AMERICAN
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Acute Management of Pulmonary Embolism

Oct 24, 2017　|　<u>Vikas Aggarwal, MBBS, MPH , FACC</u>; <u>Charles D Nicolais, MD</u>; <u>Aaron Lee, MD</u>; <u>Riyaz Bashir, MBBS, FACC</u>

Expert Analysis

Introduction

Venous thromboembolic disease (VTE) is estimated to occur in at least 1 to 2 persons per 1000 population annually, manifesting as deep vein thrombosis (DVT), pulmonary embolism (PE) or in combination.[1-3] It is the cause of over 100,000 deaths annually and is the most preventable cause of death in hospitalized patients in the United States.[4] Despite treatment with anticoagulant therapy, a significant proportion of survivors of acute DVT or PE are at risk of suffering from the disabling sequelae such as the post thrombotic syndrome (PTS), recurrent VTE or chronic thromboembolic pulmonary hypertension (CTEPH).[1,5] Given the limitations of medical therapy, promising endovascular treatment modalities have evolved over the past two decades in an effort to mitigate the acute and chronic disability from VTE.[6,7] The purpose of this review is to discuss the rationale and evidence for an endovascular treatment approach for high-risk acute DVT and PE patients.

The Rationale for an Interventional Approach to Massive and Submassive PE

The most dreaded acute complication of PE is death; it is estimated that over 100,000 deaths in hospitalized patients in the United States are attributable to acute PE each year.[4] The severity of PE is stratified into massive (PE causing hemodynamic compromise), submassive (PE causing right ventricular dysfunction demonstrable by echocardiography, computed tomography or elevated cardiac biomarkers) and non-massive or low-risk (PE without evidence of RV dysfunction or hemodynamic compromise). The International Cooperative Pulmonary Embolism Registry (ICOPER) demonstrated 90-day mortality rates of 58.3% in

patients with massive PE versus 15.1% in sub-massive PE.[20] Several studies demonstrate short-term mortality rates of less than 2% in patients with low-risk PE.[21-23] Features suggestive of adverse prognosis in acute PE are listed in Table 2. Up to 4% of patients who survive will develop CTEPH.[24] Untreated CTEPH carries a poor prognosis, especially if associated with pulmonary hypertension and right ventricular dysfunction.[25] Recurrent DVT as well as a large thromboembolic burden has been observed in the literature to correlate with an increased likelihood of developing CTEPH.[24] While in acute PE, obstructive pathophysiology is almost certainly the cause of right ventricular failure and death,[26] histologic and surgical studies suggest that complex factors involving shear stress, remodeling of the pulmonary vascular bed and microvascular inflammation appears to play a role in the development of CTEPH.[27] In patients with massive PE, systemic thrombolytic therapy has been shown to reduce mortality,[28] decrease the risk of developing CTEPH and improve quality of life.[29,30] A recent meta-analysis suggests that systemic thrombolytic therapy also reduces mortality in patients with submassive PE (OR 0.48; 95% CI 0.25 - 0.92).[31] This, however, appears to be at the expense of significant major bleeding complications (OR 2.91; 95% CI 1.95 - 4.36) including intracranial hemorrhage (OR 3.18; 95% CI 1.25 - 8.11). These bleeding-related adverse events as well as treatment failure seen with systemic thrombolysis have resulted in the exploration of catheter-based thrombus removal as an alternative therapeutic option for these patients.[32,33] In contemporary practice, catheter-based endovascular therapy for acute PE can be considered in patients where there is a clear contraindication to full dose thrombolytic therapy or when risk stratification in a patient with stable hemodynamics indicates an increased likelihood of morbidity and mortality.[34]

Table 1: Features Suggestive of Adverse Prognosis in Acute PE

Electrocardiography (ECG)
Sinus tachycardia
New-onset atrial arrhythmias

| New right bundle branch block (complete or incomplete) |
| QR pattern in V1 |
| S1Q3T3 |
| T wave inversion in V1 through V4 |
| ST segment migration in V1 through V4 |
| **Biomarkers** |
| Elevated troponin (cTnI and cTnT) |
| Elevated natriuretic peptides (BNP and N-terminal pro-BNP) |
| **Computed Tomography** |
| RV diameter / LV diameter >0.9 |
| Ventricular septal bowing from right to left |
| Presence of RV enlargement |
| **Echocardiography** |

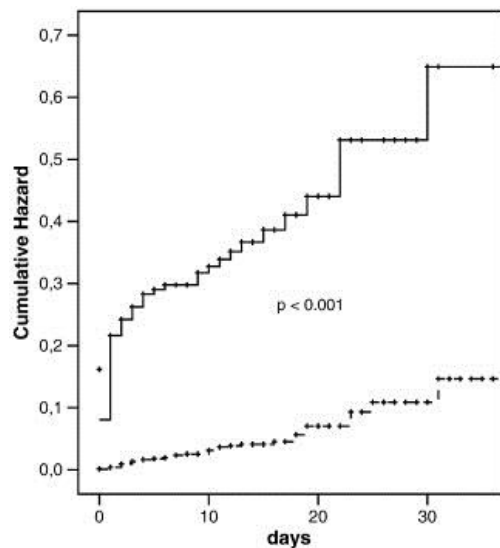| |
|---|
| RV dilatation and hypokinesis
RV diameter / LV diameter >0.9 |
| Interventricular septal flattening and paradoxical leftward septal motion |
| Presence of TR |
| Presence of PH (peak tricuspid jet velocity greater than 2.6m/s and loss of respirophasic IVC collapse |
| RV free wall hypokinesis with apical sparing (McConnell's sign) |

