

Supplement to

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Pulmonary Embolism Response Teams

Optimizing care for patients with PE.

Risk Stratification

Anticoagulation

Catheter-Based Therapy

Multidisciplinary Team Approach

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Dear Colleagues,

Welcome to the 2019 *Endovascular Today* PERT Supplement! We hope you enjoy the articles we have assembled from members of the PERT Consortium™. The Pulmonary Embolism Response Team (PERT) concept has spread rapidly across the United States and beyond as those involved with management of this devastating, underrecognized, and undertreated condition see the opportunity to improve care and awareness of pulmonary embolism (PE) with a multidisciplinary, team-based approach. Each individual PERT has unique features, and while there are somewhat variable operative modes, the common goal is responding rapidly to the PE patient in need and a commitment to improving outcomes.

The PERT Consortium™ is a voluntary 501(c)(3) organization that was created to bring together PERTs from around and outside of the United States to share experiences, educate one another, and work collaboratively to define best practices. By promoting the multispecialty team-based approach, the Consortium aims to encourage the highest quality of PE care, define the role of novel therapies for PE, and increase overall awareness of PE. The PERT quality registry and database, by providing highly functional and relevant quality assurance dashboards, will enable institutional PERTs to benchmark their PE management and outcomes to those of other participating PERTs. Ultimately, this registry will define what constitutes PE quality and appropriateness of care.

Does your institution have a PERT already? Or are you interested in exploring the PERT model of care for PE? We welcome you to join the Consortium and take advantage of the educational and organizational programs offered, share your knowledge, and join the registry to participate in quality initiatives and research. Our PERT Partners program can help you get started and engaged in all available Consortium activities. Please feel free to contact the PERT Consortium™ staff at admin@pertconsortium.org, or call our team at (617) 872-7338.

Finally, we welcome you to attend the 5th Annual PE Scientific Session, the first and largest CME program dedicated solely to the science and practice of PE care. The meeting will be held in Boston, Massachusetts, on October 4 and 5, 2019, and is preceded by workshops and the annual business meeting of the PERT Consortium™ on October 3rd. Please visit pertconsortium.org to register for this exciting event.

We look forward to seeing you there, and in the meantime, keep PERT-ing!

Sincerely,

Kenneth Rosenfield, MD, MHCDS

Immediate Past-President, The PERT Consortium™

Victor F. Tapson, MD

President, The PERT Consortium™

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Pulmonary Embolism: An International Crisis

BY AARON S. WEINBERG, MD; MICHAEL R. JAFF, DO; AND VICTOR F. TAPSON, MD

Venous thromboembolic disease (VTE) is a worldwide crisis. There are over 10 million cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) diagnosed globally per year, with 1 million cases occurring in the United States and over 700,000 in France, Italy, Germany, Spain, Sweden, and the United Kingdom combined each year.¹⁻³ In 2008, the rates of VTE were so alarming that the United States' Surgeon General declared a formal call to action.^{4,5} In China, the incidence of acute PE tripled from 3.9 per 100,000 in 2000 to 11.7 per 100,000 in 2010 to 2011, and we expect this absolute number to continue to climb as China's population has risen to over 1.4 billion people, representing 18.5% of the world's total population.^{6,7} Whether this rise is due to an absolute increase versus an increased recognition of the disease is unclear. From 2007 to 2016, the rates of VTE-related hospitalization in China increased from 3.2 to 17.5 per 100,000 population.⁸ Thus, acute PE is a major health concern around the world.

Many predisposing risk factors for VTE are also on the rise, which will contribute to the future incidence of the disease. The world is becoming more sedentary and overweight, with one in three Americans (over 93 million adults) considered obese.⁹ The incidence and prevalence of cancer, trauma, surgery, and oral contraceptive/hormonal therapy use, as well as international travel (over 4 billion airline passengers in 2017), is also increasing, which will add to the overall risk of VTE.¹⁰⁻¹⁵ At least 60% of VTE cases occur during or right after hospitalization, making many cases potentially preventable causes of hospital-related death.² This also portends a large future health care expenditure, with the United Kingdom and United States already spending £640 million and \$15.5 billion per year, respectively, for the diagnosis and treatment of VTE.^{16,17}

DVT and PE are part of the same continuum of disease, with over 95% of emboli originating in the lower extremities.¹⁸ When PE occurs, the severity depends on the embolic burden and its effect on the right ventricle as well as underlying cardiopulmonary comorbidities. Death can result from the acute increase in pulmonary artery pressure with increased right ventricular (RV) afterload and dysfunction. The direct obstruction of the pulmonary vasculature as well as vasoconstriction from the release of localized hypoxic and acidotic mediators causes impaired RV contractility as well as increased RV myocardial oxygen consumption and RV ischemia. The reduced RV contractility eventually impacts left-sided filling, causing decreased left ventricular (LV) preload and decreased cardiac output. Anatomically, the

myocardial fibers of the heart encompass both the right and left ventricles and this ventricular interdependence results in decreased LV and RV output. This process can eventually lead to cardiogenic shock and death.¹⁹⁻²¹

PE therefore poses a serious mortality threat. There are over 100,000 PE-related deaths in the United States per year, and 544,000 VTE-related deaths in Europe annually.^{5,22} This translates to approximately one person dying of PE every 6 minutes in the United States and every 15 seconds elsewhere around the world. PE is the third-leading cause of cardiovascular death behind coronary artery disease and stroke, with a 30% 30-day mortality rate if untreated, and 11% of patients die within the first hour of presentation to the hospital.²³

Unfortunately, diagnosing PE can be a serious clinical challenge, and based on autopsy data, patients who die from acute PE are most commonly not diagnosed or even suspected until they are already dead.²⁴ A study of 1,032 patients autopsied patients found 231 cases of PE but with premortem clinical suspicion in only 18%.²⁵ Some of the difficulty in diagnosis stems from the nonspecific signs and symptoms of the disease, with the most common being dyspnea (73%), chest pain (44%), tachypnea (54%), and tachycardia (24%).¹⁸ These findings can be easily mistaken for other conditions, and we have too often seen patients worked up for nephrolithiasis due to flank pain, palpable intercostal tenderness attributed to a musculoskeletal injury, or cardiac catheterization undertaken only to discover later that their symptoms and troponin elevation were, in fact, due to acute PE. Recently, a jury awarded a family \$40 million after their college student died of PE after being sent home from the emergency department with a "viral illness," highlighting the tragic nature and medical legal ramifications of this difficult diagnostic conundrum.²⁶

There are also long-term comorbidities and consequences that arise with VTE. Approximately 20% to 30% of patients with DVT develop postthrombotic syndrome, 1% to 3% of patients with acute PE develop chronic thromboembolic pulmonary hypertension, up to 50% may have exercise limitation, and 33% with DVT/PE will have recurrence within 10 years.²⁷⁻²⁹

