Supplement to

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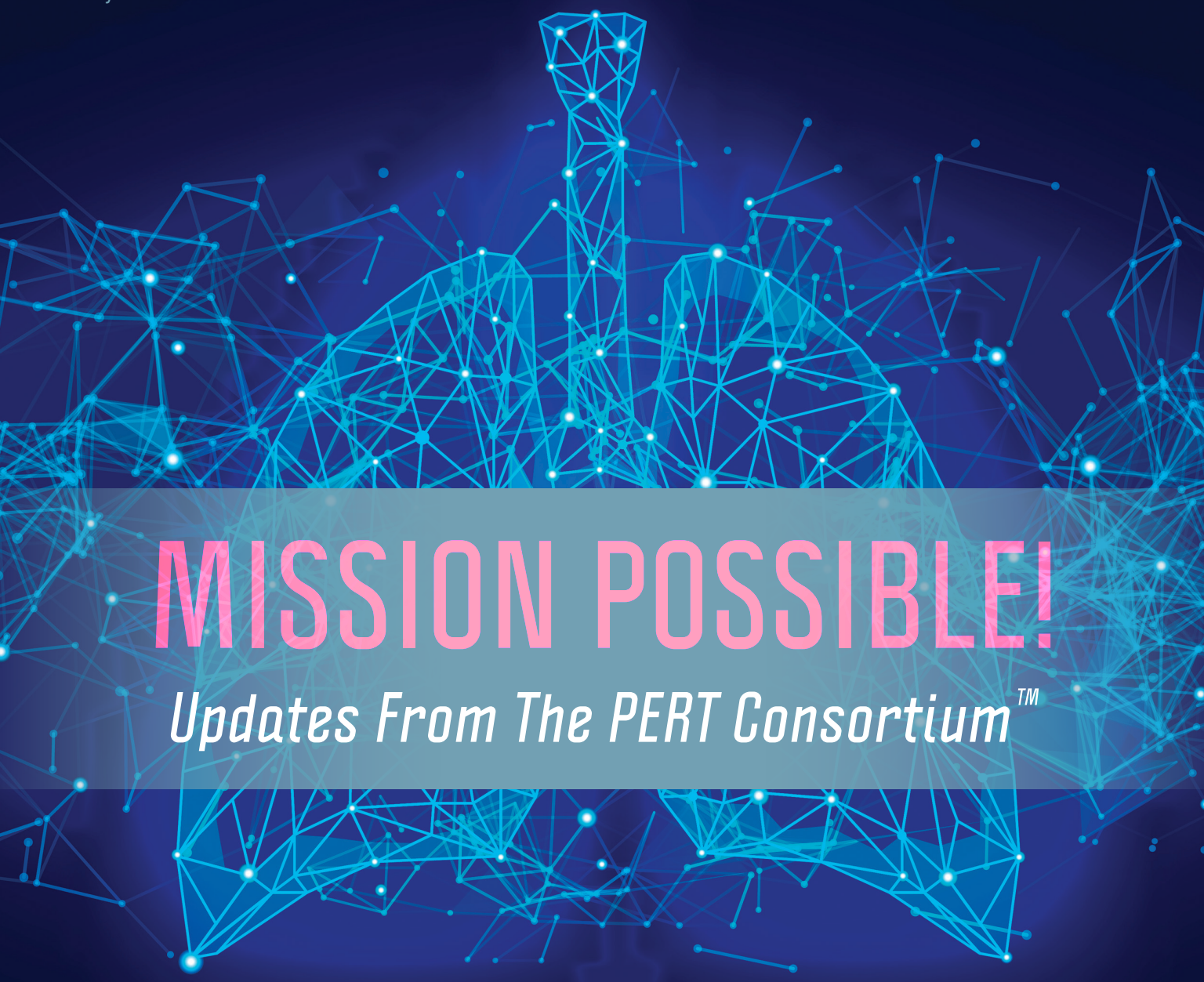
Endovascular TODAY

July 2022



MISSION POSSIBLE!

Updates From The PERT Consortium™

PERT CONSORTIUM®

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MISSION POSSIBLE! Updates From The PERT Consortium™

INTRODUCTION

The National Pulmonary Embolism Response Team (PERT) Consortium™ is honored to host this supplement of *Endovascular Today* for the fourth year in a row, entitled *Mission Impossible! Updates From The PERT Consortium™*. The National PERT Consortium™ is a 501(c)(3) organization founded in 2015. Our organization is dedicated to the multidisciplinary, team-based treatment of pulmonary embolism (PE). We are a multinational organization and strive to improve the care and outcomes for patients with PE and related disorders. The Consortium comprises pulmonologists, emergency physicians, cardiologists, surgeons, pharmacists, radiologists, hospitalists, hematologists, advanced practice providers, nurses, physicians in training, and patient advocates. We encourage the participation and input of individuals in allied health fields and welcome collaborative efforts with other organizations.

Over the past year, The Consortium has expanded its membership by recruiting additional member institutions in the United States, Canada, South America, Europe, and Asia. These additions resulted in an explosion of new ideas and proposals for future clinical trials and educational activities. The growing impact of The Consortium is reflected by the international participation that we enjoy during our annual and intercurrent meetings, as well as by the introduction of new programs and projects. The PERT Consortium™ PE Registry remains the largest PE-centered quality assurance database in the world, with > 7,500 patients. The value of The PERT Consortium™ PE Registry is exemplified by the recent Pulmonary Embolism Research Collaborative (PERC™) initiative, which kicked off live in Washington, DC, on April 22, 2022. PERC™ brought together key stakeholders in the treatment of PE, including physician experts, industry thought leaders, and the United States FDA. PERC™ was designed to analyze and refine the data elements in The PERT Consortium™ PE Registry, with the purpose of establishing standards for care and research for PE.

The Consortium continues to partner with corporate sponsors to advance PE research. In collaboration with trial sponsor Boston Scientific Corporation and the University Medical Center Mainz in Germany, The Consortium is proud to comanage the higher-risk PE study, HI-PEITHO: a randomized trial of ultrasound-facilitated, catheter-directed thrombolysis versus anticoagulation for acute intermediate-high–risk PE. We are also pleased to have partnered with AngioDynamics to help launch and execute the APEX-AV study, an investigational device exemption study using the company's AlphaVac F18^{85} PE system for the treatment of acute PE.

Our educational efforts continue to have positive impacts on both clinicians and the general public. Our webinars have welcomed > 1,000 participants from around the world and focus on addressing specific clinical issues. Sessions allow for audience participation and are hosted by internationally known experts in PE, venous thromboembolism, and anticoagulation. PERTCasts™ are short and sweet podcasts that bring together global thought leaders to discuss specific issues regarding PE. PERTinent™ Updates are released monthly and inform our members about the latest scientific articles related to PE and related disorders. In 2019, via a generous grant from Boston Scientific Corporation, we began the Interhospital Transfer (IHT) Project. The IHT Project aims to develop a step-by-step guide to the stabilization and transfer of critically ill PE patients, while additionally identifying existing barriers in the IHT process and increasing awareness and education for PE care. We are delighted to share that The Consortium's webinars, PERTCasts™, and PERTinent™ Updates are available for free on our website: www.pertconsortium.org.

The PERT Consortium™ has made diversity a priority. In a new collaboration with the Women as One CLIMB PE program, we intend to enhance critical skills and relationships between female clinicians and industry partners and diversify scientific decision-making to activate innovative ideas to improve PE care.

Finally, The PERT Consortium™ will host our 8th Annual Scientific Symposium, "What Is Known, and What We Need to Know: A State-of-the-Art and Scientific Update" in Tampa, Florida, from September 29 to October 1, 2022. We expect to sell out, with > 600 participants, and will discuss new developments in the diagnosis, treatment, and prevention of PE. The Consortium remains honored to collaborate with *Endovascular Today*, and we hope the articles included within reflect our passion for and commitment to the treatment of PE. ■

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Board of Directors

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Board of Directors

Pulmonary Embolism Research Collaborative (PERC™): A New Initiative to Standardize Pulmonary Embolism Care Internationally

An overview of the inaugural PERC™ meeting, which tasked participants with developing consensus regarding components of clinical care and outcomes that should be tracked in PE care.

By Terry R. Bowers, MD; Kenneth Rosenfield, MD, MHCDS; and Eleni Whatley, PhD

The inaugural meeting of PERC™, the Pulmonary Embolism Research Collaborative, was convened in Washington, DC, on April 22, 2022, bringing together an international group of experts in pulmonary embolism (PE) to work in collaboration with the United States FDA, patient representatives, and industry leaders to explore gaps in recognition, diagnosis, and treatment of patients with acute PE. The National Pulmonary Embolism Response Team (PERT) Consortium™ has been at the center of this "movement," promoting the concept of high-quality, multidisciplinary team–based care; educating the medical community, patients, and other stakeholders regarding the state of the art in PE care; and establishing a robust quality assurance data registry that has rapidly expanded to include > 35 participating institutions in the United States. The National PERT Consortium™ sponsored the inaugural PERC™ meeting, tasking participants to develop consensus regarding the components of clinical care and outcomes that should be tracked in PE care. The PERC™ initiative aims to standardize data collection in PE patients undergoing evaluation and treatment and thus establish the foundation for an expanding evidence base that may inform future care for acute PE. The hope is that the development of a more robust evidence base for PE diagnosis and treatment will enable better identification, ensure more accurate risk stratification, facilitate appropriate triage, and enhance consistency in employing escalation of care strategies. Evidence produced through PERC™ promises to eventually reduce the high degree of variation in PE management and foster treatment of the right patient at the right time with the right therapy. Uniform data collection with standardized definitions is a powerful tool that will inform treatment strategies for PE patients, enhancing clinical care, quality assurance, and research endeavors, including clinical trials and regulatory oversight.