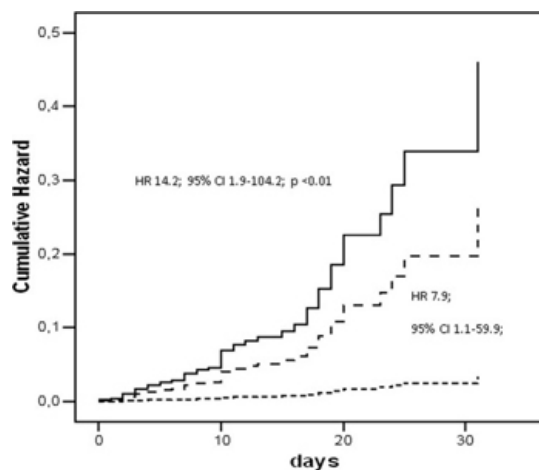BNP = brain natiuretic peptide; RV = right ventricle; LV = left ventricle
TR = tricuspid regurgitation; PH = pulmonary hypertension; IVC = inferior vena cava

Figure 1: Cumulative hazard for death in Acute PE

Dashed line= hemodynamically stable. Solid line= hemodynamically unstable

Figure 2: Adjusted cumulative hazard for in-hospital death or clinical deterioration in hemodynamically stable patients with acute pulmonary embolism.

Solid line= patients with right ventricular dysfunction by echocardiography and elevated troponin levels. Dashed line= patients with right ventricular dysfunction or elevated troponin levels. Dotted line= patients without right ventricular

dysfunction and normal troponin levels. HR = hazard ratio.

Patient Selection and Risk Stratification

Careful patient selection should be the foundation upon which an individualized endovascular strategy is adopted in clinical practice. Three key considerations should be factored into the decision to proceed with an endovascular approach: 1) disease severity and acuity; 2) likelihood of a major adverse bleeding event; and 3) patient-specific considerations.

Systemic thrombolysis is associated with lower all-cause mortality in patients with massive PE and should be the treatment of choice in this subset of patients.[31,39] Current US and European societal guidelines recommend endovascular treatment strategies in the event of treatment failure in this subset of patients.[32,40,41] A pulmonary embolism response team (PERT) approach, whereby a multi-disciplinary team determines the optimal course of action in critically ill patients with massive PE,[42] should be considered when extracorporeal membrane oxygenation (ECMO) and/or surgical pulmonary embolectomy can be life-saving alternatives.[43,44] In submassive PE, use of systemic thrombolysis is associated with a mortality benefit yet significantly increases the risk of major bleeding, including intracranial hemorrhage.[39,45] For this subset of patients ACCP guidelines currently recommend systemic thrombolytic therapy when cardiopulmonary deterioration is evident yet frank hypotension has not occurred. The ACC/AHA guidelines suggest that catheter embolectomy can be considered when cardiopulmonary deterioration is evident or in submassive PE when patients have clinical evidence of adverse prognosis. The European Society of Cardiology (ESC) recommends two-step risk stratification, first with a validated clinical prognostic assessment tool (Pulmonary Embolism Severity Index or simplified Pulmonary Embolism Severity Index) followed by imaging and biomarker risk assessment.[46,47] When both clinical and objective risk assessment tools are positive, catheter-directed therapy can be considered if cardiopulmonary deterioration is felt to be imminent. The divergence in recommendations clearly reflects a paucity of large randomized trial data in this area. Existing data demonstrates that ultrasound-assisted catheter directed thrombolysis (UA-CDT) is superior to heparin anticoagulation alone in improving right ventricular dilatation within 24 hours without major bleeding complications or recurrent VTE.[33] In a single-arm multicenter study of 150 patients, UA-CDT reduced the mean pulmonary artery systolic pressures by 30% and decreased the mean RV/LV diameter ratio by

25%.[48] At 90 days there was a statistically significant difference in RV systolic function favoring UA-CDT, while RV/LV ratio a trend toward improvement in the UA-CDT arm, it did not reach statistical significance (p = 0.07). None of the patients had an intracranial bleed while one patient suffered a major bleeding complication. This approach appears to be promising and perhaps favorable in this subset of patients although definitive safety outcomes and medium to long-term mortality data are not known. Patients with low-risk PE should not be considered for endovascular therapy owing to the low associated morbidity and mortality rates. The only exception being patients who have a large saddle embolus without any adverse hemodynamics or right ventricular effects. Ongoing safety and efficacy trials assessing optimal dose and duration of therapy are eagerly awaited.[49]

Bleeding Risk Assessment

All patients being considered for catheter-based endovascular therapies for either acute PE or LE-DVT should undergo a rigorous assessment of bleeding risk. Active bleeding, recent cerebrovascular or intracranial pathology (cerebrovascular accident, transient ischemic attack, cranial trauma, recent neurosurgery) or absolute contraindications to anticoagulation are absolute contraindications to any type of endovascular treatment strategy involving thrombolytics. Relative contraindications (Table 1), especially if not correctible should be carefully reviewed on an individualized basis.