There is also a crisis in terms of finding the optimal way to risk stratify and treat these patients. The clinical classification of the severity of acute PE is generally based on the estimated early mortality risk defined by in-hospital or 30-day mortality. Patients are generally risk stratified as high risk (massive), low risk, and intermediate risk (submassive). The most recent European Society of Cardiology guidelines have further

risk stratified these patients into intermediate-low and intermediate-high risk categories.³⁰ This system helps to guide clinical decision-making; however, it is imperfect and neglects certain clinical considerations such as residual proximal lower extremity DVT, degree of pulmonary obstruction index, clot-in-transit, severity of the RV dysfunction, and extent of hemodynamic changes. Decisions in clinical practice cannot be made by, for example, simply distinguishing intermediate-low-risk and intermediate-high-risk patients. In addition, there is now a plethora of treatment options, including multiple percutaneous clot extraction devices, varying doses of systemic and catheter-directed thrombolytic protocols, surgical techniques, different anticoagulants, as well as reduced-dose/prophylactic long-term anticoagulant regimens in the appropriate patients.³¹⁻³⁴

Pulmonary embolism response teams (PERTs) have emerged at hospitals around the world to help navigate this challenging international crisis. A PERT is a multidisciplinary team, analogous to a code stroke or myocardial infarction team, that rapidly evaluates a patient and their risks, formulates a patient-specific treatment plan, and coordinates/mobilizes necessary resources to provide the highest level of care.³⁵ Many PERTs have now also expanded to the outpatient setting through the creation of clinics that specialize in long-term VTE care. The PERT Consortium™ organization has developed into an international thought leader for the guidance and influence of PE care, education, and research.³⁶

Elevating a disease to the level of an international crisis should not be paralyzing but rather should generate recognition and serve as an important call to action. The next few chapters of this treatise will highlight the current state of PE care. Although tremendous strides have been made, more research is needed to improve all facets of PE management, from patient selection and diagnosis to risk stratification and optimal short-/long-term therapeutic modalities to ameliorate both acute and chronic complications of PE. ■

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

BY MICHAEL C. McDANIEL, MD, FACC, FSCAI; D. MARK COURTNEY, MD; AND TERRY R. BOWERS, MD, FACC

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

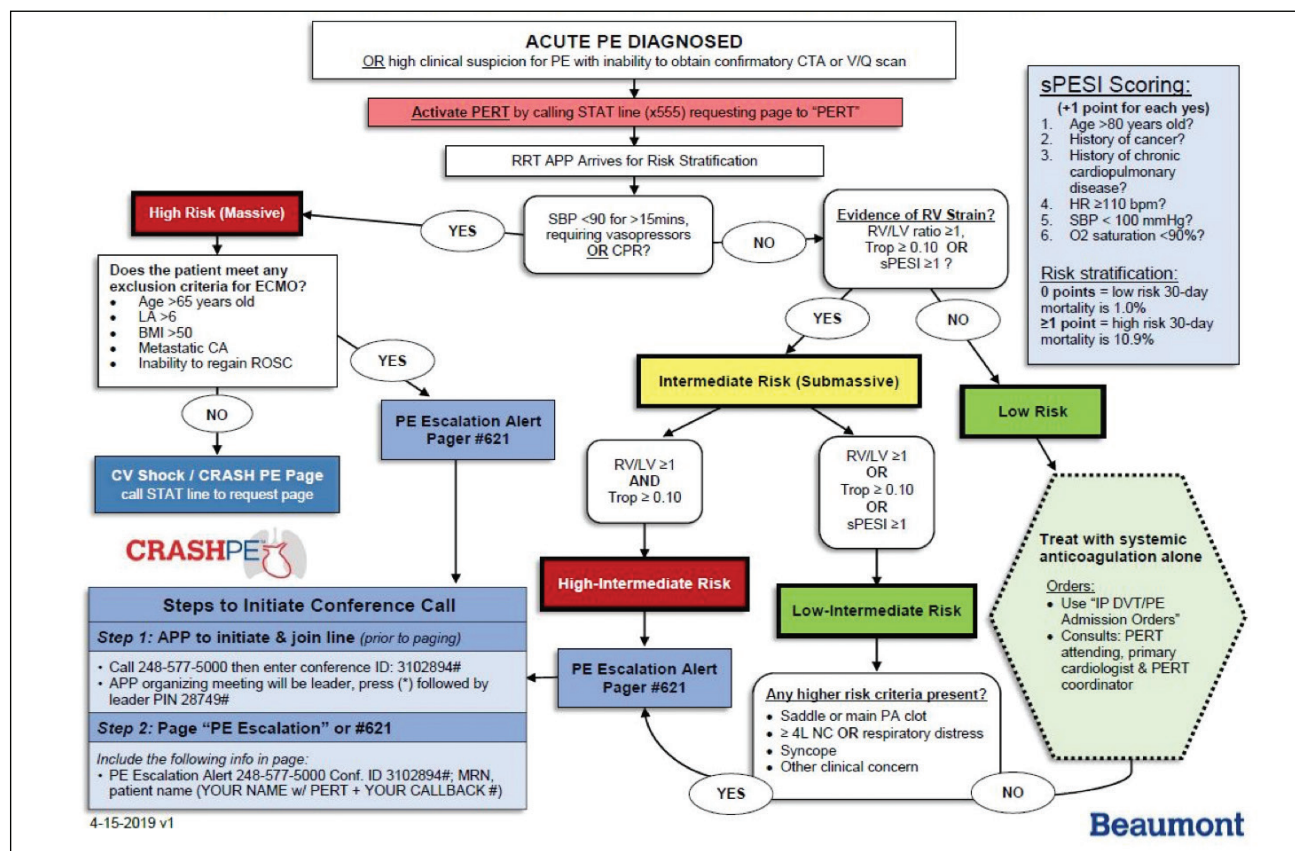


Figure 1. Representative PERT activation and risk stratification process from one member of the PERT Consortium™ (Beaumont).

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

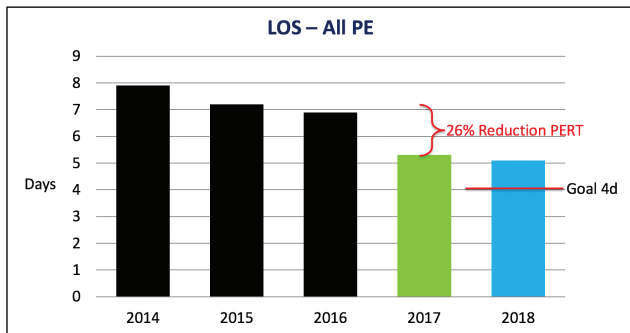


Figure 2. Beaumont's PE LOS.

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.

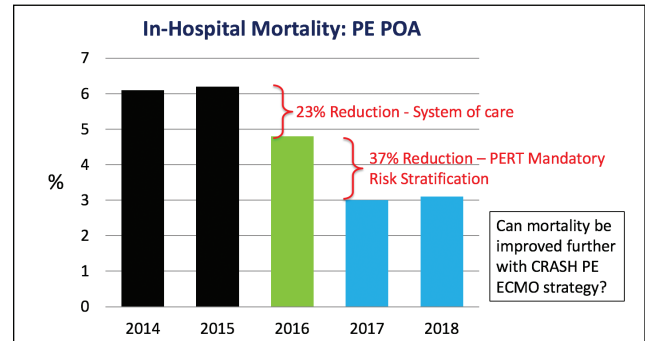


Figure 3. Beaumont's in-hospital mortality rate for present-on-admission PE.