PARTICIPANTS AND MEETING ORGANIZATION

The PERT Consortium™ Board of Directors selected Drs. Terry Bowers and Kenneth Rosenfield as Co-Chairs for the inaugural PERC™ meeting, also inviting Dr. Eleni Whatley to serve as a Co-Chairs in her capacity as an FDA representative from the Center for Devices and Radiological Health. The co-chairs then assembled a steering committee, which in turn identified the various stakeholders to invite as participants. These included diverse international physician experts from multiple specialties involved in PE management, as well as regulatory partners active in the venous thromboembolism (VTE)/PE space, industry collaborators, sister VTE organizations, and patient advocacy groups. All invitees enthusiastically accepted the opportunity to participate, underscoring the timeliness and importance of this PERC™ initiative.

The PERC™ Steering Committee met to establish goals and objectives for the inaugural meeting. These goals centered

TABLE 1. PERC™ MEETING WORKING GROUP LEADERSHIP BY STAGE OF THE PATIENT'S PE JOURNEY (GROUPS 1-5)	
Group/Topic	**Leaders**
Group 1: Initial assessment, acute treatment, and risk stratification	Jay Giri, MD; Jeffrey Kline, MD; and Philip Wells, MD
Group 2: Interventional procedural parameters	Terry Bowers, MD; Robert Lookstein, MD; and Eleni Whatley, PhD
Group 3: Acute adverse events and outcomes	Eric Secemsky, MD; Akhilesh Sista, MD; and John Moriarty, MD
Group 4: Hospital course: monitoring and management following initial treatment	Andrew Sharp, MD; Brent Keeling, MD; and Kenneth Rosenfield, MD
Group 5: Postdischarge management	Roy Smith, MD, and Rachel Rosovsky, MD

around expanding data collection in patients with PE and identifying the most appropriate data to collect, while at the same time streamlining processes to encourage sites to enter data on their patients. Perhaps most important was the mandate to standardize data elements and their definitions. Ultimately, PERC™ intends to establish a consensus set of data elements and standard definitions for these elements.

MORNING FOCUS: ESTABLISHING THE DATA ELEMENTS TO COLLECT DURING THE PE PATIENT'S JOURNEY

The first half of the PERC™ meeting was dedicated to critically reviewing the current data typically collected on PE patients and brainstorming what other data might be useful or important to obtain to complete the evidence base that will inform future management of PE. Acknowledging the enormity of this task, the steering committee established five working groups, each responsible for identifying the relevant data to be collected from each of five distinct stages during the timeline of a patient's PE journey, starting with initial presentation and ending with long-term outpatient follow-up. Group leaders were then appointed based on their expertise in various aspects of the PE treatment spectrum, and invitees were placed in the various groups with the intent of creating diverse perspectives. This strategy proved to be a tremendous success, with all PERC™ members contributing significantly to a spirited discussion within their working groups. The topics for groups 1 through 5 and their assigned leaders are listed in Table 1.

Each working group met several times during the 4 weeks prior to the inaugural PERC™ meeting in Washington, DC, to review and discuss all of the potential data elements that might be collected for their respective phase of the PE journey. Groups were instructed to have an open mind and cast a big net—to consider novel parameters not collected in previous databases or investigational device exemption trials, which nonetheless might influence decision-making and outcomes for PE. During the preparatory meetings, each group achieved consensus regarding the appropriate data elements to collect for their respective PE timeline and summarized these findings for presentation to the larger group of experts. An enormous number of data elements were ultimately suggested by each group, and there was overlap in data points across groups, as expected. All parties recognized that it would be challenging to collect and enter all desired data into The PERT Consortium™ PE Registry for each patient. Accordingly, the groups were tasked with identifying "core" elements versus those that might be part of an "enhanced" data collection. Core data elements are those deemed essential to collect on every single patient, because they are well established as important data points that inform treatment strategies and outcomes. Enhanced data elements are those that are considered interesting and potentially useful for decision-making and might influence outcome, but their contribution is yet to be defined. Exhaustive lists were generated in each category for each working group, with the goal of incorporating these as data elements in the next version of The PERT Consortium™ PE Registry. Importantly, we aim to publish a list of these data elements, as well as the overall proceedings of PERC™, as part of an expert consensus document in the future. The intent is to provide a template for data collection internationally for all patients with PE.

AFTERNOON FOCUS: HOT TOPICS/KEY FACTORS THAT GUIDE DECISION-MAKING AND TREATMENT RECOMMENDATIONS

Importantly, it was not the goal of this inaugural PERC™ meeting to arrive at consensus regarding specific algorithms of care for PE. Rather, the focus was to clarify what information should be collected and analyzed to ultimately inform therapeutic decisions and best practices. Accordingly, and in keeping with the themes of (1) critically evaluating the definitions and true value of existing data elements and (2) broadening the scope to include additional potentially important factors, the afternoon sessions of the PERC™ meeting were dedicated to addressing specific critical aspects of PE care in more depth. Five topics were selected that represent opportunities for refinement of data and/or expansion of evidence to be collected. The afternoon groups were tasked with identifying key questions that remain unanswered regarding their assigned topic and proposing data collection necessary to address these issues in the future. The group topics and their assigned leaders are listed in Table 2.

TABLE 2. PERC™ MEETING WORKING GROUP LEADERSHIP TO DETERMINE INFORMATION NEEDED TO GUIDE DECISION-MAKING AND TREATMENT RECOMMENDATIONS (GROUPS 6-10)

Group/Topic	Leaders
Group 6: Risk stratification: standardizing and harmonizing current tools	Menno Huisman, MD; Stavros Konstantinides, MD; Christopher Barnett, MD; and Kenneth Rosenfield, MD
Group 7: Pharmacologic management: periprocedure, in-hospital, and postdischarge	George Davis, MD; Roy Smith, MD; and Beverley Hunt, MD
Group 8: Redefining endpoints and outcomes: focus on role of clot burden	Robert Lookstein, MD; Terry Bowers, MD; and John Moriarty, MD
Group 9: RV/LV ratio pre- and posttherapy: methodology and role in decision-making and outcome assessment	Jay Giri, MD, and James Horowitz, MD
Group 10: Quality-of-life assessment posttreatment: the voice of the patient	Rachel Rosovsky, MD; Fionnuala Ní Áinle, MD; and Erik Klok, MD

Abbreviation: RV/LV, right ventricular/left ventricular.

Several important gaps in the existing PE knowledge base were identified by each of these groups. Notable discussion topics included: how to consolidate the numerous risk-scoring algorithms available; determining the metrics required to inform decisions regarding escalation of care, for both current and future therapies; data points regarding pharmacologic therapy (eg, specific agents and doses) necessary to provide insight into outcome variations based on the dosing scheme and adjunctive therapies; and measurement and tracking of outcomes posttherapeutic intervention. Dedicated discussions also focused on the value of clot burden reduction as a credible and measurable endpoint; the methodology used, and the reliability of CT and echocardiography in assessing right ventricular/left ventricular ratio; and establishing standardized quality-of-life metrics and their standardization moving forward. Specific outcomes of these discussions and recommended data points will be provided in the white paper consensus document.

CONCLUSIONS AND FUTURE STEPS

PERC™ provides an important starting point to achieve standard data acquisition to populate The PERT Consortium™ PE Registry and other research in PE. Significant headway was made toward identifying important core data elements, standardized definitions, and needs for additional data to inform patient care. Recognizing the mandate to address the evidence gap in PE and spurred by the enthusiasm generated and momentum gained from this inaugural meeting, PERC™ leadership has begun the process of publishing a white paper to disseminate this important information. Notably, a byproduct of this inaugural PERC™ meeting—and perhaps what may be most consequential—has been that PE stakeholders and leaders have been able to network and exchange ideas and align regarding shared goals to reduce the impact of PE worldwide. Expanding and standardizing data collection should help fill the evidence gap that exists for PE management. Information obtained from a uniform data collection effort will inevitably lead to improved care and better outcomes for all patients with PE worldwide. ■

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The PERT Consortium™ PE Registry and Research Committee: Updates and Future Directions

The development of a real-world pulmonary embolism registry and research committee to inform providers on best practices, establish a mechanism for initiating and funding investigator-led projects, and provide a platform for prospective clinical research trials.

By Amir Darki, MD, MSc, and Wissam A. Jaber, MD

Acute pulmonary embolism (PE) is the third-leading cause of cardiovascular mortality and is estimated to affect 100,000 patients per year.[1] Despite the improved diagnostics and treatment modalities in the late 20th century, there is a paucity of resources allocated for PE research compared with the top two causes of cardiovascular death: myocardial infarction and stroke. To address this concern, the National Pulmonary Embolism Response Team (PERT) Consortium™ established a modern PE registry to help inform providers on diagnosis, management, and outcomes derived from real-world patients presenting with acute PE.

MAJOR DEVELOPMENTS IN PE REGISTRIES

The last large, multicenter, prospective registry dedicated to the study of acute PE was ICOPER, which was conducted in the mid-1990s.[2] It enrolled 2,454 patients with acute PE at 52 institutions across North America and Europe, elucidating significant key aspects related to acute PE, including presenting signs and symptoms, prognostic factors, and outcomes.

Since ICOPER was conducted, there have been several important developments in the field of PE. First, a series of randomized trials investigated the effects of systemic thrombolytic administration on the outcome of acute intermediate-risk PE, with results indicating an incremental benefit to such therapy, albeit at a risk of significant bleeding.[3,4] The desire to mitigate bleeding risk while harnessing the therapeutic benefits of thrombolytics led to increasing interest in the use of catheter-based therapies as a potentially safer strategy. Although the field was initially focused on catheter-based thrombolysis, newer devices that combine fragmentation and aspiration of thrombus have emerged. This rapid development of various endovascular therapies has outpaced the design and execution of appropriately sized trials to fully investigate their safety and efficacy. Additionally, new therapies have also emerged, such as direct oral anticoagulants for long-term management of PE patients and mechanical support for patients in postobstructive shock from acute PE.

