction and abnormal biomarkers are classified as intermediate-high risk, while patients with RV dysfunction and normal biomarkers are classified as intermediate-low risk. The rationale for subdividing intermediate-risk patients into two categories is that patients with both RV dysfunction and abnormal biomarkers have higher in-hospital mortality compared to either alone, and this may help gauge risk of decompensation and suggest the possible need for more aggressive PE treatment.[7] The most commonly used biomarkers for risk stratification are cardiac troponin, brain natriuretic peptide (BNP), and lactic acid. In a meta-analysis of 1,132 patients with acute PE, patients with elevated BNP had a 10% (95% CI, 8%–13%) risk of early death and a 23% (95% CI, 20%–26%) risk of adverse clinical outcomes.[8] In a separate meta-analysis of 1,985 patients, mortality was significantly higher in patients with acute PE and elevated troponin and normal blood pressure (odds ratio, 5.9; 95% CI, 2.68–12.95).[9] Adding lactate levels to these biomarkers may identify an

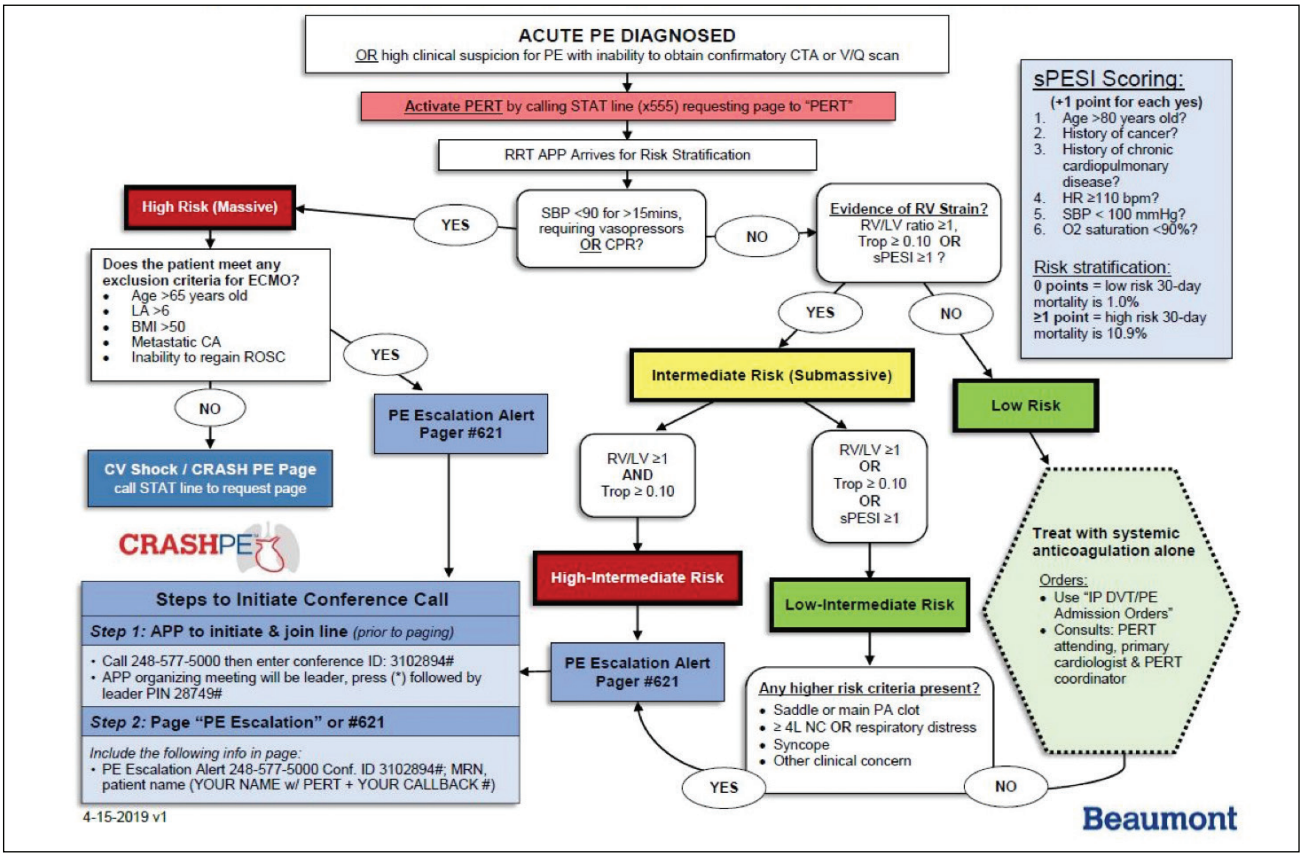

Figure 1. Representative PERT activation and risk stratification process from one member of the PERT Consortium™ (Beaumont).

even higher-risk group for early decompensation. In a study of 496 normotensive patients with acute PE, the combination of elevated lactic acid, RV dysfunction, and elevated troponin was associated with a 17.9% incidence of in-hospital mortality or nonfatal hemodynamic collapse.[10]

In patients without shock, no single variable is adequate to predict the risk of decompensation, and a combination of methods are employed. Clinical risk scores have also been applied to assess individual patients' risk. The Pulmonary Embolism Severity Index (PESI) score is the most validated risk prediction tool to predict 30-day mortality. However, this tool is difficult to remember how to use, highly dependent on age, and does not address what acute care clinicians want to know immediately, which is risk for shorter-term deterioration. There is currently no existing well-validated tool to predict 