(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 Beaumont 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

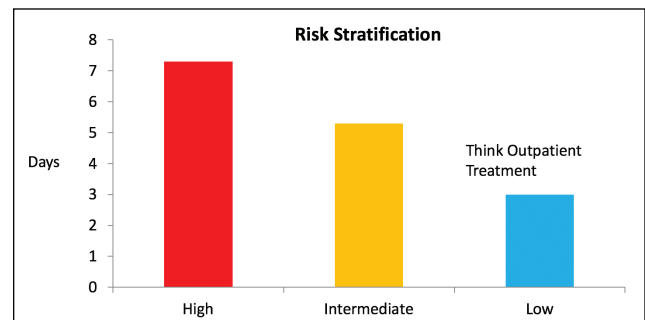


Figure 4. Beaumont LOS by risk stratification between August 1, 2017 and April 12, 2019. Risk stratification identifies low-risk patients who can be discharged early.

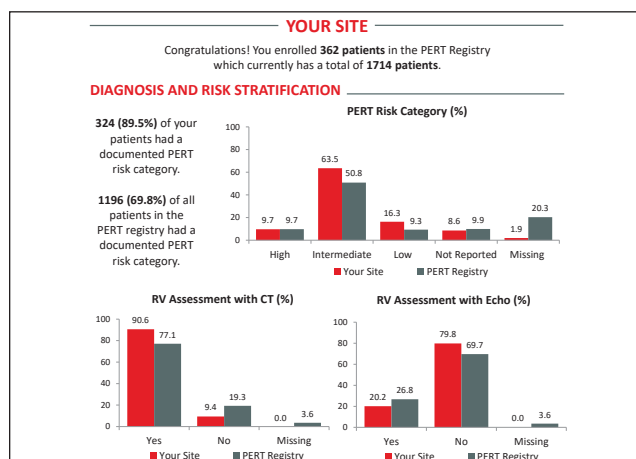


Figure 5. Example of the dashboard created for each participating institution in the PERT quality assurance registry.

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), Flowtrier (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 institutions 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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DOACs: Oral Anticoagulant Treatment of Choice for Pulmonary Embolism?

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Venous thromboembolism (VTE), which constitutes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality worldwide. There are approximately 900,000 cases of VTE and 60,000 to 100,000 deaths from PE in the United States each year.¹ Anticoagulation is the mainstay of therapy for VTE, and prior to this decade, treatment options were limited to parenteral agents and vitamin K antagonists (VKAs). The emergence of direct oral anticoagulants (DOACs) offers patients a more convenient and accessible alternative. Oral availability, rapid onset, minimal drug interactions, decreased bleeding risk, and comparable efficacy to warfarin/heparin lend agency to the use of DOACs for the treatment of VTE. Presently, dabigatran, rivaroxaban, apixaban, and edoxaban are approved and used routinely for treatment and secondary prevention in patients with DVT and PE. This article focuses on the use of DOACs in patients with PE and highlights the factors involved in deciding on an anticoagulant, different doses and regimens, use in special populations, and recommended duration of anticoagulation.

OVERVIEW OF DOACs

It is well established that early therapeutic anticoagulation improves mortality and decreases acute PE recurrence risk.² However, selecting the anticoagulant can be challenging, and the decision depends on factors related to the patient (severity of PE, comorbidities [adequate organ function], bleeding risks, need for invasive procedures, adherence behaviors, preferences, concomitant medications, and weight), anticoagulant (properties of DOACs and potential drug-drug interactions), and clinical judgment. Often, equally important is prescription affordability and insurance coverage.

There are currently four FDA-approved DOACs for the treatment of VTE. Unlike warfarin, DOACs inhibit only one component in the coagulation cascade. Apixaban (Eliquis, Bristol-Myers Squibb Company), rivaroxaban (Xarelto, Janssen Pharmaceuticals, Inc.), and edoxaban (Savaysa, Daiichi Sankyo, Inc.) are factor Xa inhibitors, whereas dabigatran (Pradaxa, Boehringer Ingelheim) is a factor II or direct thrombin inhibitor. The DOACs have several advantages over the older anticoagulants, including a rapid onset of action with predictable pharmacokinetics and pharmacodynamics, fixed dosing, significantly fewer drug

and dietary interactions, no discomfort from subcutaneous injections, and no need for routine laboratory monitoring or intravenous access. According to the most recent CHEST guidelines, anticoagulation therapy with one of these four DOACs is suggested over VKAs as long-term therapy in patients with DVT of the leg or PE and no evidence of cancer (grade 2B).³ This recommendation arose after all four DOACs demonstrated noninferiority to warfarin in preventing recurrent VTE or VTE-related death as well as similar to improved bleeding safety profiles.⁴⁻⁹

Currently, there are no head-to-head trials comparing the DOACs. However, because each DOAC has different doses and dosing regimens, it is important for prescribing clinicians to know and understand their nuances (Table 1). For example, rivaroxaban and apixaban are initially given at a higher dose and are approved for the initial therapy of VTE. On the other hand, edoxaban and dabigatran require an initial 5- to 10-day lead-in course of parenteral anticoagulation prior to first dose. Rivaroxaban (after the first 21 days) and edoxaban are taken once daily, whereas apixaban and dabigatran are taken twice daily. Rivaroxaban must be taken with food to maximize oral bioavailability.

The clinical trials evaluating the efficacy of dabigatran, rivaroxaban, apixaban, and edoxaban have convincingly demonstrated the efficacy and safety benefits of these drugs (Table 2).⁴⁻¹⁰ Results from meta-analyses pooling data from these trials suggest that DOACs have a similar efficacy (recurrent VTE or death related to VTE) and safety in patients presenting with PE and DVT with a nonsignificant heterogeneity between the groups (risk ratio [RR], 0.90; 95% confidence interval [CI], 0.72–1.13 in PE patients and 0.93; 95% CI, 0.75–1.16 in DVT patients).¹¹ DOACs reduce the risk of both major and clinically relevant nonmajor bleeding compared to VKAs, with a nonsignificant heterogeneity between the groups (RR, 0.49; 95% CI, 0.26–0.95 in PE patients and 0.74; 95% CI, 0.51–1.06 in DVT patients).¹²

Furthermore, results of randomized clinical trials and meta-analyses indicate that DOACs are as effective as warfarin for VTE treatment (including PE), with lower bleeding risks. The XALIA study is an international, prospective, noninterventional, observational cohort study evaluating the safety and efficacy of rivaroxaban in 5,142 patients with DVT, including patients with concomitant PE.¹³ In this real-world study, patients receiving