The second major development since ICOPER has been the conception and promulgation of the multidisciplinary PERT model of care delivery. PERT emphasizes the rapid evaluation of acute PE patients by an expert multispecialty team that benefits from ongoing experience, education, and standardized protocol creation and dissemination.[5]

A third development has been the progressive shift in health care delivery toward a value-based system, with an emphasis on identifying quantifiable measures of quality, cost, and patient experience. These key developments fueled the need for a modern multicenter PE registry.

THE PERT CONSORTIUM™ PE REGISTRY

The PERT Consortium™ PE Registry was conceived in 2015 in Boston, Massachusetts, at the inaugural meeting of The PERT Consortium™. The goal was to develop a modern observational database to help improve patient outcomes, catalyze funded investigator-led projects, and provide a platform for prospective clinical research trials. Currently, the registry collects prospective data on a large cohort of patients presenting with intermediate- and high-risk PE from diverse settings across many hospital systems.

There are currently > 40 medical centers nationwide voluntarily contributing prospective data on acute PE patients, with > 7,500 patients enrolled as of May 2022 (Figure 1). Data elements are secured in a REDCap

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Beth Israel Deaconess Medical Center
Nebraska Methodist Health System
University of Chicago
Oklahoma Heart
UT Southwestern
Rush University
Lundquist Institute at UCLA Harbor
Loma Linda University

Figure 1. Participating centers in The PERT Consortium™ PE Registry.

database and include baseline demographic and clinical characteristics, imaging and laboratory data, therapy recommended by PERT, implemented treatments and their timing, and in-hospital adverse events and outcomes.

A raw descriptive analysis of the registry revealed the following current information:

- Mean age was 61 years, 47% were female, 24% were minorities, and 50% had body mass index > 30 kg/m^2.
- Of all intermediate-risk patients seen by PERT and entered in the registry, 32% received catheter-directed therapies, and 7% had an inferior vena cava (IVC) filter placed.
- For high-risk patients, 37% had catheter-directed therapies, 25% received tissue plasminogen activator, 12% had an IVC filter implanted, and 14% were placed on extracorporeal membrane oxygenation machine.
- The 30-day mortality of low-, intermediate-, and high-risk patients was 5.2%, 6.7%, and 27.7%, respectively. Figure 2 displays the 30-day and 1-year mortality rates of the registry patients according to risk categories.

The PERT Consortium™ PE Registry and Quality

The PERT Consortium™ PE Registry, in collaboration with the Boston Clinical Research Institute, also serves as a data repository for internal quality control by providing quarterly updates to inform member institutions of

	All patients	PERT Risk Category		
		High Risk	Intermediate Risk	Low Risk
30-day mortality	10.2%	**27.7%**	6.7%	5.2%
1-year mortality	20.1%	**35.6%**	17.7%	12.5%

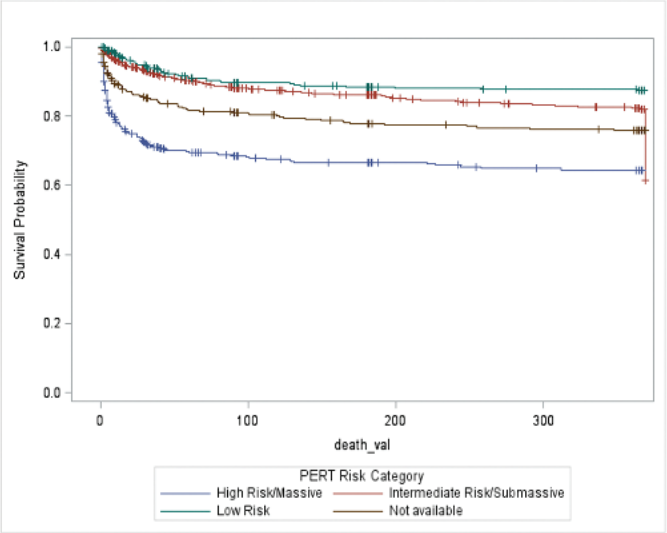

Figure 2. Mortality rates of patients in The PERT Consortium™ PE Registry.

their performance benchmarked to the national data. Included in that dashboard is the total number of patients and distribution across PE risk categories, right ventricular assessment, timely anticoagulation, advanced PE therapy use within the first 24 hours, median length of stay, in-hospital bleeding and death, PE clinic visit after discharge, and readmission rates. Figure 3 shows a partial example of such a dashboard.

The PERT Consortium™ PE Registry and Research

The PERT Consortium™ PE Registry has produced a number of early publications, including the discriminatory accuracy of common PE mortality risk scores[6] and a survey of 100 PE experts on the risk stratification and management of acute submassive and massive PE.[7] Another study evaluating the early PERT experience revealed wide variation in practice patterns among participating centers.[8] Specifically, the implementation of advanced therapy ranged from 16% to 46% and 30-day mortality ranged from 9% to 44%. Further refinement and awareness of protocols will likely standardize care and achieve more consistent practices

Last year, The PERT Consortium™ formally established a dedicated Research and Publication Committee composed of 12 diverse multidisciplinary members with established experience in PE and PE research. The committee meets monthly and is tasked with overseeing all research projects and publications derived from The PERT Consortium™ PE Registry. A formal mechanism for research project proposals was developed. Submitted proposals (both from centers contributing to the registry and noncontributing centers) are reviewed in detail, discussed, and ranked in order of relevance, importance, and urgency. The investigators with proposals receiving the highest scores are supplied with national data access to conduct the study. Although funding from applying investigators is welcome, The Consortium has earmarked a budget for funding highly ranked projects from member institutions. From 2021 to 2022, two proposals have been selected from a competitive field, and manuscript preparations are underway. One is focused on high-risk PE and use of mechanical support, and the other is focused on gender disparities in the management of acute PE.

Other tasks of the Research and Publication Committee are to harmonize The PERT Consortium™ PE Registry to help inform best practices, enhance the registry for regulatory decision-making, and provide a platform for prospective clinical research trials. Further direction on these tasks is expected pending results of PERC™, the inaugural Pulmonary Embolism Research Collaborative meeting, which is discussed elsewhere in this supplement.

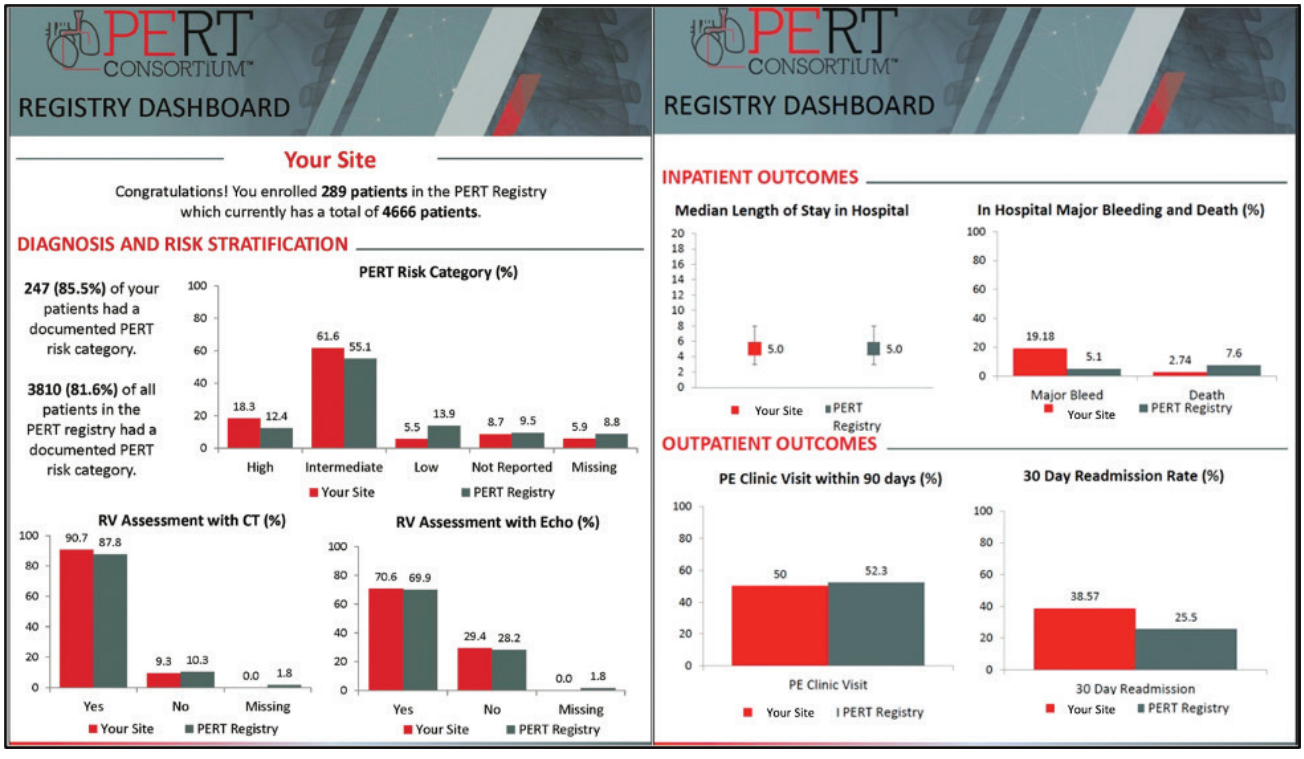

Figure 3. An example of The PERT Consortium™ PE Registry dashboard. RV, right ventricular.