Patient-Specific Considerations

Patient preference should be central in determining whether an endovascular treatment approach is appropriate. It is the responsibility of the physician to delineate the risks and benefits outlined above and discuss these in the context of each individual patient's life expectancy and functional status. This is especially important when presenting endovascular treatment strategies for LE-DVT as they are not performed to prevent death, but with the goal of improving quality of life and function in the long term.[41] Careful consideration must be given to the effect of chronic co-morbidities to the patients' functional status as well as their ability to tolerate the procedure itself.

Contemporary Treatment Strategies for Acute PE

Anticoagulation

Anticoagulation therapy is the primary treatment option for most patients with acute PE. The utilization of factor Xa antagonists and direct thrombin inhibitors, collectively termed Novel Oral Anticoagulants (NOACs) are likely to increase as they become incorporated into societal guidelines as first line therapy.[38] Adoption of these newer agents may mitigate the major limitation of VKA therapy, frequently found in studies of VTE/PE to have sub-therapeutic INRs in a significant number of patients.[50] Low molecular weight heparin is superior to unfractionated heparin in both treatment and thrombo-prophylaxis in cancer patients.[27,51] This is reflected in the recommendations made by the American College of Chest Physicians who recommend the use of low molecular weight heparin on the basis of the strength of evidence available.[38] The importance of prompt initiation of anticoagulation cannot be over emphasized; objective assessment of bleeding risk, set in the context of the risk of choosing not to use anticoagulation, should prevent overly conservative practices founded upon theoretical concerns over bleeding.

Inferior Vena Cava Filters

The role of inferior vena cava filters (IVCF) in the contemporary management of acute VTE has not been truly defined owing to a paucity of high quality evidence. At present the benefit of IVCF use seems to be in reducing the risk of acute PE in patients who have a clear contraindication to anticoagulation in the form of active bleeding.[54,55] In the absence of such a contraindication there appears to be no clear benefit and non-retrieval of IVCF exposes the patient to risk of recurrent VTE, PTS and other mechanical complications such as filter fracture or migration.[56,54,19] Societal guidelines appear to be congruent with this data but importantly differ in their recommendations where high quality evidence is lacking.[32,38,57,58] Notable examples of these disparate recommendations include free floating proximal LE-DVT, acute PE in the presence of a pre-existing IVCF, poor medication compliance and IVCF use as VTE prophylaxis in the setting of immobility, trauma or major surgery. The need for definitive evidence related to IVCF use in some of these circumstances has long been recognized though randomized control data continues to be lacking.[58]

Percutaneous Mechanical Thrombectomy (PMT) for Massive and Submassive Acute PE

Several percutaneous approaches have been used alone or in combination in patients with an absolute contraindication to thrombolysis. These include: 1) thrombus fragmentation with a rotating pigtail catheter; 2) aspiration thrombectomy; 3) rheolytic thrombectomy; and 4) suction embolectomy. Thrombus fragmentation techniques using balloon angioplasty or rotation of pigtail catheters are probably the earliest examples of catheter-based intervention for acute PE. This technique is rarely utilized as a stand-alone procedure and carries a significant risk of distal and proximal embolization. Advanced fragmentation catheters such as the Amplatzer-Helix thrombectomy catheter (EV3, Endovascular, Plymouth, MN) improves upon clot fragmentation through use of an impeller to macerate the thrombus but lacks the capability of aspirating the resultant debris and cannot be advanced over a wire. Rheolytic thrombectomy catheters (AngioJet, Medrad Interventional, PA) work by creating a vacuum behind an area of high-pressure saline jets at the tip of the catheter. This enables simultaneous thrombus fragmentation and aspiration. Additionally, this device can be used to forcefully infuse ("power-pulse spray") a thrombolytic agent such as r-tPA instead of saline, which is likely to enhance the thrombolytic efficacy. When used in conjunction with thrombolytics, bradycardia, hypoxia and vasospasm has been observed, possibly due to adenosine release as a result of platelet disruption, which has resulted in a FDA black box warning regarding use of the device in the treatment of acute PE. These side effects can be overcome with aminophylline infusion and with the use of transvenous pacing prior to fragmentation.[81] Caution must be exercised during the placement of all catheters into the pulmonary arterial circulation. Ensuring proper positioning is vital in order to prevent the risk of catastrophic vessel injury as well as distal embolization of thrombus when using high-pressure injection systems. For this reason, we advocate the use of available computed tomography to help guide the optimal placement of any drug delivery system. Suction embolectomy devices such as the Greenfield catheter benefit from being large bore catheters capable of achieving thrombus removal without the side effects associated with fragmentation and rheolytic techniques.[82] Despite this, technical difficulties related to catheter size have precluded its widespread adoption. Emerging devices such as the FlowTriever System (Inari Medical, Irvine, CA) and the Indigo System (Penumbra Inc., Alameda, CA), which are specifically designed for use in patients with an absolute contraindication to thrombolytic therapy, currently remain only in investigational stages.[83]