TABLE 1. PHARMACOKINETIC PROFILES OF DOACs FOR THE TREATMENT AND SECONDARY PREVENTION OF VTE

| Key Points | Rivaroxaban | Apixaban | Edoxaban | Dabigatran |
|---|--|---|--|--|
| Mechanism of action | Factor Xa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Direct thrombin inhibitor |
| Time to peak | 2–4 h | 3–4 h | 1–2 h | 1.5 h |
| Half-life | 9–13 h | 12 h | 10–14 h | 12–17 h |
| Oral bioavailability | 66% | > 50% | 62% | 3%–7% |
| Excretion | Kidney, 36%; feces, 7% | Kidney, 28.8%; feces, 56%; minimal biliary | Kidney, 50%; rest is biliary/intestinal and metabolism | Kidney, 80% |
| Plasma protein binding | 92%–95% | ~ 90% | 55% | 35% |
| Absorption | Primarily proximal small intestine; some gastric absorption | Primarily proximal small intestine; some gastric absorption | Proximal small intestine | Lower stomach and duodenum |
| Dosing: for initial VTE treatment | 15 mg twice daily for 21 d followed by 20 mg daily (with largest meal) | 10 mg twice daily for 7 d followed by 5 mg twice daily | Parenteral agent for 5–10 d followed by 60 mg daily or 30 mg daily if any of following: CrCL 15–50 mL/min, weight ≤ 60 kg, or concomitant P-glycoprotein inhibitor | Parenteral agent for 5–10 d followed by 150 mg twice daily |
| Dosing: for VTE prophylaxis or extended treatment | 10 mg daily after at least 6 mo of therapeutic anticoagulation | 2.5 mg twice daily after at least 6 mo of therapeutic anticoagulation | Not studied | No dose adjustment |
| Special considerations | Avoid if CrCL ≤ 30 mL/min or Child-Pugh class B and C; must be taken with food | Avoid if CrCL ≤ 15 mL/min or Child-Pugh class B and C | Avoid if CrCL ≤ 15 mL/min or Child-Pugh class B and C | Avoid if CrCL ≤ 30 mL/min or Child-Pugh class B and C, if dyspepsia, upper GI symptoms |
| Dose adjustments* | None (no adjustments for age, weight, or sex) | None (no adjustments for age, weight or sex) | Decrease to 30 mg daily if any of following: CrCL 15–50 mL/min, weight < 60 kg, or concomitant P-glycoprotein inhibitor | None (no adjustments for age, weight, or sex) |
| Drug interactions | P-glycoprotein, CYP 3A4/5 | P-glycoprotein, CYP 3A4/5 | P-glycoprotein | P-glycoprotein, PPIs |
| Laboratory measurement (to determine if present/not present only) | Anti-Xa | Anti-Xa | Anti-Xa | Dilute thrombin time |
| Reversal agent | Andexanet (specific) or 4F-PCC (nonspecific) | Andexanet (specific) or 4F-PCC (nonspecific) | 4F-PCC (nonspecific) | Idarucizumab (specific) |

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; CAD, coronary artery disease; CrCL, creatinine clearance; DOAC, direct oral anticoagulant; GI, gastrointestinal; PAD, peripheral artery disease; PPI, proton pump inhibitor; VTE, venous thromboembolism.

*No dose adjustments are necessary for the treatment and secondary prevention of VTE. There are different doses and dose adjustments for the use of DOACs in other indications such as prevention of stroke in atrial fibrillation, prevention of VTE in elective hip/knee surgery, and prevention of cardiovascular events with PAD or CAD.

rivaroxaban had a lower risk of major bleeding (hazard ratio [HR], 0.77; 95% CI, 0.40–1.50) and recurrent VTE (HR, 0.91; 95% CI, 0.54–1.54) compared with conventional anticoagulation (initial treatment with unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or fondaparinux followed by a VKA). In all of these trials, the administration of dabigatran or edoxaban was preceded by

a course of LMWH or UFH, whereas the remaining DOACs were frequently used from the time of therapy initiation.

INITIAL TREATMENT

After a diagnosis of acute PE and risk stratification for mortality, the treating provider must perform an initial risk/benefit assessment of anticoagulation, which includes the

TABLE 2. DOAC CLINICAL VTE TRIALS WITH INDEX PE OUTCOMES⁴⁻¹⁰

| Trial | Index PE/ Total VTE, n/N (%) | DOAC | Standard AC | Treatment Duration, mo | Primary Efficacy Outcome (Recurrent VTE or VTE-Related Death) | | Primary Safety Outcome (Major or NMCR Bleeding) | | Safety Outcome (Major Bleeding Episode) | |
|--------------------------------|------------------------------------|--|--------------------|------------------------------|--|----------------------------|---|----------------------------|---|----------------------------|
| | | | | | DOAC, n/N (%) | Standard AC, n/N (%) | DOAC, n/N (%) | Standard AC, n/N (%) | DOAC, n/N (%) | Standard AC, n/N (%) |
| RE-COVER and RE-COVER II | 1,602/5,107 (31) | UFH or LMWH for ≥ 5 d then dabigatran 150 mg twice daily | UFH or LMWH/VKA | 6 | 23/795 (2.9) | 25/807 (3.1) | 36/759 (4.7) | 55/768 (7.2) | 4/759 (0.5) | 8/768 (1.0) |
| EINSTEIN DVT | 23/3,447 (< 1) | Rivaroxaban 15 mg twice daily for 21 d followed by 20 mg daily | LMWH/VKA | 3, 6, or 12 | 36/1,731* (2.1) | 51/1,718* (3.0) | 139/1,718* (8.1) | 138/1,711* (8.1) | 14/1,718* (0.8) | 20/1,711* (1.2) |
| EINSTEIN PE | 4,832/4,832 (100) | Rivaroxaban 15 mg twice daily for 21 d followed by 20 mg daily | LMWH/VKA | 3, 6, or 12 | 50/2,419 (2.1) | 44/2,413 (1.8) | 249/2,412 (10.3) | 274/2,405 (11.4) | 26/2,412 (1.1) | 52/2,405 (2.2) |
| AMPLIFY | 1,836/5,395 (34) | Apixaban 10 mg twice daily for 7 d followed by 5 mg twice daily | UFH or LMWH/VKA | 6 | 59/2,609* (2.3) | 71/2,635* (2.7) | 115/2,676* (4.3) | 261/2,689* (9.7) | 15/2,676* (0.6) | 49/2,689* (1.8) |
| HOKUSAI- VTE | 3,319/8,240 (40) | UFH or LMWH for ≥ 5 d then edoxaban 60 mg daily | UFH or LMWH/VKA | 3, 6, or 12 | 47/1,650* (2.8) | 65/1,669* (3.9) | 349/4,118* (8.5) | 423/4,122* (10.3) | 56/4,118* (1.4) | 66/4,122* (1.6) |

Abbreviations: AC, anticoagulant; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; NMCR, nonmajor clinically relevant; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist (goal international normalized ratio, 2.0–3.0); VTE, venous thromboembolism.

*Includes overall VTE study results.

risks of achieving therapeutic anticoagulation balanced by the bleeding risk of the patient on anticoagulation. If the decision is to initiate anticoagulation, a practical approach is to divide treatment into three phases: initial (first 5–10 days and may include parenteral and/or oral anticoagulant), long term (> 10 days to 3–6 months), and extended (> initial 3–6 months). For the acute setting, anticoagulation options include UFH, LMWH, fondaparinux, rivaroxaban, or apixaban. Dabigatran and edoxaban are also effective treatments, but as previously mentioned, both require 5 to 10 days of an initial parenteral anticoagulant and are not approved for stand-alone therapy initially.

With multiple anticoagulant options now available, including the DOACs that do not require an initial parenteral agent, inpatient versus outpatient management of PE has become a part of the initial assessment. Patients with acute PE who are otherwise stable and have no other reason for hospitalization may be considered for outpatient

management. Hemodynamic instability (blood pressure < 90 mm Hg, pressor support, or other evidence of shock) is often associated with massive PE, and these patients may be candidates for thrombolytic therapy, whereas hemodynamically stable patients may be considered low risk (small PE, no evidence of right heart strain), in which case systemic anticoagulation is often the only treatment merited. On the other hand, patients with larger PE accompanied by evidence of right heart strain may be candidates for more advanced therapies in addition to systemic anticoagulation. Clearly, the treating physician must consider anticoagulant options in the context of the patient's comorbidities, which include baseline bleeding risk (since this varies with age), renal function, and the type of anticoagulant administered.

