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Updates on Advanced Therapies for Acute Pulmonary Embolism

Bavand Bikdeli [1, 2], Behnood Bikdeli [3, 4, *]

[1] Division of Medical Subspecialties, Lyell McEwin Hospital, Adelaide, Australia
[2] School of Medicine, University of Adelaide, Adelaide, Australia
[3] Center for Outcomes Research and Evaluation, Yale University School of Medicine, New Haven, USA
[4] Division of Cardiology, Columbia University Medical Center, New York, United States

** Corresponding author: Behnood Bikdeli, Church Street, Suite 200, New Haven, CT 06510. Tel: 203-7645653, E-mail: behnood.bikdeli@yale.edu; bb2813@cumc.columbia.edu*

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Abstract

Venous thromboembolism is the third common vascular disease after acute myocardial infarction and stroke, and acute pulmonary embolism (PE) remains as the most common preventable cause of in-hospital mortality. In addition to routine anticoagulant therapy, several advanced treatment options have been introduced over the past three decades. We provide a succinct and contemporary summary of the evidence base and important indications for inferior vena caval filter placement, systemic and catheter-based thrombolytic therapy, as well as percutaneous and surgical thrombectomy. Appropriate case selection for advance therapies for PE could minimize the adverse effects and costs, while optimizing the outcomes.

INTRODUCTION

Acute pulmonary embolism (PE) is a common and potentially lethal medical condition. Annually, there are an estimated 1,000,000 cases of PE in the Western countries [1, 2]. Thirty-day mortality rates have been variably reported between 6-9% in contemporary registries, and up to as high as 50% in patients with massive PE, defined by development of systemic hypotension [3-5]. Beyond systemic anticoagulation, advanced treatment approaches have opened their way in several subgroups of patients with PE. Such options include inferior vena caval (IVC) filters, thrombolytic therapy (with or without ultrasound facilitation), and surgical or percutaneous thrombectomy. Here, we provide a succinct review of the latest evidence and recommendations relating to advanced treatments for acute PE.

IVC Filters

A recent analysis of Medicare beneficiaries > 65 years old demonstrated that roughly 17% of patients hospitalized with a PE, an unexpectedly high proportion, received an IVC filter [6]. Such findings are particularly striking taking into consideration the limited available evidence for efficacy of IVC filters.

So far, there have only been two major randomized controlled trials published on the use of IVC filters [7, 8]. The PREPIC trial, an open-label study of 400 patients with proximal deep vein thrombosis (DVT) randomized to IVC filter placement plus anticoagulation versus anticoagulation alone did not show a mortality difference between the two groups at 2-year or 8-year follow-up, and the reduced rates of PE in the study were counterbalanced by increased rate of recurrent DVT [7-9]. With technological advances, such as introduction of retrievable filters (that would have potentially mitigated the increased risk of recurrent DVT below the filter), use of IVC filters continued to grow despite the dearth of clinical evidence for improved outcomes. In recent years, results of the PREPIC II trial, an open-label study of 400 patients hospitalized with acute symptomatic PE with concomitant lower extremity DVT and at least one feature increasing the risk of PE recurrence, who were randomized to anticoagulation alone versus anticoagulation plus (retrievable) IVC filters, became available. At 3-month follow-up, the study did not detect a difference in mortality rates, and reported statistically similar but numerically higher rates of PE in patients who did receive an IVC filter [10]. Several other recent studies have also shown that many patients have received IVC filters in scenarios other than those recommended by the expert guidelines [11].

In summary, the overall existing evidence for the use of IVC filters is quite limited, and these devices should only be used as a last resort once there is no other evidence-based option available. Expert guidelines recommend against use of IVC filters as a routine treatment for acute PE. The limited reasonable indications for IVC filter placement would

include contraindication to anticoagulant therapy [12], and recurrent events despite adequate anticoagulation (i.e. recurrence despite anticoagulation with good adherence and objective evidence of therapeutic anticoagulant levels). There is no consensus for use of IVC filters in other scenarios, such as presence of poor cardiopulmonary baseline reserve, or in the case of massive PE.

Systemic Thrombolytic treatment

Along with the conceivable benefits of thrombolytic therapy for an acute thrombotic condition such as PE comes the cost in the form of bleeding events, with the absolute risks increasing by increased age, including that of intracranial hemorrhage, the most feared bleeding complication of thrombolytics. Appropriate use of thrombolysis is associated with more rapid resolution of symptoms, cardiorespiratory (hemodynamic) stabilization, improvement in right ventricular function, improved exercise tolerance, prevention of PE recurrence, and according to a recent systematic review of the literature (predominated driven by the PIETHO trial participants), improved survival [13-16].
Increased risk of bleeding is well known with thrombolytic therapy, especially among older adults. Yet, the benefits of thrombolytic therapy among older adults are frequently underrated [17] while the risk of bleeding from thrombolysis in elderly PE patients is traditionally exaggerated; although this idea has been challenged in several recent studies [18-20]. Nevertheless, several studies suggest that use of thrombolytic therapy is rare in older adults [18, 21].
Use of ultrasound-facilitated thrombolysis emerged as a fascinating option in recent years, which was associated with an excellent safety profile in a small randomized trial and a prospective single arm study of patients with sub-massive or massive PE. The improved safety profile is likely due to lower dose of thrombolytics (up to a quarter of regular systemic dose) and administration over 12-24 hours according to various protocols, as opposed to bolus administration of regular systemic thrombolytics [22, 23]. Reduced-dose systemic thrombolytic therapy has been also successfully tried in a small study of patients with "moderate PE" (defined as computed tomographic pulmonary angiographic evidence of involvement of > 70% in ≥ 2 lobar or left or right main pulmonary arteries) [14].
Massive PE, i.e. PE along with hemodynamic instability, represents the clearest indication of thrombolytic therapy. Risks and benefits of thrombolytic therapy in patients with non-massive PE should be seriously considered (Fig 1). While reduced-dose thrombolysis could be reasonable in a select group of patients with sub-massive (or even moderate) PE, routine use of thrombolytic therapy in all-comers with PE is not recommended.