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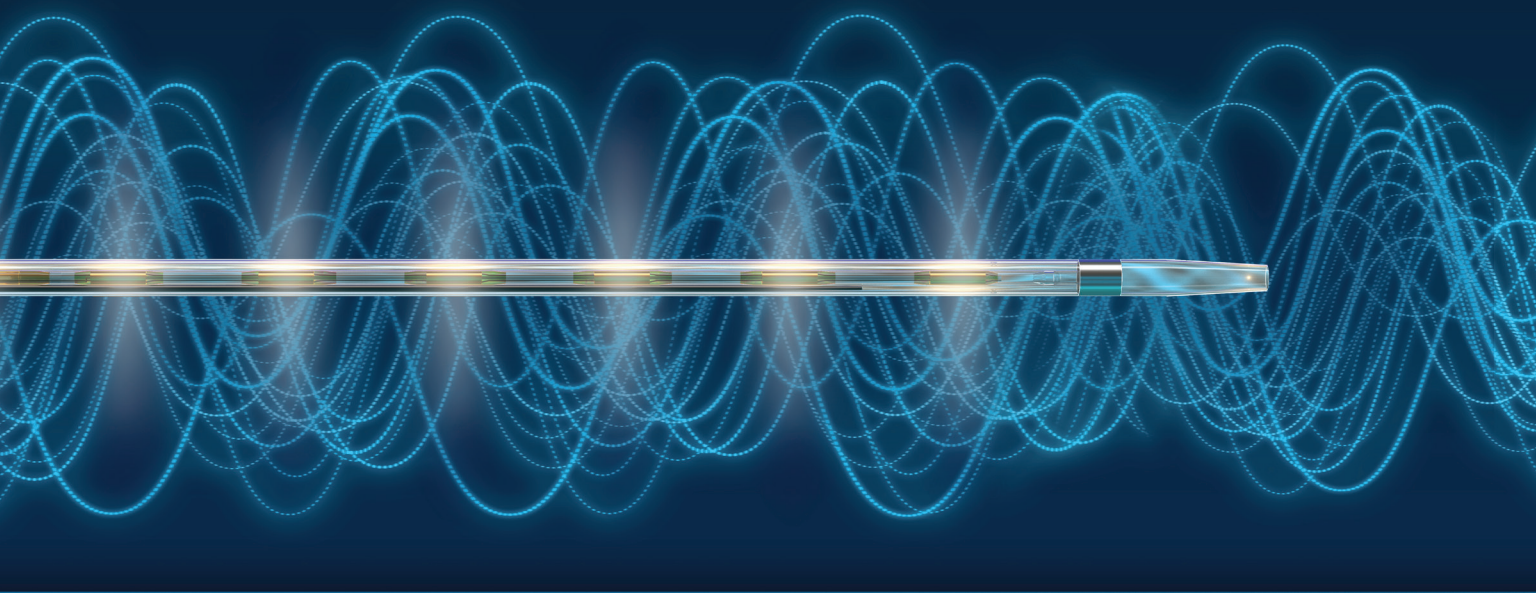

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CONCLUSION

The PERT Consortium™ PE Registry is a unique real-world registry designed to address diagnostic dilemmas and provide guidance on best practices in the management of intermediate- and high-risk PE, two subpopulations of PE that still have unacceptably high mortality and where management controversies remain. Additionally, the Research and Publication Committee arm of The Consortium was created to help oversee selected research projects and provide a vehicle for future clinical trials. ■

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Rationale for the APEX-AV, HI-PEITHO, and PE-TRACT Trials

A review of the objectives, study design, outcome measures, and potential impact of three upcoming pulmonary embolism studies.

By Mona Ranade, MD; Peter Monteleone, MD; and Akhilesh K. Sista, MD

Intermediate-risk (submassive) pulmonary embolism (PE) has been the subject of active clinical study over the last 8 years. In 2014, the small, randomized controlled ULTIMA trial demonstrated the promise of catheter-directed thrombolysis (CDT) delivered via the Ekos catheter (Boston Scientific Corporation).[1] The SEATTLE II trial followed in 2015, leading to FDA clearance of the Ekos catheter, the first percutaneous endovascular medical device with a specific PE indication.[2] In 2018, the OPTALYSE PE randomized uncontrolled trial explored the safety and efficacy of Ekos-delivered low-dose CDT.[3] In 2019 and 2021, two studies (FLARE[4] and EXTRACT-PE[5]) described the safety and efficacy of two novel aspiration thrombectomy devices, the FlowTriever device (Inari Medical) and the Indigo aspiration system (Penumbra, Inc.), resulting in two additional devices being cleared for PE.

This article describes the rationale of three upcoming PE studies, one investigating a novel thrombectomy device seeking a PE indication (APEX-AV) and two others aiming to address long-standing deficiencies in our knowledge of catheter-based therapy for intermediate-risk PE (HI-PEITHO and PE-TRACT).

APEX-AV

APEX-AV is a new clinical study aimed at evaluating the efficacy and safety of the AlphaVac multipurpose mechanical aspiration (MMA) F18[85] system (AngioDynamics) in the treatment of acute intermediate-risk PE. The study is being initiated in partnership with The National Pulmonary Embolism Response Team (PERT) Consortium™. Mona Ranade, MD, and William Brent Keeling, MD, are the Co-Principal Investigators of the study.

The AlphaVac F18[85] system is a mechanical aspiration thrombectomy device redesigned with the benefits of the AngioVac system, allowing for rapid large-volume aspiration without the need for extracorporeal bypass.

The AlphaVac MMA F18[85] device uses an 18-F, 105-cm cannula with an 85° angled tip to access the pulmonary circulation*, with the goal of large-volume mechanical thrombus extraction. The cannula retains a nitinol basket–reinforced, self-expandable, funnel-shaped distal tip similar to the AngioVac device, with the addition of a proprietary handle designed to create an off-circuit method of action. The device encompasses features such as a volume-limiting switch, which limits blood loss during the procedure. The AlphaVac F18[85] cannula is currently indicated for the removal of thrombi or emboli from the venous vasculature.

APEX-AV is a single-arm investigational device exemption study that will enroll patients with confirmed acute intermediate-risk PE at up to 20 hospital-based sites in the United States. Patient enrollment is anticipated to commence in summer 2022. The primary efficacy endpoint of the APEX-AV study is the difference in right ventricular/left ventricular (RV/LV) ratio between baseline and 48 hours postprocedure. The primary safety endpoint is the rate of major adverse events, including device-related death and major bleeding within the first 48 hours. Patients will be followed for 30 days after the index procedure. The study will also evaluate secondary efficacy endpoints, including thrombolytic use within 48 hours of the procedure, length of stay in the intensive care unit/hospital, and change in modified Miller Index from baseline to 48 hours postprocedure as assessed by CTA. The secondary safety endpoints include rate of device-related complications, comprising clinical deterioration, cardiac injury, pulmonary vascular injury, major bleeding, and device-related death within 48 hours of the index procedure.

Despite the extensive work done thus far to assess novel catheter-based therapies, we remain without clear societal guidelines dictating use of these devices in intermediate-risk PE. The primary reason is the lack of large randomized clinical trials evaluating their efficacy and safety compared to anticoagulation (AC) alone and best supportive therapy. More than 1,500 patients have been randomized to systemic thrombolysis trials, whereas (prior to current trials in recruitment) only 59 have been randomized to catheter-based therapy versus AC

alone. A second reason is the use of surrogate outcomes rather than clinical ones. Since SEATTLE II, the standard outcome measure has been RV/LV ratio 48 hours postprocedure. However, to understand the value (and the risks) of catheter-based therapy, we need data on short-term fatal and nonfatal clinical deterioration, serious bleeding, and recurrent thromboembolism and longer-term exercise tolerance, functional capacity, and quality of life in the year after PE. An understanding of these outcomes is absolutely required to truly assess catheter-based therapy and advance clinical guidelines for intermediate-risk PE.

HI-PEITHO

The HI-PEITHO study is a multinational, multicenter, randomized controlled trial that has enrolled 27 patients at 29 active sites as of May 11, 2022.[6] It is currently the only funded and actively enrolling randomized clinical trial studying optimized endovascular therapy of patients with PE. Patients with intermediate-high–risk are identified and defined as having (1) confirmed acute PE, (2) evidence of RV dysfunction on imaging, (3) elevated cardiac troponin, and (4) clinical criteria indicating an elevated risk of early death or imminent hemodynamic collapse. Patients are identified and randomized 1:1 to treatment with a standardized protocol of ultrasound-facilitated CDT (USCDT) with the Ekos catheter plus AC versus AC alone. The primary outcome measure is a composite of PE-related mortality, cardiorespiratory decompensation or collapse, or nonfatal symptomatic and objectively confirmed PE recurrence within 7 days of randomization. Secondary outcomes include assessment of bleeding risks and longer-term outcomes, including all-cause mortality, functional status, and quality-of-life indices out to 12 months. Through this study design, HI-PEITHO seeks to not only assess safety and efficacy of USCDT with Ekos but also provide the landmark randomized data for high-value clinical outcomes necessary to impact clinical guidelines and change standards of care.

Although randomized data on interventional versus conservative therapies are required to change guidelines and advance clinical practice, champions of advanced interventional therapies for PE may have reservations about randomizing intermediate-high–risk PE patients to AC alone. The design of HI-PEITHO ensures safe escalation of care without implicit bias of treatment through implementation of the National Early Warning Score (NEWS). The cardiorespiratory collapse or decompensation primary outcome for the trial is composed of (1) cardiac arrest, (2) signs of shock, (3) extracorporeal membrane oxygenation initiation, (4) intubation or noninvasive mechanical ventilation, and/or (5) a NEWS score ≥ 9 between 24 hours and 7 days confirmed after randomization on two consecutive measurements performed 15 minutes apart. Implementation of a standardized, easy-to-use clinical tool recommended by the National Health Service in the United Kingdom allows HI-PEITHO investigators to clearly and reliably identify decompensating patients and escalate care without awaiting progression to a highly morbid clinical stage. NEWS scores prevent patients from being "crossed over" between treatment arms unnecessarily or for vague clinical reasons, which would complicate interpretation of trial results. However, most importantly, use of the NEWS scores will help prevent patients from severely deteriorating clinically without recognition and escalation of care as directed by their clinical teams. The HI-PEITHO investigators have also developed a unique and class-leading iPhone-based application tool to allow for both facilitated trial patient identification and rapid and easy calculation of NEWS scores.

