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Quarterly Medical Review - Venous thromboembolic disease: a tribute to Professor Guy Meyer

Advancing the management of acute intermediate-high-risk pulmonary embolism: The enduring legacy of Professor Guy Meyer

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ABSTRACT

Only few years after the first report on diagnosing acute pulmonary embolism (PE) with pulmonary angiography, studies began to investigate the effectiveness and safety of thrombolytic therapy for achieving early reperfusion. In 1992, Guy Meyer demonstrated the fast improvement of pulmonary haemodynamics after alteplase administration; this drug has remained the mainstay of thrombolysis for PE over almost 35 years. In the meantime, algorithms for PE risk stratification continued to evolve. The landmark Pulmonary Embolism International Thrombolysis (PEITHO) trial, led by Guy Meyer, demonstrated the clinical efficacy of thrombolysis for intermediate-risk PE, albeit at a relatively high risk of major, particularly intracranial bleeding. Today, systemic thrombolysis plays an only minor role in the real-world treatment of acute PE in the United States and Europe, but major trials are underway to test safer reperfusion regimens. Of those, the PEITHO-3 study, conceived by Guy Meyer and other European and North American experts, is an ongoing randomised, placebo-controlled, double-blind, multinational academic trial. The primary objective is to assess the efficacy of reduced-dose intravenous thrombolytic therapy against the background of heparin anticoagulation in patients with intermediate-high-risk PE. In parallel, trials with similar design are testing the efficacy and safety of catheter-directed local thrombolysis or mechanical thrombectomy. Increasingly, focus is being placed on long-term functional and patient-reported outcomes, including quality of life indicators, as well as on the utilization of health care resources. The pioneering work of Guy Meyer will thus continue to have a major impact on the management of PE for years to come.

1. Management of acute pulmonary embolism: the early years

In 1964, Arthur Sasahara and colleagues described the early, direct diagnosis of pulmonary embolism (PE) in living patients with the use of selective pulmonary angiography [1]. Only four years later, Jack Hirsh et al. reported on the fibrinolytic (thrombolytic) treatment of severe, or 'major' PE (as it was called at that time) with streptokinase infusion. Throughout the following decade, several studies investigated the effectiveness and safety of streptokinase and urokinase and introduced the term 'massive' PE in an attempt to define the appropriate candidates for thrombolytic therapy with the help of angiographic (thrombus load) and inasive haemodynamic (pulmonary artery pressure and vascular resistance) criteria [2-6]. The modern era of intravenous thrombolysis in acute PE was inaugurated several years later, in the late 1980′s, following the introduction and successful testing of recombinant tissue-type plasminogen activator (rtPA; alteplase) [7-9]. Guy Meyer and the European Cooperative Study Group on Pulmonary Embolism demonstrated the faster (within two hours) improvement of pulmonary artery pressure, cardiac index, and total pulmonary resistance after the start of alteplase administration, compared to the older thrombolytic agent, urokinase [10]; the latter needed a much longer, 12-hour infusion period, also considered more likely to increase the risk of bleeding complications. The rapid effects of alteplase on alleviating vascular obstruction (the

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Miller index) and on improving haemodynamics were reported by an Italian multicentre study [11]. Alteplase was approved for use in PE by the US Food and Drug Administration (FDA) in 1990. Its favourable effects on haemodynamic and imaging parameters were confirmed three years later in a large randomised controlled trial [12,13]. Since then, the regimens of systemic (intravenous) thrombolysis for PE have remained unchanged because the testing of further thrombolytic agents has not led to further drug approvals for this indication [14].

2. Evolution of risk stratification and risk-adjusted treatment of pulmonary embolism

Despite the successful testing and approval of thrombolytic agents for acute PE, the exact clinical indications for, and the expected clinical and prognostic benefits of this type of treatment, remained uncertain. In an editorial accompanying the above mentioned publication by Guy Meyer in 1992, Samuel Goldhaber elegantly pointed out the need for a large multinational effort to address these issues and determine the clinical setting in which thrombolysis could favourably affect prognosis in the acute phase as well as over the long term [15]. As it became increasingly clear that the safety profile of thrombolysis might be improved by employing an overall noninvasive approach to PE management [16], attention turned to emerging echocardiographic indicators of right ventricular (RV) pressure overload and dysfunction, which could be used to assess prognosis. Echocardiographic findings in patients with 'major' PE started appearing in the literature in the 1980′s [17] and evolved thereafter [18,19], increasingly gaining acceptance among experts and clinicians [12]. By the late 1990′s, echocardiography had become a widely used bedside examination for assessing the severity of acute PE [20,21]. In a large prospective multicentre registry, thrombolytic treatment was associated with improved survival in hemodynamically stable patients with 'major' PE defined by echocardiographic criteria [22].