Catheter Directed Treatments Other Than Thrombolytic Therapy

Catheter directed treatment may refer to any or a combination of catheter directed thrombectomy, catheter directed fragmentation and catheter directed thrombolysis. Catheter-directed thrombolytic therapy could be performed alone, or in conjunction with thrombus aspiration using catheters such as the regular 8F guide catheters [24]. Several other percutaneous thrombectomy devices are also under early investigation, and at least one of them (the AngioVac Cannula) has received FDA approval for removal of detrimental intravascular material, such as soft thrombi [24].

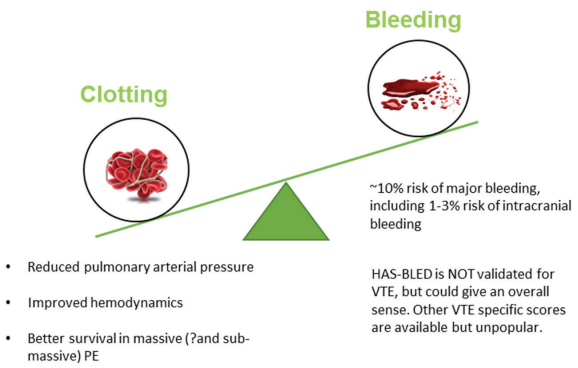

Figure 1: Risks and Benefits of Thrombolytic Therapy in Patients with PE

Surgical Thrombectomy

Surgical embolectomy, a procedure that requires much expertise and is performed under cardiopulmonary bypass, occurs only in very experienced centers. In patients suffering from massive PE who have contraindications to, or are not good candidates for thrombolytic therapy, and have a reasonable operative risk, surgical thrombectomy, with or without extracorporeal membrane oxygenation (ECMO) could be life-saving. However, because of the extreme level of illness of such patients, conducting high-quality prospective comparative effectiveness in such patients has not been yet feasible. Data from the US indicates a declining trend for utilization rates of surgical thrombectomy, likely as a result of more widespread availability of other advanced therapies [21].

CONCLUSIONS

With new emerging evidence for more aggressive treatment of PE with potentials for decreased mortality and long-term morbidity, it appears that options for PE treatment will broader in future. Prior to choosing advanced therapies, however, risk stratification would be crucial. The concept of a pulmonary embolism response team (PERT) is now growing in several centers around the world and might help improve decision-making for the choice and timeliness of PE advanced therapies, where needed. With wise use of PERT teams, collaborative interdisciplinary efforts, and other initiatives to raise the awareness for optimal diagnosis and treatment of PE we can aim to reduce the burden of venous thromboembolism, one of the most common and yet underappreciated cardiovascular conditions.
Careful consideration of benefits and risks is key, particularly for patients with hemodynamically-stable PE who have other features of increased risk of adverse events. Risks of hemorrhagic complications should be particularly weighed in the case of older adults. Reduced-dose thrombolytics are a fascinating option with a seemingly better safety profile and currently under intense investigation (Table 1).

Table 1: Summary of Select Indications for Advanced Therapies for Acute PE

	Therapies
Inferior Vena Caval (IVC) Filters	
Acute PE with clear contraindications to anticoagulant therapy	IVC filter placement is reasonable
Recurrent PE despite adequate anticoagulant therapy	IVC filter placement is reasonable
Acute PE with poor cardiopulmonary reserve, including massive PE	IVC filter placement might be considered in select cases.
Acute hemodynamically-stable PE in patients tolerant of anticoagulants	IVC filter placement is not recommended.
Thrombolytic Therapy	
Massive PE (hemodynamic instability not attributable to other factors)	Thrombolytic therapy is recommended
PE with elevated cardiac biomarkers and imaging evidence of right ventricular dysfunction	Thrombolytic therapy (preferentially low-dose or ultrasound-facilitated) may be considered in select cases.
Hemodynamically stable PE without evidence of biomarkers rise and right ventricular dysfunction (all-comers with acute PE)	Thrombolytic therapy is not recommended.
Catheter Directed Therapies Other Than Thrombolysis	
Acute severe PE (large burden, clot in-transit)	Catheter directed techniques (e.g. aspiration/ thrombectomy) might be considered in experienced centers for select cases.
Surgical Thrombectomy	
Acute massive PE and acceptable surgical risk	Surgical thrombectomy should be considered in cases of acute massive PE in highly experienced centers.
Acute severe PE (large burden, clot in-transit)	Surgical thrombectomy might be considered in select cases of large burden PE in highly experienced centers.
Acute hemodynamically-stable PE (all-comers with acute PE)	Routine use of surgical thrombectomy is not recommended.

Use of a multidisciplinary Pulmonary Embolism Response Team (PERT) can help facilitate the selection of advanced therapies in each case.
Abbreviation: IVC, inferior vena caval filter; PE, pulmonary embolism.

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CONFLICTS OF INTEREST

There is no conflict of interest.

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