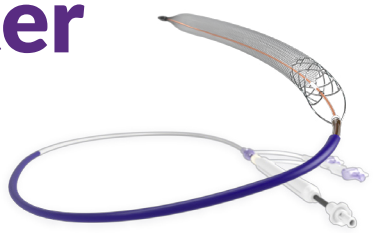
HI-PEITHO is a bold step in the progress of our understanding of PE and PE therapies. Randomized data evaluating high-impact clinically and patient-relevant outcomes will help advance our understanding of not only USCDT but also interventional therapies for this patient population. These results will be central to the development of clinical guidelines in treatment of PE and will impact use of all interventional PE therapies, including both USCDT and thrombectomy.

PE-TRACT

PE-TRACT is in submission to the National Heart, Lung, and Blood Institute within the National Institutes of Health (the same institute that funded the ATTRACT and C-TRACT trials). PE-TRACT, if funded, would randomize approximately 500 patients to catheter-based therapy plus AC versus AC alone. Although it will describe short-term outcomes such as fatal and nonfatal clinical deterioration, bleeding, and recurrent venous thromboembolism, it is powered and designed to detect differences between the two groups in peak oxygen consumption (measured via cardiopulmonary exercise testing) and New York Heart Association class at later time points (3 months and 1 year postrandomization, respectively). Quality of life, 6-minute walk test, and cost-effectiveness are secondary outcomes among many other exploratory outcomes.

PE-TRACT seeks to (1) clarify the long-term natural history of PE—we are just now starting to understand the scope of the long-term toll PE takes on patients, with nearly 50% having a below-normal peak oxygen consumption during exercise 1 year post-PE per the ELOPE study[7]; (2) identify novel risk factors (eg, blood biomarkers, baseline comorbidities, hemodynamic parameters) for the development of long-term disability and short-term deterioration; and (3) offer biological insights that will

ClotTriever BOLD Catheter



Built on the Proven ClotTriever Catheter Platform

Treat the Full Range of DVT Chronicity. Lytic-Free [1]

Clinical outcomes from the CLOUT registry for the treatment of deep vein thrombosis (DVT) in all-comer patients:

99.6%
Single-session Treatment

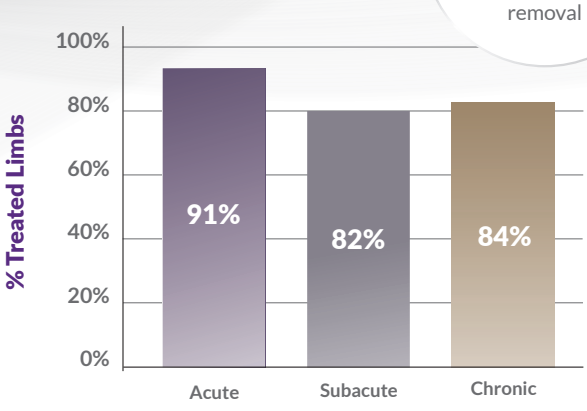
0 mg
Thrombolytics Used

50 mL
Median Estimated Blood Loss

0 Valve Damage | 0 AKI* | 0.4% SAEs

Treat a Range of DVT Chronicity [2]

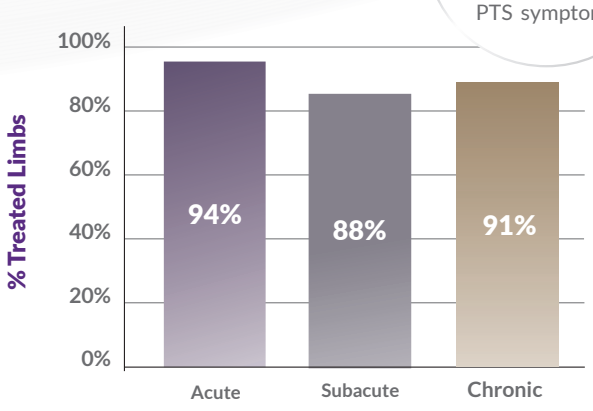
86%
complete or near-complete thrombus removal



Complete or near-complete (≥75%) thrombus removal as assessed by core-lab adjudicated Marder scores

Reduce the Long-Term Complications of DVT [2]

91%
patients free from moderate or severe PTS symptoms



% Free of moderate or severe post-thrombotic syndrome (PTS) symptoms at 6 months

*Acute Kidney Injury

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2. CLOUT Interim Analysis (n=250) presented at AVF February 2022

Indications:
The ClotTriever Thrombectomy System consists of the ClotTriever Catheter and ClotTriever Sheath. The ClotTriever Thrombectomy System is indicated for:
(1) The non-surgical removal of thrombi and emboli from blood vessels; (2) Injection, infusion and/or aspiration of contrast media and other fluids into or from a blood vessel.
The ClotTriever Thrombectomy System is intended for use in the peripheral vasculature including deep vein thrombosis (DVT).

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

See Instructions for Use for complete Indications for Use, contraindications, warnings, and precautions.

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drive research toward novel device and pharmacologic therapies. Consequently, PE risk stratification will become more refined and precise, delineating which submassive PE patients are at highest risk for short-term deterioration and death, which are at highest risk for long-term disability, and which will truly benefit in the short and long term from targeted reperfusion therapy. PE-TRACT will also begin to offer insight into some of the technical aspects of catheter-based therapy, including correlating the amount of thrombus removed with clinical outcomes. PE-TRACT will also increase precision around major bleeding estimates.

CONCLUSION

Ultimately, the PE community must demand more rigorous studies of catheter devices used to treat intermediate-risk PE. Studies such as APEX-AV introduce important and promising devices, but these studies cannot be the "last word." HI-PEITHO and PE-TRACT offer the opportunity to gain a deeper knowledge about PE, potentially improving the short- and long-term cardiopulmonary health of many thousands of patients and, at the least, pointing us toward the next steps in reducing morbidity and mortality from this vexing disease. ■

**The AlphaVac MMA F18^{85} system is not indicated for treatment of PE and is considered off-label.*

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Women Supporting Women to CLIMB in Venous Thromboembolism

Describing efforts by Women as One and The PERT Consortium™ to promote female physician thought leaders in venous thromboembolism.

By Maidah Yaqoob, MD, and Frances Mae West, MD, MS, FACP

The gender imbalance in medicine is amplified in the surgical and procedural specialties where men dominate. According to the census in 2020-2021, women represent 16.7% in orthopedic surgery, 20.4% in neurosurgery, 22% in interventional radiology (IR), and 25.5% in thoracic surgery. In contrast, women are drawn to fields such as obstetrics and gynecology (84.6%), pediatrics (71.1%), child neurology (68.7%), and allergy and immunology (61.9%). These trends have remained consistent since 2019.[1] Despite an almost equal representation of male and female medical graduates in the United States (53.4% vs 45.5%), women comprise only 15.4% of IR fellows and residents and 7.3% of faculty members.[2-4] Cardiology and pulmonary critical care specialties maintain similar gender imbalances. Fewer than 15% of practicing cardiologists and < 5% of interventional cardiologists are women, while 29.3% of critical care physicians, 40% of pulmonary physicians, and 34.9% of pulmonary and critical care physicians are female.[5] Over the past decade, the percentage of female internal medicine residents (41.9%) and the percentage of female applicants for pulmonary (29.2%), critical care medicine (26.1%), and pulmonary critical care medicine (30.7%) fellowships are declining.[6] Potential reasons in the literature include poor work-life balance, gender bias, lack of female physicians with senior academic rank, and the gender pay gap.[5,7]

Women comprise a minority of full professors in every field of medicine, with only 26% in internal medicine, 23% in radiology, and 14% in surgery.[8] Women are also underrepresented at scientific and medical society conferences and on editorial boards of major academic journals, comprising 16% of editors in chief and 18% of board members.[9] These gender disparities and lack of sponsorship lead to the invisibility of midcareer female academic physicians.[9,10] Sponsors, as opposed to mentors, have the potential ability to use their power and influence to advocate for female physicians. Considering that women rarely hold governorship positions in medical schools, clinical departments, and editorial boards, men in these positions should strive to support midlevel female physicians and elevate them to executive leadership positions using a top-down approach (Figure 1).[10]

BRIDGING THE GENDER INEQUALITY GAP: WOMEN AS ONE AND CLIMB

Efforts are being made from the bottom up to bridge the gap of gender inequality at the institutional and national levels (Figure 1). A systematic review of targeted programs designed to support the careers of women in academia has yielded positive outcomes in regard to self-rated skills and capabilities and reported improvements in promotion, retention, and remuneration.[11]

One such effort to break the ceiling is the effort by Women as One to highlight women and bring them to the forefront. Women as One was founded in 2019 by Drs. Roxana Mehran and Marie-Claude Morice with the aim of building a more inclusive, diverse, just workforce in medicine.

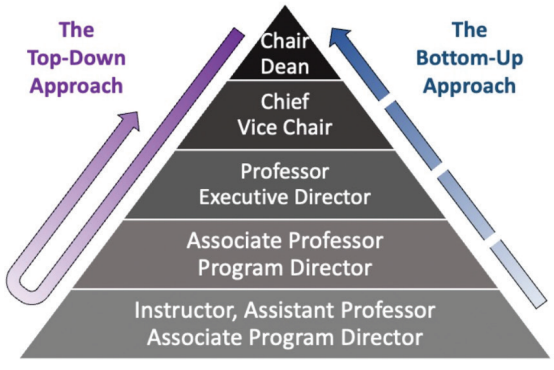

Figure 1. Strategies to promote gender equality in medicine: The top-down approach describes sponsorship of women by institutional leaders, often male, to recognize talented women and promote or assign them to leadership and authority positions. The bottom-up approach involves women mentoring women to provide skills and training to improve visibility and recognition.

It provides women with unique educational and professional opportunities consisting of educational programs, financial and mentorship awards, and opportunities to network with industry partners. A talent directory of 1,600 women physicians is freely accessible, and networking webinars focus on bringing mentors and mentees together.

