Research Priorities in Submassive Pulmonary Embolism: Proceedings from a Multidisciplinary Research Consensus Panel

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ABBREVIATIONS

CDT = catheter-directed thrombolysis, CPET = cardiopulmonary exercise testing, CTEPH = chronic thromboembolic pulmonary hypertension, ESC = European Society of Cardiology, PE = pulmonary embolism, PERT = Pulmonary Embolism Response Team, RCT = randomized controlled trial, RV = right ventricular, 6MWD = 6-minute walk distance, VTE = venous thromboembolism

Pulmonary embolism (PE) is the third leading cause of cardiovascular mortality in the United States (after myocardial infarction and stroke) (1), and its incidence is increasing. The 6-month mortality is approximately 20% (2). Patients also experience reduced exercise capacity, psychological distress, and a lower quality of life that persists long after the acute event (3–7). Most patients presenting to the hospital with PE have normal blood pressure, normal right ventricular physiology, and a low clinical severity score and therefore have a very low short-term mortality with prompt initiation of anticoagulation. However, patients with PE who present with hypotension have a 25%–65% mortality rate, and clot removal strategies, including systemic thrombolysis, catheter-based therapy, and surgical embolectomy, are often indicated (8–10). In contrast, optimal management of patients with submassive PE, who have right-sided heart dysfunction and/or ischemia in the setting of

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normal blood pressure, is uncertain. The risk-benefit ratio of thrombus removal therapies in this subgroup of patients is unfavorable for systemic thrombolysis and unclear for CDT. Expert guidelines cannot offer strong recommendations for these patients (9,10), resulting in some caregivers employing active thrombus removal strategies and others adopting a "watch and wait" approach.

To examine the key questions, data gaps, and research priorities surrounding submassive PE, a Research Consensus Panel was convened in Herndon, Virginia, on December 16, 2015, to discuss the topic "Submassive Pulmonary Embolism Short- and Long-term Outcomes: Where Are We and Where Do We Need to Be?" The meeting was sponsored by the Society of Interventional Radiology (SIR) Foundation.

ORGANIZATION

Attendees

The Research Consensus Panel comprised 19 experts from a range of clinical backgrounds (Fig). One attendee participated via webinar from Europe. Invited guests represented the US Food and Drug Administration; the National Heart, Lung, and Blood Institute of the National Institutes of Health; and industry (BTG [West Conshohocken, Pennsylvania], Inari Medical [Irvine, California], Penumbra, Inc [Alameda, California], and AngioDynamics [Latham, New York]).

Format

The Research Consensus Panel was a 1-day meeting that was divided into three sessions: Current Knowledge, Trial Design and Methodology, and Research Network Infrastructure. Each session began with presentations (12 in total among the three sessions), followed by a discussion focusing on key questions (Table 1), challenges, areas of uncertainty, and future research.

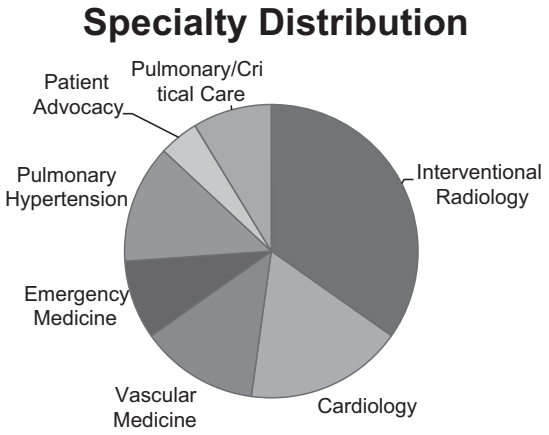

Figure 1. Specialties represented in the submassive PE Research Consensus Panel.

PRESENTATION CONTENT

Definitions

The American Heart Association guidelines and European Society of Cardiology (ESC) guidelines use the terms "submassive" PE and "intermediate-risk" PE, respectively (8,9). In their 2011 position statement, the American Heart Association broadly defined "submassive PE" as PE associated with right-sided heart dysfunction (defined by echocardiography, computed tomography [CT], electrocardiography, or elevated biomarkers [troponin or brain natriuretic peptide]), in the absence of hypotension, regardless of clinical severity on presentation. The ESC defines "intermediate-risk PE" by a Simplified Pulmonary Embolism Severity Index score of ≥ 1 and evidence of right-sided heart dysfunction/biomarker elevation. The ESC further stratifies patients with intermediate-risk PE into high-risk and low-risk subgroups. If both right ventricular (RV) enlargement (determined by echocardiography or CT) or morphologic dysfunction (echocardiography) and biomarker elevation (troponin, brain natriuretic peptide) are present, the patient is in the intermediate-risk PE high-risk category. If either enlargement/dysfunction or biomarker elevation is present (but not both), the patient is in the intermediate-risk PE low-risk category.

Table 1. Questions to Be Answered by Future Research on Submassive PE

Is CDT of benefit in patients with submassive PE?
Which short-term and long-term endpoints are most meaningful to patients and providers? Stated another way, what positive outcomes would justify the risks and costs associated with a thrombus removal procedure?
Which of these endpoints is feasible for a clinical trial?
What are the essential components of a CDT intervention that should be included in a trial?
Which patients with submassive PE should be included?
What are the key barriers to subject enrollment into a randomized trial of CDT, and how can they be overcome?
How safe is CDT?
What are the predictors of long-term disability after PE?
What is the time course for recovery after acute PE?
Should patients with active cancer be included in a trial of CDT?
Should patients > 75 years old be included in a trial of CDT?
Should patients with a large clot burden be included even if they are in the low-risk category?
Are there biomarkers that predict response to CDT?
Is there a role for reduced-dose systemic thrombolysis?
Does ultrasound-assisted CDT result in better efficacy and clinical outcomes than standard CDT?
How should novel thrombus extraction devices be studied?

Note–The questions in bold type represent the key questions, and the primary research question is listed first.
CDT = catheter-directed thrombolysis; PE = pulmonary embolism.