The optimal PMT strategy to use in patients with an absolute contraindication to systemic fibrinolysis is best determined on an individualized basis. To gain access to the diseased vasculature, we recommend the following approach recommended by the AHA/ACC guidelines.[32] Obtain access through a 6F femoral venous sheath and advance a 6F angled pigtail catheter into each main pulmonary artery. Disease burden can be visualized at this point by administering low-osmolar or iso-osmolar contrast (30ml over 2 seconds). Unfractionated heparin should be used to maintain a clotting time >250 seconds. A direct thrombin inhibitor such as Bivalirudin (0.75mg/kg as an intravenous bolus followed by 1.75mg/kg/h) can be used as an alternative if there is a non-bleeding contraindication to heparin use. A 6F guiding catheter is used to reach the thrombus which can then be crossed with a hydrophilic guidewire, over which the PMT devices are advanced. This approach should be limited to the main and lobar pulmonary artery branches and placement of a temporary transvenous pacer or use of aminophylline should be considered.

Ultrasound-Assisted CDT (UA-CDT) for Acute PE

For patients without an absolute contraindication to systemic thrombolysis, UA-CDT can be considered. Low energy ultrasound disaggregates fibrin within acute thrombi,[84] this is exploited by the EKOS device (EkoSonic, Bothell, WA), which combines emission of low energy ultrasound and infusion of a thrombolytic agent via a multi side-hole containing catheter. This strategy has been evaluated in the ULTIMA (Ultrasound-Assisted, Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism) trial,[33] which demonstrated superiority to anticoagulation alone in improving hemodynamics without a significant increase in bleeding complications. The SEATTLE II (A Prospective, Singe-arm, Multi-center Trial of EkoSonic(R) Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) study,[48] was a single arm multi-center trial of UA-CDT that demonstrated improved right ventricular hemodynamic indices in patients undergoing UA-CDT for both massive and submassive PE. There were no occurrences of intracranial hemorrhage; although 16 bleeding episodes (1 GUSTO severe, 15 GUSTO moderate) were noted.

Table 2: Absolute and Relative Contraindications to Catheter-Directed Thrombolysis

Absolute contraindications
Active bleeding disorder
Recent CVA or TIA
Recent neurosurgery
Recent intracranial trauma
Absolute contraindication to anticoagulation
Relative contraindications
Recent cardiopulmonary resuscitation
Recent abdominal, ophthalmic or obstetric surgery
Recent trauma (other than intracranial)
Known intracranial tumor or vascular abnormality
Uncontrolled hypertension: systolic BP >180 mm Hg, diastolic BP >110 mm Hg
Recent gastrointestinal bleeding

Known severe allergy or adverse reaction to thrombolyic agent or contrast media (not controlled by steroid/antihistamine therapy)
Severe thrombocytopenia
Known right-to-left cardiac or pulmonary shunt
Severe dyspnea or other condition that would preclude ability to tolerate procedure
Suspected intracardiac thrombus
Suspected infected venous thrombus
Chronic kidney disease
Active pregnancy
Severe liver disease
Active infection

Recent = <3 months

CVA = cerebrovascular accident TIA = transient ischemic attack BP = blood pressure

Given the available evidence for UA-CDT in the treatment of acute PE, the use of an ultrasound assisted CDT strategy should be explored on a highly individualized basis. We recommend the approach by Kucher et al.[33] adapted and described here. Patients with proven acute PE should be promptly anticoagulated with intravenous unfractionated heparin with a bolus of 80 units per kilogram followed by infusion. They should undergo echocardiographic evaluation to assess right

ventricular (RV) function and size along with its correlation to left ventricular (LV) dimensions (RV: LV ratio). Serum biomarkers, troponin and brain-natriuretic peptide levels should be obtained. In conjunction with the patient's clinical and hemodynamic assessment, an individualized decision should be made regarding their suitability for CDT. Should the patient be deemed a reasonable candidate then informed consent is obtained from the patient or the patient's designated decision maker after a thorough discussion of the risks and benefits of CDT.