In July 2020, Women as One launched CLIMB, an advanced-skills training program for a pilot group of interventional cardiologists. The program aims to level the playing field by providing skills and relationships with industry leaders to promote female physician participation on advisory boards and speakers' bureaus and in clinical research. The program has shown rapid growth since its inaugural course and is expanding to new audiences. This year, CLIMB 2022 has created two learning pathways: CLIMB Clinical and CLIMB Research. The clinical pathway will include webinars in coronary, cardiac electrophysiology, pulmonary embolism (PE), and pulmonary vascular disease. The program will comprise two tracks: three sessions each focusing on a variety of topics. Interested candidates for the course have been reviewed and selected by the program directors. The course is in a webinar format and spans from June to August. It will be recorded and available for viewing by Women as One members after the session is completed.

The PE program of CLIMB is cosponsored by The PERT Consortium™, which aims to advance the status of PE care and promote research in its treatment. The marriage of these two innovative organizations will provide an exciting educational, networking, and career-building opportunity for female physicians in various fields of medicine who treat patients with venous thromboembolism (VTE). The CLIMB PE program (Figure 2) is divided into two tracks: Interventions in VTE and Critical Care in VTE.

Figure 2. Women as One 2022 CLIMB skills training program. CLIMB Clinical PE Program Directors, Dr. Frances Mae West and Dr. Maidah Yaqoob. https://womenasone.org/uploads/2022/03/climb-2022-flyer-1.pdf

INTERVENTIONS IN VTE TRACK

The Interventions track is designed to appeal to interventional cardiologists, interventional radiologists, vascular surgeons, and cardiothoracic surgeons. Percutaneous methods to treat VTE have expanded in recent years. Knowledge of the functionality and limitations of these devices is important for interventionalists to expand their skill base to lead clinical programs, interact with industry partners, and participate in device-related clinical trials.

Session 1: Catheter-Based Pulmonary Artery Reperfusion Interventions

Pulmonary artery reperfusion can be obtained by one of three mechanisms: mechanical (aspiration or fragmentation), pharmacologic (catheter-directed thrombolysis [CDT]), or pharmacomechanical. Mechanical thrombectomy devices include mechanical fragmentation devices such as pigtail catheters, angioplasty, Cleaner (Argon Medical Devices, Inc.), and snares; rheolytic thrombectomy devices such as AngioJet (Boston Scientific Corporation); suction thrombectomy devices such as AngioVac (AngioDynamics), Indigo CAT8 (Penumbra, Inc.), and Jeti (Walk Vascular, LLC); and clot-extraction devices such as FlowTriever (Inari Medical).

The FLARE trial assessed the effects of using FlowTriever in patients with intermediate-risk PE. The data suggested it was safe and effective, with the absence of thrombolytic complications and need for postprocedural intensive care unit stay and with improvement in right ventricular/left ventricular (RV/LV) ratio and bleeding complications.[12] EXTRACT-PE is a single-center multicenter trial using the Indigo CAT8 for intermediate-risk PE. The study demonstrated low rates of major bleeding and adverse events, along with a significant reduction in the RV/LV ratio.[13]

CDT can be performed via a multiside-hole catheter, catheters with expandable baskets with mini-infusion catheters (Bashir Plus endovascular catheter, Thrombolex, Inc.), or an ultrasound-assisted thrombolysis (USAT) catheter (EkoSonic, Boston Scientific Corporation). The combination of USAT with conventional CDT accelerates fibrinolysis, in turn allowing for greater penetration of the fibrinolytic into the thrombus. Two randomized controlled trials (RCTs), ULTIMA and OPTALYSE PE, and one prospective study, SEATTLE II, have evaluated the use of these catheters for RV dilation reversal in intermediate-risk PE populations.[14-16]

To date, there are no large RCTs comparing these devices to anticoagulation alone or to each other, leaving much debate over the use of these therapies for treatment of intermediate-risk PE. However, the available literature

suggests that there is clinical equipoise, and trials are currently enrolling or in planning stages. We hope to enlighten the audience with real-world experience by case-based discussion led by experts in interventional fields who can share unbiased opinions of the different devices, including their limitations. We also aim to encourage attendees to join clinical inquiries as this area represents a significant knowledge gap in the field of PE.

Session 2: Interventions in Deep Vein Thrombosis

This session will shed light on the controversial data for reduction of postthrombotic syndrome (PTS) in deep vein thrombosis (DVT), as well as percutaneous interventions used to manage patients with May-Thurner syndrome, an underdiagnosed cause of lower extremity DVT predominantly in young women that leads to recurrent lower extremity DVTs.[17,18]

Thrombolytic therapy has been compared to anticoagulation alone in various trials, including CAVENT, which showed a decrease in the incidence of PTS.[19] Conversely, the ATTRACT trial showed no significant difference in PTS and an increase in the risk of major bleeding events.[20]

Understanding the caveats of conflicting data and the role of interventions in the lower extremity and having knowledge of an underrecognized condition affecting young women can arm interventionalists with clinical acumen of these complex conditions. Case-based scenarios and discussion with thought leaders can help interventionalists confidently make treatment recommendations to referring physicians and patients.

Session 3: Inferior Vena Cava Filters for Management of DVT

Initially a prophylactic measure, indications for inferior vena cava (IVC) filters have evolved over time. IVC filters have been used in trauma patients, including those with spinal cord injuries and lower limb fractures who are at exceptionally high risk for developing VTE. A retrospective analysis of a large registry suggested that prophylactic IVC filter placement in trauma patients is associated with higher rates of DVT, with no difference in mortality compared to trauma patients who did not receive IVC filters.[21] The 2019 European Society of Cardiology (ESC) guidelines recommend against routine prophylactic use of IVC filters, but use should be considered in patients with an absolute contraindication to anticoagulation or recurrence of PE despite therapeutic anticoagulation.[22] Due to associated morbidities, efforts are directed toward IVC filter retrieval, with improvements in rates accomplished by creating registries and using a multidisciplinary approach to track filters.[23]

In this session, we will explore early and late complications; share pearls and techniques to approach challenging cases, highlighting anatomic variants, difficult retrieval, and filter fracture; and discuss outline systems used by institutions to track and ensure retrieval of IVC filters.

CLIMB: CRITICAL CARE IN VTE TRACK

The Critical Care pathway will include discussions on diagnostic modalities, management of critical care patients with PE, and mechanical circulatory support for high-risk PE patients. This track is designed to appeal to medical, cardiac, and anesthesia intensivists, as well as pulmonologists, interventional cardiologists, vascular medicine specialists, and cardiothoracic surgeons.

Session 1: Diagnostic Modalities in PE

This session will elucidate the variety of imaging techniques and advancements. The assessment of RV size and function is a major component for risk stratification of PE. Several CTA findings are associated with worse outcomes: RV/LV ratio, left atrial volume, pulmonary artery diameter, pulmonary artery obstructive index, interventricular septal deviation, and IVC contrast reflux.[24-27] Alternate imaging modalities include ventilation perfusion scans, lower extremity duplex (in patients with high pretest probability of PE and inability to perform CTA), MR pulmonary arteriography, and catheter-based pulmonary angiography. Echocardiography, including point-of-care ultrasound, has evolved as an adjunctive tool for diagnosis for acute PE, with signs for RV dysfunction and PE severity including new RV strain, RV/LV ratio, tricuspid annular plane systolic excursion, McConnell's sign, and clot in transit.[28-30] Other investigational diagnostic modalities include dual-energy CT and single-photon emission CT scans. In this session, we will focus on the interpretation of these studies and the identification of high-risk features.

Session 2: Management of the Critical Care Patient

This session will incorporate complex decision-making regarding selection of vasopressors, airway management, fluid management, and thrombolytics. Hemodynamic support and oxygen management are hallmark to the care of patients with high-risk PE. A thorough understanding of PE pathophysiology (ie, the effects of fluid, vasopressors, anesthesia, positive pressure ventilation on RV afterload) is necessary for management of high-risk PE patients.[31]

Session 3: Mechanical Circulatory Devices for Management of High-Risk PE

Extracorporeal membrane oxygenation (ECMO) provides hemodynamic support and stabilization, thus providing critical time to employ anticoagulation or reperfusion interventions. ESC guidelines recommend ECMO in combination with other interventions such as surgical embolectomy and CDT in patients with hemodynamic

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instability from massive PE.[21] An expert analysis published by the American College of Cardiology included acute PE as an indication for implementation of ECMO as a bridge to definitive reperfusion therapy.[32]

A systematic review evaluating ECMO in 19 case reports and case series of patients with acute massive PE suggested that patients experiencing cardiac arrest from PE are more likely to survive and have good neurologic outcomes compared to other causes of cardiac arrest.[33] Two additional retrospective studies with a small number of patients showed improved survival compared to control groups.[34,35] There is limited literature published for the use of mechanical circulatory devices in this patient population. A small study comparing ECMO to RV assist devices suggested improved oxygenation and cardiac output with RV assist devices compared to ECMO.[36]

This session at CLIMB will include a case-based discussion with experts in the field to help understand the intricacies of these therapies in patients with high-risk PE.

CONCLUSION

The CLIMB program will culminate in a combined session for the interventions and critical care tracks during The PERT Consortium™ annual meeting September 29 to October 1, 2022, in Tampa, Florida. This networking session will focus on partnering with industry, increasing visibility to clinical trial leads, and next steps for participants after completion of the CLIMB skills training program.