The first European Society of Cardiology (ESC) guidelines on acute PE published in the year 2000 devoted a comprehensive section to the diagnostic and prognostic information provided by echocardiography, stressing the need for trials to determine which patients might benefit from thrombolytic therapy in the absence of systemic hypotension or shock [23]. The first major trial to test and validate such a risk-adjusted reperfusion (thrombolytic) treatment strategy was published two years later. The Management Strategies and Prognosis of Pulmonary Embolism −3 trial, performed in Germany, randomised 256 patients with acute PE and pulmonary hypertension or right ventricular dysfunction to heparin plus alteplase versus heparin plus placebo [24]. The incidence of the primary combined efficacy endpoint was lower in the alteplase than in the placebo group ($P = 0.006$), a difference due to the higher incidence of treatment escalation in the latter arm (24.6% vs. 10.2 %, $P = 0.004$). Overall mortality was low in both arms, and no intracranial or fatal bleeding was reported [24]. This trial helped the European PE guidelines to establish, in their 2008 update [25], the term of *intermediate-risk* PE for a large group of haemodynamically stable patients with 'some' evidence of RV dysfunction. However, this new categorization could not satisfy the need for a larger multinational trial with stricter criteria for including a population at truly elevated risk for early death or hemodynamic decompensation, and more robust clinical endpoints [26].

Debate continued on whether individual echocardiographic or laboratory markers sufficed to identify candidates for thrombolytic treatment. In 2008, the group of Guy Meyer performed a systematic review of studies estimating the relationship between echocardiography, computed tomography or cardiac biomarkers and the risk of death in patients with haemodynamically stable PE [27]. In 12 studies which ultimately met the inclusion criteria, the unadjusted risk ratio of RV dysfunction as assessed by echocardiography or CT for predicting death was 2.4 [95 % confidence interval (CI) 1.3−4.4]. The unadjusted risk ratio for predicting death was 9.5 (95 % CI 3.2−28.6) for BNP, 5.7 (2.2−15.1) for pro-BNP, and 8.3 (3.6−19.3) for cardiac troponin. However, these authors [27] as well as subsequent reviews [28] pointed out considerable constraints using these parameters. Limitations included differences in definition, the low specificity of individual imaging parameters, and different threshold values of laboratory biomarkers used in the various studies. Subsequent studies by the Paris group and others showed that imaging parameters and laboratory biomarkers may possess *additive* prognostic value in intermediate-risk PE, complementing each other [29,30] in addition to baseline clinical parameters [31,32]. This knowledge resulted in the establishment of the *intermediate-high-risk* PE category, requiring both evidence of RV dysfunction on echocardiography (or computed tomography pulmonary angiography) and elevated circulating cardiac troponin or natriuretic peptide levels. Since then, this new category has replaced older terms such as 'submassive' PE in the European guidelines [33] and in most of the world.

3. The landmark pulmonary embolism thrombolysis (PEITHO) trial

By 2010, the superior haemodynamic effects and faster onset of action (compared to heparin anticoagulation alone) of systemic thrombolytic (fibrinolytic) treatment had been firmly established, and its use was recommended by European and international Guidelines in the emergency setting of acute high-risk PE [25,34]. However, it remained controversial whether systemic thrombolysis could also improve the clinical outcome of haemodynamically stable patients with intermediate-high-risk PE [35]. Designed to address the long-standing debate, the Pulmonary Embolism International Thrombolysis (PEITHO) trial, led by Guy Meyer and an international steering committee of experts from Europe and North America, enrolled 1006 normotensive patients presenting with both RV dysfunction on imaging and a positive cardiac troponin I or T test [36]. Patients received either full-dose intravenous thrombolysis (tenecteplase) plus heparin, or heparin anticoagulation alone. In PEITHO, the clinical efficacy of reperfusion treatment was confirmed by a reduction in the clinical composite of death from any cause or haemodynamic collapse within 7 days of randomisation (Table 1). The benefit observed was mainly driven by a reduction in haemodynamic decompensation or collapse; as in the previous trial [24], early mortality was low, but in contrast to that trial, a higher rate of bleeding events, particularly intracranial haemorrhage, was observed in the thrombolysis group (Table 1) [36]. Consequently, although PEITHO was a positive trial, demonstrating superiority of tenecteplase over placebo as defined by its primary efficacy endpoint, the high risk of intracranial or other life-threatening bleeding events (subsequently confirmed by meta-analyses [37]) has served as evidence for international guidelines to recommend *against* thrombolysis as first-line treatment in intermediate-high-risk PE [14,33,38,39]. Lastly, the PEITHO trial could not show (and had not

Table 1
Efficacy and safety outcomes of the landmark Pulmonary Embolism Thrombolysis (PEITHO) trial [36].