EXTENDED TREATMENT

Duration of anticoagulation should be individualized for each patient and should include the initial and periodic

assessment of risk factors for recurrent VTE (transient or persistent) as well as age, sex, obesity, and organ function (liver and kidney). These factors need to be balanced by the risk factors for bleeding on anticoagulation. Overall, this risk/benefit assessment should also include patient preferences (including cost of the anticoagulant). In patients who had a transient risk factor that has resolved, short-term therapy (eg, 3 months) may be reasonable. Alternatively, in patients who had an unprovoked VTE (PE or proximal DVT) or a provoked VTE with ongoing risk factors, long-term anticoagulation may be warranted. All of the DOACs except for edoxaban have been evaluated in randomized trials for extended secondary VTE prevention beyond the initial 3 months. The studies investigating the use of apixaban, rivaroxaban, or dabigatran for secondary prevention of VTE demonstrated superiority in preventing the primary efficacy endpoint of symptomatic recurrent VTE as compared to placebo (AMPLIFY-EXTENSION [apixaban], EINSTEIN-EXTENSION [rivaroxaban], RE-SONATE [dabigatran]) or aspirin (EINSTEIN CHOICE [rivaroxaban]) without a significant increase in major bleeding.^{6,14,15} Dabigatran was also found to be noninferior to warfarin in preventing recurrent VTE in an extended VTE prevention trial (RE-MEDY) with significantly lower rates of bleeding.¹⁴ These results support the use of extended duration of anticoagulation in select patients to reduce the lifetime risk of recurrent thrombosis and VTE-associated death.

Importantly, anticoagulation duration should be assessed at least annually, considering risk for VTE recurrence is 7% within the first year and 40% within 5 years.¹⁶ Recent data indicate that long-term nonadherence to DOAC therapy may be as much as 40% to 70% and more severe among patients taking oral medications multiple times each day.¹⁷ Thus, when choosing a DOAC regimen for your patient, all of these issues should be taken into consideration.

All anticoagulants including the DOACs are associated with bleeding, which in rare situations can be life-threatening. Currently, there are two FDA-approved DOAC-specific reversal agents: idarucizumab for dabigatran and andexanet for rivaroxaban and apixaban. Both of these drugs were effective in reversing the anticoagulant effect when administered to patients who presented with serious bleeding.^{18,19} Four-factor prothrombin complex concentrate has been used for reversal of anti-Xa DOACs (apixaban, rivaroxaban, edoxaban) prior to andexanet alfa approval or when it is not available. Another reversal agent, ciraparantag, is presently in clinical trials.

SPECIAL POPULATIONS

The choice of DOAC must be made in the context of the specific patient, and DOACs are either contraindicated or have not yet been extensively evaluated in certain patient populations.

Antiphospholipid Syndrome

A history of antiphospholipid syndrome or a clinical presentation consistent with that diagnosis (eg, PE plus arterial thrombosis) should alert the clinician to consider the variance in efficacy of anticoagulants. Available data draw into question whether DOACs are effective or safe in patients with antiphospholipid syndromes. Indeed, apixaban recently updated its labeling to include antiphospholipid syndrome as a warning that DOACs could be associated with increased rates of recurrent VTEs compared to VKA therapy, and DOACs are not recommended in this patient population. Several ongoing trials may settle this issue shortly, but until then, DOACs should probably be avoided in these patients.

Renal Impairment

Use of DOACs in patients with renal impairment is hazardous for several reasons. With the exception of dabigatran, they are not dialyzable and may lead to overaccumulation in patients undergoing dialysis, and in patients with renal failure not on dialysis, bleeding risk increases as renal impairment worsens. In general, all of the DOACs have limited data in patients with significant renal impairment (creatinine clearance ≤ 15 –30 mL/min, depending on the DOAC) and are not recommended (Table 1). Although apixaban labeling recommends no dose adjustment for patients with VTE and renal impairment, including those with ESRD on dialysis, this recommendation is based on a very small nonrandomized controlled study (not the clinical efficacy and safety studies that led to its approval) and should be interpreted cautiously. Patients with coronary artery disease and peripheral vascular disease may be candidates for dose-modified rivaroxaban plus antiplatelet therapy. It is important to point out that coronary artery events are more common in patients treated with dabigatran than with a VKA.

Cancer

The treatment of patients with active malignancy and VTE can be challenging. Many patients have an increased risk of bleeding, additive risks of rethrombosis associated with antineoplastic therapy, and a high risk of treatment failure with standard anticoagulation. Present evidence indicates that, at least in the short term, edoxaban and rivaroxaban seem as effective as standard anticoagulation with dalteparin.^{20,21} However, both were associated with an increased risk of bleeding in cancer patients when compared to dalteparin.^{20,21} Importantly, the bleeding was primarily seen in patients with gastrointestinal cancers. There is an ongoing trial of apixaban in cancer patients. Whether any one of these DOACs is superior to another is uncertain. Given all of these data, clinicians should carefully review the pros (decreased risk of VTE) and cons (increased risk of bleeding) of the use of rivaroxaban and edoxaban in cancer patients with VTE.

and make a decision on the type of anticoagulation through shared decision-making.

Pregnancy

No DOACs have been evaluated during pregnancy. There is evidence that they are present in breast milk. Whether this is harmful to the feeding infant is unknown. For this reason, they are best avoided during pregnancy and breastfeeding.

Liver Impairment

Patients with liver impairment should not receive DOACs because the international normalized ratio may be prolonged due to liver synthetic defect during the course of treatment. This will likely increase bleeding risk and confound the use of those DOACs that often prolong the prothrombin time.

Obesity

Few patients with significant obesity have been included in DOAC clinical trials, and their efficacy in relationship to body weight and body fat percentage is unknown. As such, the International Society of Thrombosis and Haemostasis recommends avoiding DOACs in patients > 120 kg or a body mass index > 40 kg/m².²² Similarly, patients < 50 kg were not adequately represented in DOAC clinical trials, so the safety and efficacy of DOACs in this population is not known and their use should be avoided. The one exception is edoxaban, which can be dose reduced in patients < 60 kg (Table 1).

Heparin-Induced Thrombocytopenia

For patients with a recent or remote episode of heparin-induced thrombocytopenia (HIT), heparin therapy should be avoided. Although the only FDA-approved treatment for HIT is argatroban, in this setting, the clinician should consider using fondaparinux, a direct thrombin inhibitor, or possibly a DOAC, as a few cases series have demonstrated safety with the latter.²³ However, available data with DOACs and HIT are scant—there are ongoing trials in this patient population.

CONCLUSION

VTE is a common disorder and is associated with significant morbidity and mortality. DOACs have emerged as the treatment of choice for many patients given their convenience, predictable pharmacokinetics and pharmacodynamics, and their similar effectiveness in reducing VTE compared to VKAs, with significantly less major bleeding. There are some populations in which DOACs are not recommended or their safety and efficacy is not known. There are ongoing trials in many of these patient groups. When choosing the most appropriate treatment for patients, it is important for clinicians to understand the differences between the DOACs because they all have different dosing regimens. ■

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Catheter-Based Therapy: Are We Making Progress and Is the Game Changing?