24- to 72-hour death or deterioration in submassive PE. Many clinicians use a version known as the simplified PESI (sPESI) to separate low-risk patients with a score of 0 from those who are not low risk (score ≥ 1). Use of sPESI may be most useful in identifying low-risk patients for early discharge rather than in predicting high-risk patients likely to deteriorate; the score's specificity is not high.

The optimal management for patients with intermediate-high–risk PE is unknown, and society guidelines are conflicting. Currently, the 2014 ESC and 2016 CHEST PE guidelines recommend anticoagulation alone for most patients with intermediate-risk PE.[6,11] However, there are many reasons to think that anticoagulation alone may not provide optimal efficacy in the intermediate-high–risk patients. Indeed, studies suggest a higher incidence of in-hospital adverse events and mortality as well as pulmonary hypertension and poor functional status at follow-up in intermediate-high–risk PE patients who receive anticoagulation alone.[12,13] In contrast, the American Heart Association guidelines differ from the above society guidelines and recommend full-dose systemic thrombolysis (alteplase 100 mg over 2 hours) for patients with intermediate-high–risk PE (class IIb, level of evidence C).[1] Although systemic thrombolysis has better efficacy than anticoagulation alone, this strategy is limited by a statistically significant higher incidence of major bleeding complications.[13] Given the desire to maximize improvement in RV function and reduce risk of deterioration or recurrence while avoiding the higher risk of bleeding complications with full-dose systemic thrombolysis, many additional approaches have been promoted, including catheter-directed thrombolysis, reduced-dose systemic thrombolysis, and catheter embolectomy.

There are two additional points to consider in the immediate bedside decision-making. First, it is important to adopt a patient-centered approach to clinical decision-making. Patients may weigh varied outcomes and risks

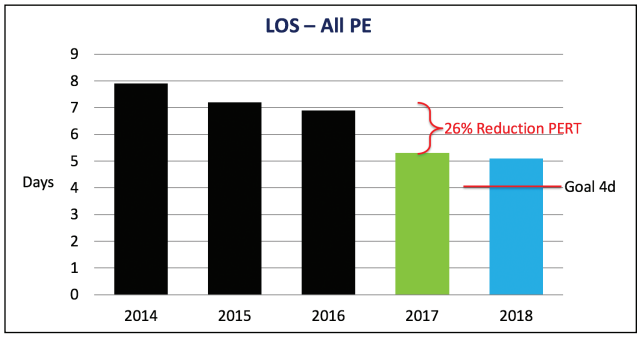

Figure 2. Beaumont's PE LOS.