The common femoral vein should be accessed with a 6F single lumen sheath for unilateral therapy or two 6F sheaths or single 10F dual lumen sheath for bilateral therapy. Standard right heart catheterization with simultaneous mixed venous and systemic oxygen saturation should be obtained. A 0.035 inch guide wire along with a standard diagnostic angiographic catheter should be used to cross the diseased segment. With the guide wire in place, the angiographic catheter should be exchanged for the desired catheter system. If using an ultrasound-assisted system, the guide wire can then be removed and the ultrasound transducer system can be attached to the catheter. A continuous infusion of rtPA at 1mg/h in each pulmonary artery can then be initiated while the patient is observed in an intensive care setting. The rTPA dose is halved at 5 hours to 0.5mg/h for an additional 10 hours. The recommended maximum dose of rTPA is 20mg for bilateral device placement and 10mg for unilateral device placement. At 15 hours the rTPA infusion should be stopped along with the ultrasound transducer system. During the active infusion phase the patients are placed on bed rest in an ICU setting with frequent monitoring of vital signs, hemoglobin, platelet count, activated partial thromboplastin time and fibrinogen levels. After the completion of therapy, the hemodynamics are repeated. The catheter system and introducer sheath should be removed with manual compression of the access site until hemostasis is achieved. Follow up echocardiography should be performed to confirm improvement of RV size and function.

Post-Procedural Care

There are no comparative studies or societal recommendations to suggest the type, dose and duration of anticoagulation therapy or antiplatelet therapy following catheter based endovascular therapies with or without angioplasty and stenting. Current recommendations suggest therapy based on VTE stratification: 1) VTE associated with reversible risk factor or "provoked" DVT (at least 3 months); 2) unprovoked or recurrent VTE (6 to 12 months); and 3) VTE in the setting of cancer (indefinitely with LMWH). Similarly, no guidelines exist for the type or duration of

antiplatelet therapy in this setting. We have adopted an empiric approach to anticoagulation and antiplatelet therapy in patients who have undergone CDT and/or venous stenting. Following the completion of CDT for either acute DVT or PE we resume anticoagulation with unfractionated heparin soon after puncture site hemostasis has been achieved. We then transition patients onto NOAC or VKA therapy, following a patient-centered discussion. Patients who have undergone stenting are also commenced on low dose aspirin and clopidogrel. We adopt this aggressive approach especially in patients with chronic VTE who have high rates of re-thrombosis and often require further intervention in up to 40% of cases within 4 years.[87] Finally, in patients with LE-DVT we utilize compression bandages until there is resolution of acute swelling and then switch to knee-high compression stockings with 30-40 mmHg pressure. Patients are followed up at regular intervals following discharge, at which time clinical assessment is made for disease recurrence, changes in quality of life as well as continued careful review of their bleeding risk on anticoagulation therapy.

Predictors of Adverse Events

As endovascular strategies continue to be refined and newer, dedicated catheter systems get adopted into contemporary practice, the ability to predict adverse events associated with catheter-based therapies for both acute DVT and PE remains critical. Contemporary trials of CDT,[33,36] and even the recently completed ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) trial,[67] are underpowered to detect differences in safety outcomes when compared to anticoagulation alone. Study of large scale observational data within the United States has demonstrated that the presence of: 1) shock; 2) cancer; 3) paralysis; 4) age greater than 75 years; 5) Hispanic ethnicity; 6) renal failure; and 7) congestive heart failure are significant predictors of death or intracranial hemorrhage in patients undergoing CDT for LE-DVT when compared with anticoagulation alone.[88] Additionally, patients with cancer and chronic kidney disease undergoing CDT for LE-DVT appear to have higher rates of acute renal failure and bleeding complications including intracranial hemorrhage.[89,90] These patient-specific risk factors should be factored into any decision to proceed with an endovascular treatment strategy for either acute DVT or PE until further prospective studies are performed to definitively address comparative safety outcomes.

Another important consideration is the direct relationship between higher institutional volume and improved in-hospital safety outcomes. This is an additional predictor of death and intracranial hemorrhage in patients undergoing CDT for LE-DVT.[88] A recent nationwide comparative outcomes study demonstrated that institutions with higher annual procedure volume (defined as greater than five procedures annually) had similar rates of death and intracranial hemorrhage in the CDT group when compared to patients treated with anticoagulation alone.[91] In contrast, low volume centers (defined as less than five procedures annually) had significantly higher mortality and ICH rates in the CDT group compared to anticoagulation alone. This relationship likely reflects heterogeneity in contemporary practice within the United States, stemming from variations in patient selection, peri- and post-procedural monitoring. Standardization of the treatment protocols for endovascular therapies for VTE is crucially needed as this may improve outcomes particularly at low volume institutions.[51] For acute PE, safety outcomes in patients undergoing CDT are largely derived from early trial data as well as small cohort studies.[33,48,92-6] The lack of robust safety outcomes data likely reflects the fact that endovascular treatment for PE is still in its infancy. Additionally, unlike CDT for LE-DVT, concerns regarding the accuracy with which acute PE is diagnosed and documented nationwide have precluded the use of administrative data to shed light on safety outcomes.[97] Recently however, Kuo et al.[98] described favorable initial safety outcomes from a prospective multicenter registry concluding that CDT is a safe and effective treatment for massive and sub-massive acute PE. Further prospective randomized comparative effectiveness trials as well as real-world registries are needed to drive continued evaluation of this treatment strategy.