BY THOMAS M. TODORAN, MD, MSc; WISSAM A. JABER, MD; AND JOHN M. MORIARTY, MD

Acute pulmonary embolism (PE) is a common and potentially fatal illness if not recognized and treated in a timely manner. Contemporary management includes systemic anticoagulation or thrombolysis, catheter-based procedures, and surgical embolectomy. Systemic thrombolysis and surgical embolectomy are not without complications. Newer catheter-based procedures allow for therapeutic benefit while minimizing complications. This article describes features of available thrombolytic and aspiration technologies and results of studies evaluating their efficacy and safety.

CATHETER-DIRECTED THROMBOLYSIS

In patients with hemodynamically significant acute PE, systemic thrombolysis improves right ventricular (RV) dysfunction, RV dilation, and reduces pulmonary artery (PA) pressures. However, systemic thrombolysis is associated with a dose-related risk of bleeding, particularly intracranial hemorrhage (ICH). An alternative to systemic thrombolysis is direct infusion into the PAs using an infusion catheter, which is appealing because it provides the therapeutic benefit of thrombus resolution with lower dose of thrombolytic drug to reduce the risk of bleeding.

There are two categories of catheters used for catheter-directed thrombolysis (CDT), multi-side-hole infusion catheters and the EkoSonic endovascular system (BTG Vascular). Ultrasound-assisted catheter-directed thrombolysis (UACDT) combines conventional CDT and high-frequency (2.2 MHz), low-power (0.5 W) ultrasound. Ultrasound accelerates fibrinolysis by disaggregating fibrin fibers, allowing greater penetration of the thrombolytic agent. The system consists of a 0.035-inch, guidewire-compatible, 5.4-F, multi-side-hole infusion catheter; an ultrasound core matched to infusion length; and a control unit. The infusion catheter is placed into the affected PA with the treatment zone embedded in the clot (Figure 1).

To date, two randomized controlled clinical trials (ULTIMA and OPTALYSE PE) and one prospective, single-arm study (SEATTLE II) have evaluated the safety and efficacy of the EkoSonic system for the treatment of acute PE and RV dilation (RV/left ventricular [LV] ratio > 0.9).

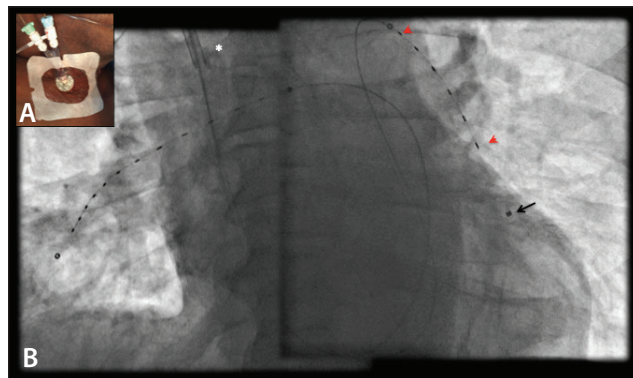


Figure 1. A 12-F Fast-Cath Duo sheath (Abbott Vascular, formerly St. Jude Medical) in the right internal jugular vein with two EkoSonic catheters inserted (A, also denoted with an asterisk in B). Bilateral placement of EkoSonic catheters in the right middle PA and the left lower PA. Infusion zone is denoted between the two red arrowheads, and the distal central lumen is denoted at the black arrow (B).

Both the ULTIMA (n = 49) and SEATTLE II (n = 150) studies showed reversal of RV dilation and reduction of PA pressures upon completion of the infusion of 10 to 20 mg tissue plasminogen activator (tPA) over 15 hours and 24 mg tPA over 12 to 24 hours, respectively. There was no occurrence of ICH in either study.^{1,2} In OPTALYSE PE (n = 101), RV dilation was reversed over shorter infusion duration (2–6 hours); however, two patients experienced ICH.³ A recent meta-analysis of 860 patients reported major bleeding or vascular injury in 4.75% and ICH in 0.35%.⁴

The PERFECT prospective multicenter registry (n = 101), which included both UACDT and multi-side-hole infusion catheters, also demonstrated improvement in RV function with a reduction in PA pressures.⁵ There has not been a head-to-head comparison of UACDT to multi-side-hole catheters; however, the PERFECT registry and subsequent retrospective studies have demonstrated no difference between the two modalities.^{6,7}

CATHETER ASPIRATION

Percutaneous mechanical removal of the PE has always been an attractive concept, with the theoretical benefits of immediate resolution of the pulmonary vascular obstruction, avoidance of thrombolytic use, and reduction of clot

burden as nidus for potential chronic obstruction. Although technologic advances have allowed successful percutaneous retrieval or aspiration of most coronary and cerebral arterial thrombi, borrowing similar technologies to treat venous thromboembolic clots has been far less successful. Regardless of the catheter size, the strength of the applied aspiration, or the innovation of the clot capture mechanism, the basic procedural challenges remain the same: very large and organized thrombus, tortuosity and unfavorable angulations, a difficult-to-navigate tapering, and rapidly branching pulmonary arterial structure.

Despite these difficulties, recent technologic advances and collective experience have yielded better results and renewed hope in venous thromboembolic aspiration. Most notable in this field is the newly FDA-approved FlowTrieve catheter (Inari Medical; Figure 2). This catheter is a 20-F, 90-cm aspiration guiding catheter equipped with a large-bore side port and an aspiration syringe. Typically introduced in the femoral vein through a 22-F sheath, the catheter and its removable dilator are advanced over a stiff wire into the desired pulmonary branch until they reach the thrombus. Initial crossing of the right heart into the PA has to be done first with a balloon-tipped catheter to avoid entrapment behind a tricuspid valve cord, before the wire exchange happens. Individual interlobar or lobar branches

can be selected using a standard coronary catheter.

Once the FlowTrieve catheter is in position, the dilator is removed and suction is applied through the provided aspiration syringe. Catheter engagement of the clot is crucial for successful aspiration. If needed, self-expanding nitinol discs can be deployed distally and retrieved into the catheter to help drag thrombi proximally while aspiration is performed. Longer, smaller (16 F) aspiration catheters may also be used, intussuscepted into the larger catheter for more distal aspiration.

The efficacy and safety of the FlowTrieve catheter were studied in the single-arm, prospective FLARE trial, which showed significant improvement in RV/LV ratio at 48 hours postprocedure in patients with intermediate-risk acute PE (RV/LV ratio > 0.9).⁸ Three patients had procedure-related (but not catheter-related) complications. In our experience, if adequate aspiration is performed, significant improvement in hemodynamic numbers and patient symptoms can be observed immediately.

Another aspiration catheter currently on the market but not yet FDA approved for acute PE is the 8-F Indigo catheter (Penumbra, Inc.). Typically advanced to the PA through a 10-F, 80-cm sheath, the catheter with a slightly angulated tip is advanced over a wire until it engages thrombi. The guidewire is then pulled and a separator wire introduced to keep clearing the tip from obstructive thrombi while a pump applies continuous mechanical suction through the back of the catheter. This device is currently under investigation in the now completed EXTRACT PE trial, a single-arm prospective trial; results have not yet been presented or published (NCT03218566).