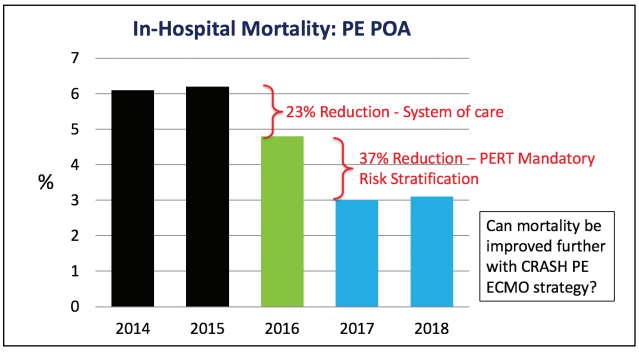

Figure 3. Beaumont's in-hospital mortality rate for present-on-admission PE.

differently, and it is important to not take a one-size-fits-all approach to submassive PE. Some patients may maximally want to avoid bleeding risk at all cost, while others may want to maximize speed of hemodynamic improvement, oxygenation, and work of breathing while tolerating increased bleeding or complication risk of advanced therapy. Also, escalated therapy risk may vary by factors such as age and cancer status. Second, time may be a valuable test in and of itself. After serial troponins, pulse blood pressure, oxygenation, and work of breathing over several hours or overnight can guide the clinician team in determining the pathophysiologic trajectory. This is not acute stroke or myocardial infarction, where the clock is ticking on making an immediate decision in the emergency department.

LOW-RISK (MINOR) PE

Approximately 55% of acute PEs are classified as low-risk or minor PE. Patients with low-risk PE have normal blood pressure, normal RV size and function, and normal biomarkers. Patients with low-risk acute PE have very low in-hospital mortality and can usually be managed with anticoagulation alone. In fact, many low-risk PE patients may be safe for early discharge without admission to the hospital, a practice endorsed by the ESC and CHEST guidelines.[11,14] In an analysis of 1,657 low-risk patients with acute PE, mortality, recurrent venous thromboembolism, and bleeding were similar in patients discharged within 24 hours of presentation compared to routine hospitalization. However, these trials were small and used different methods to assess risk.[15] In the HoT-PE trial, 525 patients were discharged within 24 hours if they were low risk based on modified Hestia criteria, lacked significant comorbidities, and had no thrombus-in-transit.[16] In these patients, the rate of recurrent symptomatic venous thromboembolism or fatal PE at 3 months was only 0.6%, and only 2.3% were rehospitalized due to suspected or recurrent PE or bleeding.

PUTTING RISK STRATIFICATION INTO PRACTICE

Risk stratification can be done quickly and efficiently even in large institutions by utilizing pulmonary embolism response teams (PERTs) in a variety of program structures. (Visit www.pertconsortium.com to see the "Focus on a PERT" series). By way of example, Beaumont, a signature member of the PERT Consortium™, utilizes a rapid response team model, where advanced practice providers (APPs) are assigned to risk stratify all patients with PE on a 24/7 basis with a note entered into EPIC within 30 minutes of evaluation. The APPs utilize an algorithmic approach supported by the PERT Consortium™ (Figure 1) and activate a PERT escalation page for all intermediate-high– and high-risk patients. The majority of these patients (85%) come through the emergency center, but the PERT is also notified by radiology for all inpatient chest CT scans that have evidence of PE so they can be risk stratified. With this approach, 892 patients at Beamont have been risk stratified since August 2017. This has been accompanied with dramatic improvements in average length of stay (LOS) (Figure 2) and PE-related mortality (Figure 3).