Future Directions

Outcomes for CDT are likely to improve with technological advances in endovascular therapies and as physicians get better at patient selection, careful risk assessment and standardization of peri- and post-procedural monitoring. Data regarding the safety and efficacy of NOACs after catheter-based thrombus removal in VTE is acutely needed both in terms of therapeutic certainty as well as patient preference when compared to VKA therapy; these measures alone may be sufficient in reducing the burden of recurrent VTE as well as the risk of PTS. Dedicated technological advances, such as the development of catheters and pharmaco-mechanical devices, especially for massive and submassive PE may see the management of these patients evolve into a predominantly endovascularly

treated disease entity. Moving toward the use of a PERT (Pulmonary Embolism Response Team) team approach, especially in complex decision-making, may also ensure that the best therapeutic plan is executed on an individualized basis while avoiding under treatment of high risk submassive PE.[42] Additionally, newer technologies such as drug-coated balloons,[99] bio-resorbable vascular scaffolds and bioresorbable IVCF are currently being studied.[100-1] Refinement of our current strategies, coupled with the exciting future technological developments will provide physicians and patients with options to relieve symptoms, delay morbidity and mortality and improve quality of life.

Conclusions

VTE is increasingly recognized as a cause of significant morbidity and mortality in the United States. An interventional approach to managing both acute LE-iliofemoral DVT and massive and submassive PE has great promise. There remains a paucity of robust long-term evidence, particularly addressing safety outcomes in therapies utilizing drugs and delivery systems that can result in bleeding complications. A highly individualized approach encompassing patient selection, type of therapy, operator and hospital level of experience should be followed to maximize the benefits of an interventional strategy as well as minimize the risk of harm.

References

1. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med* 2014;127:829-39.
2. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003;107:I22-30.
3. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107:I4-8.
4. The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Rockville (MD), 2008.
5. Hoeper MM. Chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2011;364:1677-8.
6. Comerota AJ, Throm RC, Mathias SD, Haughton S, Mewissen M. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. *J Vasc Surg* 2000;32:130-7.

7. Enden T, Wik HS, Kvam AK, Haig Y, Klow NE, Sandset PM. Health-related quality of life after catheter-directed thrombolylsis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study. *BMJ Open* 2013;3:e002984.

8. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014;130:829-36.

9. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007;92:199-205.

10. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997;349:759-62.

11. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2014;130:1636-61.

12. Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. *J Vasc Surg* 2007;46:4S-24S.

13. Guanella R, Ducruet T, Johri M, et al. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. *J Thromb Haemost* 2011;9:2397-405.

14. Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost* 2008;6:1105-12.

15. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? *Am J Med* 2001;110:515-9.

16. Meissner MH, Caps MT, Bergelin RO, Manzo RA, Strandness DE. Propagation, rethrombosis and new thrombus formation after acute deep venous thrombosis. *J Vasc Surg* 1995;22:558-67.

17. Meissner MH, Manzo RA, Bergelin RO, Markel A, Strandness DE. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg* 1993;18:596-605.

18. Plate G, Eklof B, Norgren L, Ohlin P, Dahlstrom JA. Venous thrombectomy for iliofemoral vein thrombosis--10-year results of a prospective randomised study. *Eur J Vasc Endovasc Surg* 1997;14:367-74.

19. Alkhouli M, Morad M, Narins CR, Raza F, Bashir R. Inferior vena cava thrombosis. *JACC Cardiovasc Interv* 2016;9:629-43.

20. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. *Am J Med* 1984;76:393-7.

21. Bova C, Pesavento R, Marchiori A, et al. Risk stratification and outcomes in hemodynamically stable patients with acute pulmonary embolism: a prospective, multicentre, cohort study with three months of follow-up. *J Thromb Haemost* 2009;7:938-44.

22. Palmieri V, Gallotta G, Rendina D, et al. Troponin I and right ventricular dysfunction for risk assessment in patients with nonmassive pulmonary embolism in the emergency department in combination with clinically based risk score. *Intern Emerg Med* 2008;3:131-8.

23. Post F, Mertens D, Sinning C, Peetz D, Munzel T. Decision for aggressive therapy in acute pulmonary embolism: implication of elevated troponin T. *Clin Res Cardiol* 2009;98:401-8.

24. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004;350:2257-64.

25. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest* 1982;81:151-8.

26. Tapson VF. Acute pulmonary embolism. *Cardiol Clin* 2004;22:353-65.

27. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation* 2006;113:2011-20.

28. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis* 1995;2:227-9.

29. Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest* 2009;136:1202-10.

30. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M, "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol* 2013;111:273-7.

31. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014;311:2414-21.

32. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123:1788-830.

33. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermeidate-risk pulmonary embolism. *Circulation* 2014;129:479-86.

34. Engelberger RP, Kucher N. Catheter-based reperfusion treatment of pulmonary embolism. *Circulation* 2011;124:2139-44.

35. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. *Ann Surg* 2004;239:118-26.

36. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet* 2012;379:31-8.

37. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology* 1999;211;39-49.

38. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315-52.

39. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2015;36:605-14.

40. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033-69.