THE ANGIOVAC SYSTEM

An option for large-bore catheter removal of intravascular material is the AngioVac system (AngioDynamics). The AngioVac system consists of a venovenous bypass circuit, filter, and proprietary 22-F aspiration cannula. The cannula has a coil-reinforced shaft, preventing collapse with the high suction forces generated, and a balloon-actuated, expandable, funnel-shaped distal tip. This tip enhances venous drainage flow when the balloon is inflated, which helps prevent clogging of the cannula with large clots. The cannula is inserted through a 26-F sheath and then connected to an extracorporeal bypass circuit, which passes through a filter. The filtered blood is then returned to the venous system through either a 16- or 18-F reperfusion catheter.

A closed-circuit aspiration system is particularly beneficial in the management of right heart thrombi (RHT). RHT are found in 4% of all PE according to the International Cooperative Pulmonary Embolism

Courtesy of Inari Medical.

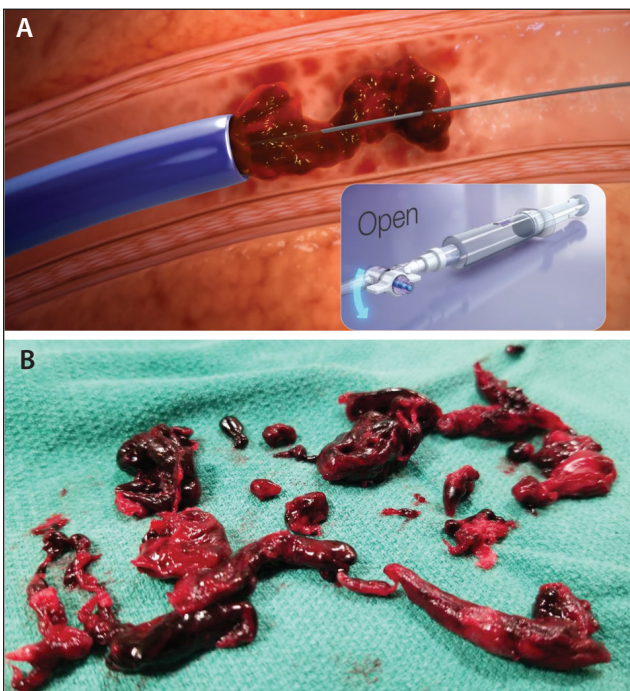


Figure 2. Image of the FlowTrieve catheter advanced into the thrombus. The aspiration syringe is turned on when the catheter engages the thrombus (A). Example of aspirated thromboemboli using the FlowTrieve (B).

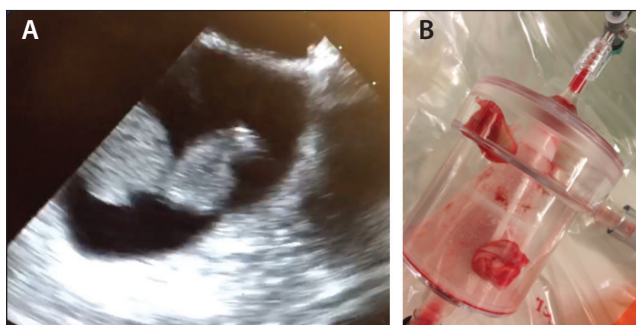


Figure 3. A transesophageal echocardiogram demonstrating a mobile “ball-like” thrombi within the right atrium in a patient with submassive PE (A). After AngioVac aspiration, the masses could be seen as organized thrombi (B).

Registry data⁹ and in up to 16% of high-risk PE.⁹ The most common morphology is a cast of femoral or iliac vein thrombus in motion in the right atrium. Previously, pharmacologic and open surgical thrombectomy were the only recognized treatment options. The AngioVac system allows for a minimally invasive endovascular option now favored in many centers (Figure 3). Several publications have demonstrated efficacy with low complications. In particular, the ability to rapidly remove RHT, theoretically preventing the future risk of PE and cardiovascular collapse, with a single procedure is enticing because it allows preservation of all other options for PE management such as CDT. An area of particular interest is the role of AngioVac aspiration of RHT in the setting of a patent foramen ovale (PFO). Recent data have shown the high prevalence of paradoxical embolism in PE patients,¹⁰ and although there is no large series of AngioVac usage in the presence of a shunt, several case reports have shown safe removal of thrombi that have partially traversed a PFO.

Compared to RHT, use of AngioVac for removal of PA thrombus has been slow to gain widespread favor. This is largely due to two factors: (1) the rigidity of the 22-F aspiration cannula can make it difficult to pass the cannula through the right heart to the PA, placing more stress on the RV outflow tract and leading to either arrhythmia or bleeding; and (2) the hemodynamic effects of aspirating up to 3.5 L/min directly from the PAs, especially in the setting of an already compromised pulmonary perfusion, can precipitate hypotension and right heart failure. Although there have been anecdotal reports of good success of PE aspiration with the AngioVac system at high-volume centers, this should be considered a second-line or bailout option.

SUMMARY

Although there are limited clinical trial data, catheter-based treatment of acute PE is promising. Small studies have

demonstrated CDT to be safe and effective in reversing RV dilation and reducing PA pressures. The risk of bleeding complications, particularly ICH, is much lower compared to systemic thrombolysis. Aspiration using the FlowTriever catheter allows for thrombus removal without the need for thrombolysis and the associated risk of bleeding. Although the Indigo catheter is currently under investigation and is not FDA approved, it appears to be promising for clot removal, particularly for more distal smaller PAs. The AngioVac system has not proven to be a viable option for extraction of PE but can be useful for treating RHT or clot in transit in the setting of acute PE. ■

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The Pulmonary Embolism Response Team Movement: Advancing Practice, Science, and Quality of Care for Acute PE

BY CHRISTINA FANOLA, MD, MSc; MICHAEL ROSENBERG, MD;
ROBERT LOOKSTEIN, MD, MHCDL, FSIR, FAHA, FSVM; AND KENNETH ROSENFELD MD, MHCDS

PULMONARY EMBOLISM: A COMPLEX AND COSTLY DISEASE STATE

Venous thromboembolism is a worldwide problem and leading cause of cardiovascular death.¹ Untreated pulmonary embolism (PE) has a mortality rate of 30%,² and historical data demonstrate that even with standard treatment, the 3-month mortality rate still ranges from 15% to 30%, especially in patients with comorbid cardiopulmonary disease.^{3,4} Those with cardiogenic shock from PE have up to a sevenfold increased mortality risk, with death often occurring within the first hour of presentation.⁵ PE is also associated with increased costs and utilization of health care resources with average hospital charges per case exceeding \$40,000 and average length of inpatient hospitalization over 8 days.⁶ Annual overall national health care expenditures are conservatively estimated to be in excess of \$1.5 billion.⁶ Recognition of the complexities and high mortality surrounding PE has led to the development of multiple risk stratification tools, novel therapies, and proposed treatment algorithms in an effort to improve outcomes.