We are honored to be selected as the program directors for the Women as One CLIMB Clinical program in PE. We hope female physicians will find these sessions enlightening, inspiring, and empowering to take their career to the next step and continue to CLIMB toward gender equality in medicine. ■

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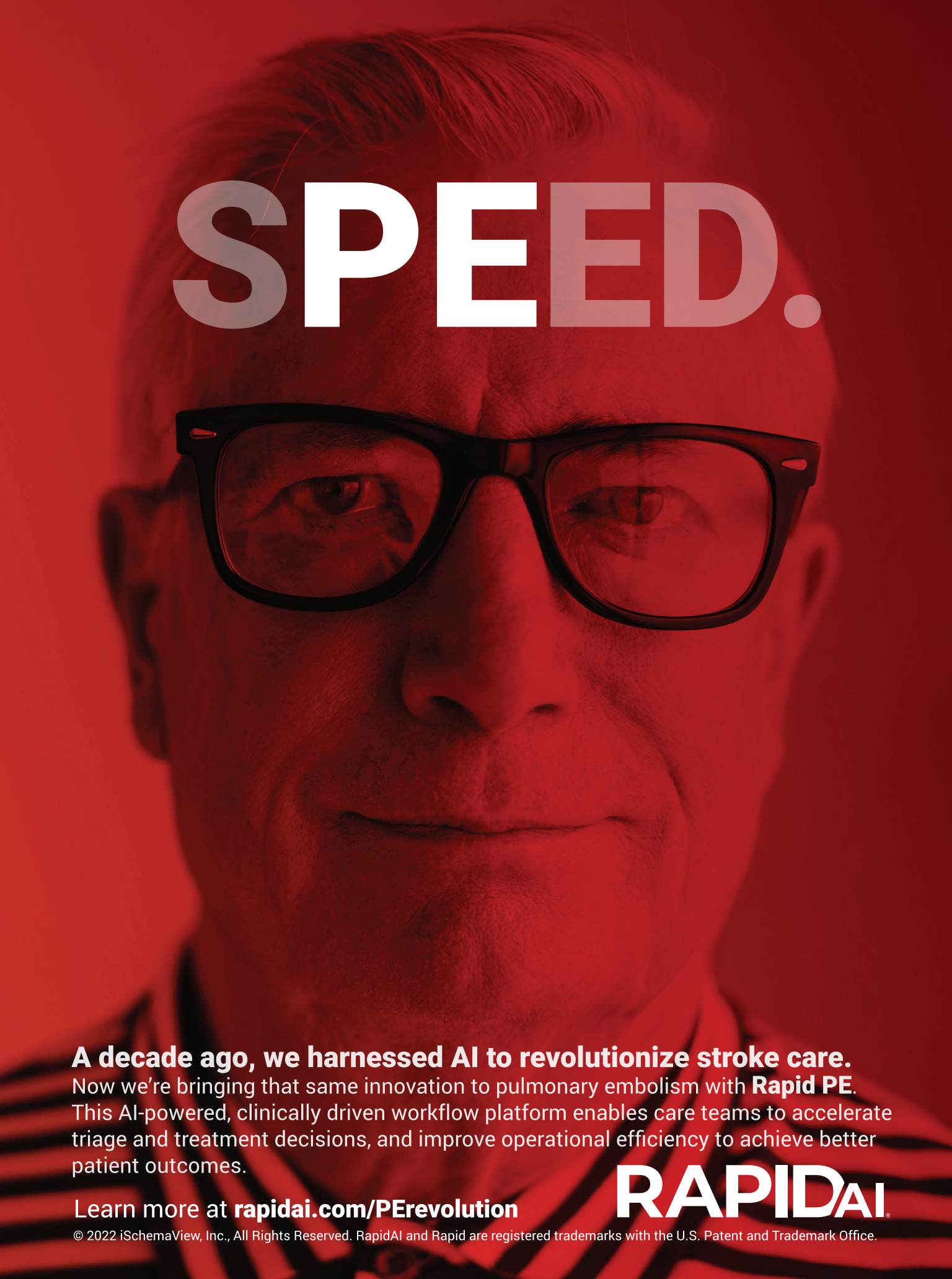

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RAPIDAI

PERTs Around the World

Pulmonary embolism experts share how pulmonary embolism response teams have changed pulmonary embolism care globally.

By Rachel P. Rosovsky, MD, MPH; Karen Breen, MD, MRCPI, FRCPATH; Menno V. Huisman, MD, PhD, FESC; Beverley J. Hunt, OBE; David Jiménez, MD, PhD, FERS; Barry Kevane, MB, BCh, BAO, PhD, MRCPI, FRCPath; Frederikus A. Klok, MD, PhD, FESC; Carlos Elzo Kraemer, MD, PhD; Jose Montero-Cabezas, MD, PhD; and Fionnuala Ní Áinle, MD, PhD

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Pulmonary embolism (PE) is a major cause of morbidity and mortality worldwide.[1,2] Over the past decade, numerous therapeutic tools and strategies have been developed to treat patients with PE. Despite these advances, PE remains a potentially serious disease, killing four to 10 people per 100,000 population in the Western world.[3,4] To address this crisis, pulmonary embolism response teams (PERTs) have been developed to coordinate and expedite the diagnosis and treatment of PE. These teams immediately and simultaneously engage multiple different specialists to decide on the best course of action for each patient.[5] Since the launch of the first PERT in 2012, hundreds of PERTs have formed

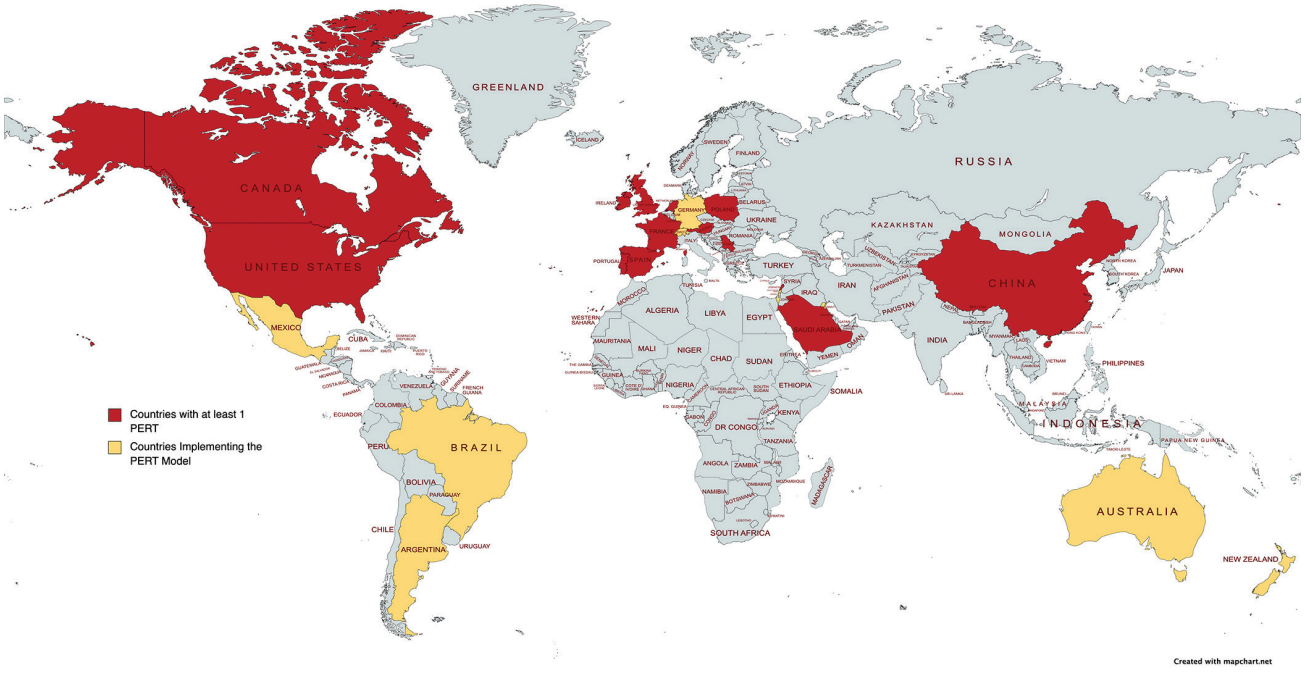

Figure 1. PERTs around the world.*

*This map is constantly evolving as new PERT sites are developed.

throughout the world (Figure 1). With this expansion, a growing body of evidence has emerged, demonstrating that the implementation of a PERT improves the time to PE diagnosis and initiation of therapy, cost of care, length of stay, and, in some studies, even mortality.[6-9] In line with these findings, the 2019 European Society of Cardiology/European Respiratory Society guidelines recommended setting up PERTs for management of patients with intermediate- and high-risk PE when resources and expertise are available because they address the needs of modern system-based health care (class IIa recommendation).[10] PERTs have the potential to transform PE care, and in this article, PE experts from Ireland, Spain, the United Kingdom (UK), and the Netherlands share how PERTs have changed the care of PE patients in their countries.

PERT Perspectives in Ireland

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In the years since the launch of the first PERT in the United States in 2012, clinicians and other stakeholders in the Republic of Ireland have become increasingly aware of the potential for this model of care to revolutionize the management of acute PE. Although one would expect the broad implementation of such a treatment model across all hospitals and hospital networks in this country to be challenging in the short term, we have seen a progressive stepwise approach to the development of PERTs in a number of large centers in Ireland.

In recent years, improving outcomes for patients with venous thromboembolism (VTE) has become a priority for the Ireland East Hospital Group (IEHG), the largest hospital network in the Republic of Ireland, serving a population of > 1 million individuals. In collaboration with the patient organization Thrombosis Ireland, the IEHG VTE team (comprising clinicians, scientists, data analysts, and allied health professionals) has worked toward improving all aspects of VTE care within the IEHG network. A PERT was established in 2018 within the Mater Misericordiae University Hospital (MMUH; a large academic center within the IEHG). The establishment of this formalized PE management pathway within the hospital has forged strong working relationships between all various stakeholders involved in PE care at this institution. Moreover, this collaborative approach to PE management has also provided us with opportunities to more effectively advocate for patients with complex care requirements. The development of a PERT has also served to highlight the complexity underlying PE care to other health care providers and hospital administrators across the institution. In line with the overarching goals of the IEHG and with the support of international PERT colleagues, an expansion of the MMUH PERT is currently underway to provide guidance in a hub-and-spoke model to other hospitals that may lack the same level of expertise and resources. This initiative will proceed in parallel with the establishment of the Centre for Integrated Thromboembolism Care at the MMUH site.