41. Vedantham S, Piazza G, Sista AK, Goldenberg NA. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. *J Thromb Thrombolysis* 2016;41:68-80.

42. Dudzinski DM, Piazza G. Multidisciplinary pulmonary embolism response teams. *Circulation* 2016;133:98-103.

43. Aklog L, Williams CS, Byrne JG, Goldhaber SZ. Acute pulmonary embolectomy: a contemporary approach. *Circulation* 2002;105:1416-9.

44. Yusuff HO, Zochios V, Vuylsteke A. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a systematic review. *Perfusion* 2015;30:611-6.

45. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402-11.

46. Aujesky D, Obrosky DS, Stone RA, et al. Dereivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172:1041-6.

47. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383-9.

48. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv* 2015;8:1382-92.

49. Tapson V. Optimum duration of acoustic pulse thrombolysis procedure in acute pulmonary embolism (OPTALYSE PE). 2016.

50. van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. *J Thromb Haemost* 2005;3:939-42.

51. Vedantham S, Sista AK, Klein SJ, et al. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol* 2014;25:1317-25.

52. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet* 2014;383:880-8.

53. Subbiah R, Aggarwal V, Zhao H, Kolluri R, Chatterjee S, Bashir R. Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. *Lancet* Haematol 2016;3:e293-300.

54. PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation* 2005;112:416-22.

55. White RH, Brunson A, Romano PS, Li Z, Wun T. Outcomes after vena cava filter use in noncancer patients with acute venous thromboembolism: a population-based study. *Circulation* 2016;133:2018-29.

56. Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA* 2015;313:1627-35.

57. Caplin DM, Nikloc B, Kalva SP, et al. Quality improvement guidelines for the performance of inferior vena cava filter placement for the prevention of pulmonary embolism. *J Vasc Interv Radiol* 2011;22:1499-506.

58. Kaufman JA, Rundback JH, Kee ST, et al. Development of a research agenda for inferior vena cava filters: proceedings from a multidisciplinary research consensus panel. *J Vasc Interv Radiol* 2009;20:697-707.

59. Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. *Radiology* 1994;191:487-94.

60. May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. *Angiology* 1957;8:419-27.

61. Bookstein JJ, Fellmeth B, Roberts A, Valji K, Davis G, Machado T. Pulsed-spray pharmacomechanical thrombolysis: preliminary clinical results. *AJR Am J Roentgenol* 1989;152:1097-100.

62. Haig Y, Enden T, Slagsvold CE, Sandvik L, Sandset PM, Klow NE. Determinants of early and long-term efficacy of catheter-directed thrombolysis in proximal deep vein thrombosis. *J Vasc Interv Radiol* 2013;24:17-24.

63. Kasirajan K, Gray B, Ouriel K. Percutaneous AngioJet thrombectomy in the management of extensive deep venous thrombosis. *J Vasc Interv Radiol* 2001;12:179-85.

64. Cyanamon J, Stein EG, Dym RJ, Jaqust MB, Binkert CA, Baum RA. A new method for aggressive management of deep vein thrombosis: retrospective study of the power pulse technique. *J Vasc Interv Radiol* 2006;17:1043-9.

65. Kim HS, Patra A, Paxton BE, Khan J, Streiff MB. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. *J Vasc Interv Radiol* 2006;17:1099-104.

66. O'Sullivan GJ, Lohan DG, Gough N, Cronin CG, Kee ST. Pharmacomechanical thrombectomy of acute deep vein thrombosis with the Trellis-8 isolated thrombolysis catheter. *J Vasc Interv Radiol* 2007;18:715-24.

67. Vedantham S. Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis--The ATTRACT Trial. ClinicalTrials.gov: National Library of Medicine (US) 2000 - 2016, 2016.

68. Donaldson CW, Baker JN, Narayan RL, et al. Thrombectomy using suction filtration and veno-venous bypass: single center experience with a novel device. *Catheter Cardiovasc Interv* 2015;86:E81-7.

69. Sharifi M, Bay C, Mehdipour M, Sharifi J, TORPEDO Investigators. Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial: midterm results. *J Endovasc Ther* 2012;19:273-80.

70. Sharifi M, Mehdipour M, Bay C, Smith G, Sharifi J. Endovenous therapy for deep venous thrombosis: the TORPEDO trial. *Catheter Cardiovasc Interv* 2010;76:316-25.

71. Hartung O, Loundou AD, Barthelemy P, Arnoux D, Boufi M, Alimi YS. Endovascular management of chronic disabling ilio-caval obstructive lesions: long-term results. *Eur J Vasc Endovasc Surg* 2009;38:118-24.

72. Neglen P, Tackett TP Jr, Raju S. Venous stenting across the inguinal ligament. *J Vasc Surg* 2008;48:1255-61.

73. Raju S, Neglen P. Percutaneous recanalization of total occclusions of the iliac vein. *J Vasc Surg* 2009;50:360-8.

74. Comerota A. Evaluation of the Zilver® Vena™ Venous Stent in the Treatment of Symptomatic Iliofemoral Venous Outflow Obstruction. ClinicalTrials.gov: National Library of Medicine (US) 2000 - 2016, 2016.