Risk prediction scores, such as the Geneva Score and Pulmonary Embolism Severity Index, were developed to quantify risk of short-term mortality in those with acute PE.⁷ Mortality varies greatly based on comorbidities and hemodynamics in “major” acute PE, ranging from 8% for stable patients versus 65% for those requiring cardiopulmonary resuscitation.⁸ As the wide variation in outcomes was further understood, categories of severity emerged, defining PE as minor (low risk), submassive (intermediate) with low- and high-risk subtypes, and massive (high risk). These categories incorporated existing (limited) data regarding risk of in-hospital mortality, hemodynamic status, and imaging and biomarker findings indicative of right ventricular dysfunction.⁷

Treatment options (standalone or in combination) can include intravenous or subcutaneous anticoagulation, full- and half-dose systemic thrombolytics, full- or

reduced-dose catheter-directed thrombolytics, catheter-based embolectomy, and/or surgical embolectomy. The use of mechanical circulatory support has also come into the equation, both in patients who demonstrate ongoing hemodynamic instability despite advanced therapies and in select patients at risk for clinical decompensation during an intervention or procedural sedation/intubation. Although there has been a significant movement to advance PE care—particularly in patients with submassive and massive PE who are at the highest risk for mortality—the complexity of the disease, the large number of available diagnostic and treatment options, and the paucity of controlled clinical trial data have limited the establishment of standardized guidelines for acute PE.^{7,9,10} Consequently, there remains a high degree of variability in therapeutic decision-making surrounding PE management. A patient with a given clinical presentation will receive very different treatment from hospital to hospital, and often even within the same institution, depending upon the service provider. Such a high degree of variability should not exist within medicine; it is a reflection of our need to close the existing knowledge gap in PE and to better define what constitutes high-quality PE care.

ADDRESSING UNMET CLINICAL AND SCIENTIFIC PE NEEDS: RISE OF THE MULTIDISCIPLINARY PERT

The concept of a multidisciplinary team-based approach in complex cardiovascular disease has been promoted by the European Society of Cardiology, European Association for Cardiothoracic Surgery, American College of Cardiology, and American Heart Association for coronary revascularization and transcatheter aortic valve replacement.¹¹ Such teams engage multiple specialties in an effort to synthesize complex treatment options and optimize shared decision-making with patients and their families. This

approach enhances the cognitive interchange among medical specialties and reduces the risk of individual physician bias, which benefits both patients and physicians alike. Better decision-making aims to improve quality of care and patient outcomes.¹¹

There is growing recognition that a multidisciplinary approach has the potential to greatly enhance care for patients with complex PE. The first formal multidisciplinary pulmonary embolism response team (PERT) was established at Massachusetts General Hospital.¹² Goals and objectives of this initial effort are listed in the sidebar. This single-institution effort fueled a worldwide movement in the development of similar treatment teams, with over 150 institutions currently managing acute PE with a multidisciplinary PERT. This approach not only helps to advance clinical care in submassive and massive (intermediate to high risk) PE but also to develop an educational platform and research infrastructure to address current gaps in scientific evidence surrounding the multitude of available advanced treatment options.

Acute PE requires prompt diagnosis and treatment decision-making, especially when associated with hemodynamic instability. In this regard, the PERT concept differs from transcatheter aortic valve replacement, cancer care, and other teams that require less urgent decision-making. The optimal PERT can rapidly establish communication involving multiple specialties as needed for an individual PE patient, including but not limited to cardiology, pulmonary, critical care, cardiovascular surgery, anesthesia, interventional radiology, hematology, vascular medicine, vascular surgery, emergency medicine, and pharmacology. An organized and coordinated approach to the utilization of information technology for connectivity; bed placement and/or hospital transfer; pharmacy, echocardiography, and radiology services; and perfusion and respiratory therapy is also critical for successful program implementation. Because mortality is high within the first hour of a hemodynamically significant PE, there is major potential for improved outcomes with a successful PERT if it can quickly and effectively mobilize personnel and resources to deliver advanced therapies and mechanical support when required.

QUALITY IMPROVEMENT ASSOCIATED WITH PERTs

A major challenge in PE has been the establishment of standards of care and what constitutes “high-quality care.” This is in large part due to the evidence gap in PE, but also due to the rapid evolution of technology and challenges/inconsistencies in defining and reporting outcomes. There are limited multicenter prospective outcomes registries for diagnosis and treatment of acute PE. The ICOPER

The Pulmonary Embolism Response Team Concept

GOALS

- Advance the diagnosis, treatment, and outcomes of patients with severe PE
- Improve patient outcomes using a collaborative, multidisciplinary team-based urgent consult to treat massive and submassive PE

OBJECTIVES

- Respond expeditiously to treat patients with acute PE
- Provide best therapeutic option(s) available for each individual patient
- Coordinate care among services involved in management of PE
- Develop protocols for the full range of available therapies
- Collect data on clinical presentation, treatment efficacy, and outcomes (short- and long-term)

FUNCTIONALITY

- Modeled on the rapid-response concept
- Multidisciplinary team of experts convened on an urgent basis, using digital or other available means of communication
- Evaluate and offer full range of available treatments

registry recorded outcomes of patients with high-risk PE as compared to intermediate- and low-risk patients.³ This registry laid the foundation for the aggressive management of high-risk cases, specifically with the use of thrombolytics and inferior vena cava filters.

In the modern era, there is a tremendous need to redefine the role of thrombolytics and establish the appropriate role of novel endovascular therapies for both high- and intermediate-risk patients. The exact role and timing of the use of direct oral anticoagulants is also currently poorly understood for the high-, intermediate-, and even low-risk populations. Results from surgical thrombectomy have improved, and use of advanced support (eg, extracorporeal membrane oxygenation, right ventricular support devices) clearly has impacted survival. The major advances in PE treatment options are a positive step, yet there remains an absence of comparative data regarding use and outcomes and what constitutes “best practice” and “high-quality care” for PE.

The emergence of PERTs across the United States and the world has created a unique pathway to engage these highly motivated clinical teams and redefine what

constitutes best practice in the modern era. In 2018, the national PERT Consortium™ partnered with the Boston Clinical Research Institute to establish the national PERT quality database to prospectively record all encounters for intermediate- and high-risk PE around the country and, ultimately, the globe. At present, over 1,700 unique patient encounters have been recorded, and almost two dozen clinical sites are receiving regular feedback related to diagnosis and triage, initiation of medical therapy, and escalation to advanced therapies. The response thus far has been uniformly positive, and another 50 clinical sites are about to start enrolling their patients.

In the near future, based on ongoing conversations with federal regulatory bodies, this database will allow for refinement of what is considered best practice and will likely lead to prospective research as new medical, endovascular, and surgical therapies are introduced into clinical practice. The database is uniquely designed to provide feedback to the clinical sites based on predetermined quality metrics, enabling PERTs at each institution to benchmark their practice and outcomes to those of the entire consortium. Equally powerful is the opportunity for the PERT registry to serve as a backbone for comparative effectiveness research, as well as postmarket device and drug safety and efficacy studies.

In summary, the national PERT quality database is uniquely positioned to establish quality standards and define best practice for years to come. We strongly encourage any institutions with an existing PERT, or an interest in developing a PERT, to contact the national PERT Consortium™ and participate in this new opportunity (through the registry and other PERT programs) to redefine best practice for the treatment of acute PE in the 21st century. ■

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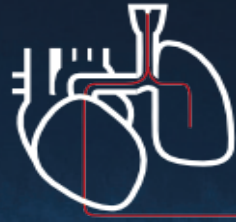
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