As evidence for the impact a formalized PERT can have on hospital metrics, prior to the 2015 start of the Beaumont PERT initiative, LOS with PE was unacceptably high due to delays in escalation of therapy and transition to oral anticoagulants. Risk stratification identifies the low-/low-intermediate–risk patients that fare well with anticoagulants alone and provide a marked reduction in LOS in this low-risk group (eg, 70% of patients at Beaumont). The primary reduction in overall PE LOS is driven by identifying this low-risk group (Figure 4). However, a streamlined

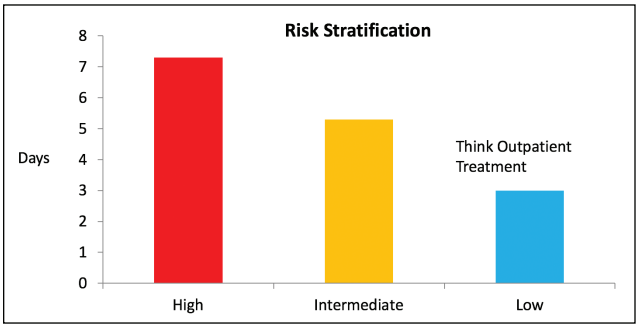

Figure 4. Beaumont LOS by risk stratification between August 1, 2017 and April 12, 2019. Risk stratification identifies low-risk patients who can be discharged early.

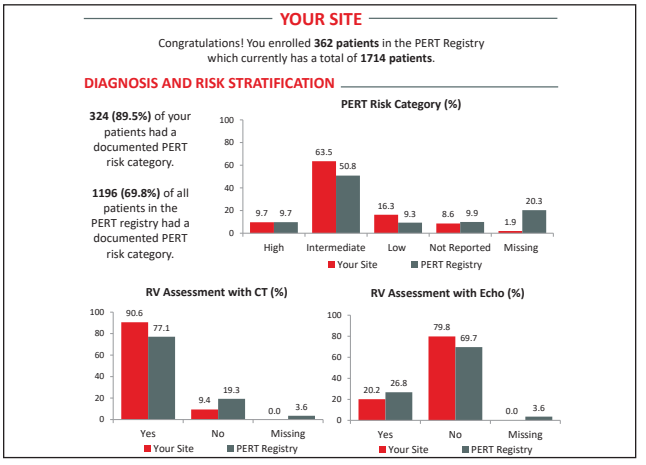

Figure 5. Example of the dashboard created for each participating institution in the PERT quality assurance registry.

approach with PERT oversight can also reduce LOS in the intermediate-risk groups by efficiently managing these patients who have received escalated therapies, particularly in the intermediate-high–risk group. With new developments in recent years such as ultrasound-facilitated thrombolysis (EkoSonic endovascular system, BTG Vascular), Flowtriever (Inari Medical), Indigo (Penumbra, Inc.), and ECMO, we anticipate an expanded level of aggressiveness with a higher rate of escalation in patients with profound RV dysfunction who have been excluded due to unacceptably high bleeding risk for systemic thrombolysis. However, more data are required to establish the benefit of these strategies. The PERT Consortium™ quality registry/database promises to provide some clarity on these different escalation strategies.

The PERT quality assurance registry will also allow sites to compare their risk stratification strategy, therapeutic decision-making, resource utilization, and PE outcomes to those of other participating institutional PERTs. In addition to providing a standardized template for instutitions to track and optimize their own therapeutic decision-making and outcomes for PE patients, the registry will provide quarterly dashboards (Figure 5) to enable each PERT to benchmark their own strategies, practice patterns, and outcomes against those of other participating sites. Such regular feedback is critical to quality assurance and performance improvement. The registry is open to all member institutions and will provide a rich source of data and information.

In summary, optimization of risk stratification using the PERT multidisciplinary approach has already led to improvements in PE outcomes at centers like Beaumont, where mortality has decreased to 3%. The University of Kentucky, which has championed a rapid mechanical support strategy for high-risk PE as part of its PERT, is seeing survival rates of > 50% in patients with historically much lower rates of survival.[17] PERT provides a coordinated and structured response for patients with PE based on risk stratification to provide the best therapeutic outcomes for each individual patient. ■

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