75. W M. VIRTUS-OUS Safety and Efficacy of the Veniti Vici™ Venous Stent System (Veniti, Inc.) When Used to Treat Clinically Significant Chronic Non-malignant Obstruction of the Iliofemoral Venous Segment. ClinicalTrials.gov: National Library of Medicine (US) 2000 - 2016, 2016.

76. Forauer AR, Gemmete JJ, Dasika NL, Cho KJ, Williams DM. Intravascular ultrasound in the diagnosis and treatment of iliac vein compression (May-Thurner) synrdome. *J Vasc Interv Radiol* 2002;13:523-7.

77. McLafferty RB. The role of intravascular ultrasound in venous thromboembolism. *Semin Intervent Radiol* 2012;29:10-5.

78. Murphy EH, Broker HS, Johnson EJ, Modrall JG, Valentine RJ, Arko FR 3rd. Device and imaging-specific volumetric analysis of clot lysis after percutaneous mechanical thrombectomy for iliofemoral DVT. *J Endovasc Ther* 2010;17:423-33.

79. Neglen P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. *J Vasc Surg* 2002;35:694-700.

80. Birn J, Vedantham S. May-Thurner syndrome and other obstructive iliac vein lesions: meaning, myth, and mystery. *Vasc Med* 2015;20:74-83.

81. Sobieszczyk P. Catheter-assisted pulmonary embolectomy. *Circulation* 2012;126:1917-22.

82. Greenfield LJ, Proctor MC, Williams DM, Wakefield TW. Long-term experience with transvenous catheter pulmonary embolectomy. *J Vasc Surg* 1993;18:450-7.

83. Rosenfield K. FlowTriever Pulmonary Embolectomy Clinical Study (FLARE). 2016.

84. Braaten JV, Goss RA, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. *Thromb Haemost* 1997;78:1063-8.

85. Protack CD, Bakken AM, Patel N, Saad WE, Waldman DL, Davies MG. Long-term outcomes of catheter directed thrombolysis for lower extremity deep venous

thrombosis without prophylactic inferior vena cava filter placement. *J Vasc Surg* 2007;45:992-7.

86. Kuy S, Dua A, Lee CJ, et al. National trends in utilization of inferior vena cava filters in the United States, 2000-2009. *J Vasc Surg Venous Lymphat Disord* 2014;2:15-20.

87. Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clincial, and hemodynamic result. *J Vasc Surg* 2007;46:979-90.

88. Bashir R, Zack CJ, Zhao H, Comerota AJ, Bove AA. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone to treat lower-extremity proximal deep vein thrombosis. *JAMA Intern Med* 2014;174:1494-501.

89. Brailovsky Y, Zack C, Gaughan J, Bove A, Bashir R. Comparative outcomes of catheter-directed thrombolysis with anticoagulation versus anticoagulation alone in cancer patients with deep vein thrombosis. *J Am Coll Cardiol* 2013.

90. Brailovsky Y, Zhao H, Bashir R. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation versus anticoagulation alone in the treatment of proximal deep vein thrombosis in patients with chronic kidney disease. *J Am Coll Cardiol* 2014;63.

91. Jarrett H, Zack CJ, Aggarwal V, et al. Impact of institutional volume on outcomes of catheter directed thrombolysis in the treatment of acute proximal deep vein thrombosis: a 6-year US experience (2005-2010). *Circulation* 2015;132:1127-35.

92. Akin H, Al-Jobouri M, Assi Z, Acino R, Sepanski D, Comerota AJ. Catheter-directed thrombolytic intervention is effective for patients with massive and submassive pulmonary embolism. *Ann Vasc Surg* 2014;28:1589-94.

93. Dumantepe M, Uyar I, Teymen B, Ugur O, Enc Y. Improvements in pulmonary artery pressure and right ventricular function after ultrasound-accelerated catheter-directed thrombolysis for the treatment of pulmonary embolism. *J Card Surg* 2014;29:455-63.

94. Lin PH, Annambhotla S, Bechara CF, et al. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. *Vascular* 2009;17:S137-47.

95. Liu FY, Wang MQ, Duan F, et al. Management of acute massive pulmonary thrombosis embolism with interventional techniques. *Zhonghua Yi Xue Za Zhi* 2012;92:1343-5.

96. Quintana D, Salsamendi J, Fourzali R, Narayanan G. Ultrasound-assisted thrombolysis in submassive and massive pulmonary embolism: assessment of

lung obstruction before and after catheter-directed therapy. *Cardiovasc Intervent Radiol* 2014;37:420-6.

97. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med* 2011;171:831-7.

98. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest* 2015;148:667-73.

99. Scheller B, Speck U, Abramjuk C, Bernhardt U, Bohm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 2004;110:810-4.

00. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 2009;373:897-910.

01. Thors A, Muck P. Resorbable inferior vena cava filters: trial in an in-vivo porcine model. *J Vasc Interv Radiol* 2011;22:330-5.

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