Achieving further advancements in PE care in the future will require high-quality data generated through the conduct of high-quality clinical trials. Conducting clinical trials in acute PE management is seen as potentially challenging in this country in light of the heterogeneity of PE care (particularly with respect to the access to expertise in interventional techniques) that may exist between hospitals and within the various disciplines of internal medicine. It has been our experience in the MMUH that the establishment of a PERT has also served to lay the foundation for the necessary infrastructure required to allow us to participate in such clinical trials.

As we look to the future of PE care in Ireland and as the evidence in support of the PERT model continues to accumulate, we are confident that PERTs will become the norm in this country and will lead to improved interdisciplinary collaboration and patient outcomes.

PERT Perspectives in Spain

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The development of specialized PERTs has been a landmark innovation in the care of patients diagnosed with acute PE.[10] However, the theoretic advantages and growing scientific evidence supporting PERT to provide clinical attention for patients with acute PE do not correspond to the level of practical implementation in Spain. In fact, only a few hospitals in Spain have PERTs. A number of reasons might explain why the PERT concept is not growing rapidly in our country: (1) initial lack of definitive evidence supporting the benefits for patients with PE[11,12]; (2) lack of robust information about the cost-effectiveness of the PERT model; and (3) lack of proper infrastructure, resources (ie, endovascular devices), and medical expertise required to manage these patients.

In 2017, Hospital Ramón y Cajal in Madrid was the first Spanish center to activate Code PERT (Figure 2), which is ready 24 hours per day to quickly evaluate patients with suspected and/or confirmed PE and initiate interventions. This innovative process brings together a team of highly trained respirologists, cardiologists, cardiovascular surgeons, intensivists, and radiologists who specialize in PE diagnosis and treatment, along with emergency department physicians, to ensure that the most appropriate management is initiated as quickly as possible. Our specialists not only provide treatment for complex patients (ie, intermediate and high risk) with acute PE but also accept transfers from hospitals that are challenged in caring for these cases. In addition, the team is available to colleagues at other centers to discuss therapeutic strategies or management of treatment-associated complications over the phone. Since its institution in 2017, our Code PERT has attended to 157 patients with acute symptomatic PE (36 patients with high-risk PE, 98 with intermediate-high–risk PE, and 23 with diagnostic or therapeutic challenges such as pregnancy or absolute and relative contraindications to anticoagulation) (Jiménez D, unpublished data, 2022). Particularly in the era of COVID-19, our PERT has played an important role in the diagnosis and management of patients with COVID-19 pneumonia and suspected and/or confirmed thrombotic complications.

Figure 2. Code PERT at Ramón y Cajal Hospital in Madrid, Spain.

Currently, health authorities in Madrid are updating the process of care for patients with suspected, confirmed acute PE according to the best available evidence,[13] and PERTs will play a central role in this process.

PERT Perspectives in the United Kingdom

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In England, the National Institute for Health and Care Excellence set the standard of care for patients with acute PE by providing evidence-based guidance and quality standards for diagnosis and management.[14] However, while National Health Service (NHS) England has this exemplary system, political devolution has meant that each country in the UK has its own health care units (ie, NHS England, NHS Scotland, NHS Wales, NHS Northern Ireland). As a result, there is no standard approach to PE care across the nations. Furthermore, which clinical specialty manages PE has fallen to one of

many different specialties, which in turn is dependent on the institution and their available facilities. Increasingly, the management of acutely unwell patients with PE is falling to general physicians, respiratory clinicians, or cardiologists 24/7, with input from intensivists for those requiring ventilatory or circulatory support, and clinical hematologists are playing a larger role, especially in outpatient follow-up.

The goal of establishing PERTs at a number of centers is to provide a multidisciplinary team to care for patients presenting with intermediate PE, focusing on their management and, more specifically, acting as a forum to discuss the potential need for advanced interventions, such as embolectomy, thrombolysis (systemically or catheter directed), and, occasionally, the role of adjunctive therapies such as extracorporeal membrane oxygenation (ECMO) in high-risk PE. Low-risk PE management is usually straightforward, although it is recognized that management can often be suboptimal. Care of patients with intermediate-high–risk PE can often be particularly disjointed. A 2019 National Confidential Enquiry into Patient Outcome and Death report suggested that areas of improvement for PE management in the UK include timely access to imaging, commencement of anticoagulation, and establishment of PERT networks to help offer access to interventional therapies.[15]

The PERT concept is evolving in the UK. Some larger regional centers are already providing a PERT service. At Guy's and St Thomas' in London, we've had a PERT service since 2017 and have received > 150 referrals from within the region. Preliminary patient outcomes have shown decreased morbidity and risk of chronic thromboembolic pulmonary hypertension (CTEPH) at 6-month follow-up postpresentation (Hunt BJ and Breen K, unpublished data, 2022).

However, major obstacles to setting up PERTs in the UK remain. Perhaps the most important is that busy clinicians are reluctant to engage with thrombolysis for intermediate-risk PE given the evidence concerning lack of improved clinical outcomes in the medium to longer term. Additionally, UK clinical services are crippled by staffing shortages across all disciplines and services. Moreover, lack of resources, limited funding, and determining ownership of the service are current blocks to PERT service development. These problems have been intensified given the strains on the NHS due to COVID-19. Going forward, it may be more practical to have the support of a regional PERT network where smaller centers can refer their patients. We feel that now is the time to try to empower and educate clinicians to establish PERT networks throughout the UK given the potential shown in the United States for PERT to improve PE care.[6]

PERT Perspectives in the Netherlands

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In the Netherlands, acute and chronic care for patients with acute PE is provided by pulmonologists (approximately 60% of all patients) and internists (approximately 40% of all patients). Cardiologists are much less involved because of a historic focus on primary cardiac disease. Reperfusion therapy is primarily reserved for patients with high-risk PE who present in shock and mainly consists of full-dose thrombolysis. The age-standardized annual PE-related mortality rate in the Netherlands is among the lowest in Europe, at 3.0 deaths per 100,000 population in 2014—compared to 8.9 per 100,000 in the UK, 4.6 per 100,000 in Spain, 5.0 per 100,000 in France, and 9.1 per 100,000 in Germany.[3]

The development of PERTs in the United States, the first evidence on the use of catheter-directed therapy, and the wider availability of ECMO treatment has resulted in the introduction of multidisciplinary teams in the Netherlands focused on ad hoc decisions regarding optimal management of severe PE cases. These teams are called ALERT (in Dutch, *acute longembolie* response team) or EXPERT-PE teams, and they are currently emerging foremost in academic medical centers.[16] These teams may consist of cardiologists, internists, pulmonologists, intensivists, and emergency physicians.

Reasons for activation of the EXPERT-PE teams differ. In our hospital, the team is led by internal (vascular) medicine and activated on presentation of patients with (suspected) PE in shock; patients with proven acute PE who are at high risk of hemodynamic decompensation or are respiratory compromised and may require admission to the medium/intensive care unit; or patients with proven PE in which other important treatment dilemmas occur, such as strong contraindication for initiation of anticoagulant therapy. A high risk of decompensation is defined by gestalt or a high national early warning score.[17,18]

On activation, the team assesses the patient and, if relevant, performs additional diagnostic tests, such as point-of-care ultrasound of the heart. After initial actions to stabilize the patient (ie, volume resuscitation, initiation of inotropics or ECMO) and the start of anticoagulant treatment, the team discusses whether the patient requires admittance to the intensive care unit and, if so, whether the patient may benefit from advanced reperfusion therapy. The need and timing for reassessment by the team is decided on and noted in the patient chart. During out-of-office hours, the discussion is done online via a secure application, and the patient assessment is performed by the attending intensivist. The team is kept updated on the clinical course of the patient by the physician responsible for the patient at that time, and all patients are followed for 3 to 6 months at a dedicated thrombosis outpatient clinic. There, patient-reported outcomes are used: the post-VTE functional status scale to capture recovery milestones

and the presence of persistent functional limitations, the PE Quality of Life Questionnaire to capture quality of life, and the Medical Research Council dyspnea scale to assess persistent dyspnea.[19-21]

We expect that EXPERT-PE teams will continue evolving in the Netherlands with the anticipated standardization of team composition and thresholds for decision-making in the Dutch national guidelines for antithrombotic therapy. Collaboration between the Dutch EXPERT-PE teams may also be a very suitable platform to perform the much-needed randomized trials in severe PE and provide the evidence necessary to develop strong guideline recommendations for optimal application of reperfusion techniques in PE patients.

Conclusion

By Rachel P. Rosovsky, MD, MPH

The treatment of PE is evolving with the emergence of PERTs, which are currently forming throughout the world. In this article, we learned how PERTs in four different European countries are affecting the care of PE patients. From our PE experts in Ireland, we heard how PERTs have led to the development of strong working relationships between the many providers who care for PE patients, the improvement in advocacy for these complex patients, and the formation of the infrastructure to carry out much-needed clinical trials in this space. From our colleague in Spain, we were informed that despite the initial challenges in adopting the PERT concept, PERTs played an important role in the COVID era in the diagnosis and management of these patients, and they will likely play a central role in the process of updating the operational care for PE patients in this country. In England, our experts described how the concept of PERTs is evolving in the UK, detailed the advantages of having a multidisciplinary team to care for PE patients, listed the barriers to developing a PERT service, and shared preliminary outcome data from

Guy's and St Thomas' in London demonstrating how the implementation of PERT decreased morbidity and risk of CTEPH. Finally, our PE experts in the Netherlands outlined the various specialists involved in PE care and the process of activating their PE team (EXPERT-PE), as well as discussed how collaboration between Dutch PERTs could inform and carry out important PE trials, which would allow for strong guideline recommendations regarding interventions for these patients.

PERTs are not only changing the way patients with PE are treated but also helping form stronger relationships among specialists, offer a venue for collaboration, and provide a platform to advance our understanding of PE care through research, clinical care and education, with the ultimate goal of improving outcomes. ■

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