	Tenecteplase ($n = 506$)	Placebo ($n = 499$)	P value
All-cause mortality or haemodynamic collapse within 7 days of randomisation	13 (2.6 %)	28 (5.6 %)	0.015
All-cause mortality within 7 days	6 (1.2 %)	25 (5.0 %)	0.43
Haemodynamic collapse within 7 days	8 (1.6 %)	25 (5.0 %)	0.002
Stroke within 7 days	12 (2.4 %)	1 (0.2 %)	0.003
Major non intracranial bleeding within 7 days	32 (6.3 %)	6 (1.5 %)	<0.001
Minor non intracranial bleeding within 7 days	165 (32.6 %)	43 (8.6 %)	<0.001

been designed to show) an impact of thrombolysis on long-term mortality or on the incidence of thromboembolic pulmonary hypertension (CTEPH) over the long term [40].

4. The post-PEITHO era: in search of safer reperfusion options for PE

Although PEITHO used an experimental thrombolytic drug, tenecteplase, instead of the established alteplase regimen, concerns about catastrophic bleeding hampered the popularity of thrombolytic treatment in clinical practice [41]. Today, systemic thrombolysis plays an only minor role in the real-world treatment of acute PE in the United States and Europe, with administrative data reporting its use in less than 4 % of all hospitalised PE patients and less than 12 % of hospitalisations related to 'severe' (intermediate-high-risk or high-risk) PE [42-44].

Meanwhile, technical innovations in percutaneous catheter-directed treatment (CDT) have provided an increasing number of options for removing pulmonary emboli. A number of CDT systems, applying various pharmacomechanical, aspiration-based thrombus removal, or hybrid combination devices, have received approval by the US FDA and the European Medicines Agency [45,46]. Data from a few small randomised trials and several cohort studies suggest that CDT may effectively reduce RV size as a surrogate outcome of RV pressure overload and failure, with a low risk of bleeding complications and low in-hospital mortality [47,48]. In the US, CDT use has steadily increased in recent years [49,50], paralleled by growing implementation of multidisciplinary PE response teams (PERT) to optimise local expertise and resource allocation [51,52]. In Europe, access to CDT began more recently but is now entering a phase of accelerating growth [44]. The 2019 update of the European guidelines on PE, co-chaired by Guy Meyer (Fig. 1), stated that high-quality data from randomised controlled trials using robust clinical endpoints are needed before endorsing CDT as first-line therapy in PE patients without haemodynamic collapse [14]. This assessment has been echoed by other guidelines and position papers [45,53] . In addition, the incremental direct costs of catheter systems and procedures for advanced PE therapy need to demonstrate cost-effectiveness [54], that is, answer the question: "Are the costs of these new interventional devices justified and offset by a reduction of early complications, length of hospital and intensive care unit stay, and prevention of late PE sequelae?"

Fig. 1. Professor Guy Meyer preparing the first presentation of the 2019 European Society of Cardiology (ESC) Guidelines on the Management of Acute Pulmonary Embolism together with his Task Force Co-Chair Stavros Konstantinides. Photograph taken on 1st September 2019 before the main guidelines session at the ESC Congress in Paris, France.

5. Moving forward: how ongoing trials advance risk stratification and reperfusion strategies, and outcome measures, in intermediate-high-risk pulmonary embolism

As the bleeding risk of full-dose intravenous thrombolysis is too high to justify its use as first-line therapy in the intermediate-high-risk class, reduced-dose thrombolysis regimens are becoming increasingly popular in clinical practice [55-59]. This is despite the explicit warning by scientific societies and guidelines that the available evidence is not (yet) sufficient to prove their efficacy and safety [14]. The Pulmonary Embolism International Trial (PEITHO)−3 study (ClinicalTrials.gov Identifier: NCT04430569), conceived and planned by Guy Meyer and other European and Canadian experts, is an ongoing randomised, placebo-controlled, double-blind, multicentre, multinational academic trial with long-term follow-up aiming to resolve this issue [60]. The primary objective is to assess the efficacy (defined as the ability to prevent death, haemodynamic decompensation or PE recurrence) of reduced-dose intravenous thrombolytic therapy with alteplase against the background of standard care (heparin anticoagulation), in patients with acute intermediate-high-risk PE, 30 days after randomisation. The secondary objectives are to assess (i) the safety, net clinical benefit, and impact of reduced-dose thrombolytic therapy on overall mortality in patients with intermediate-high-risk PE as well as (ii) the effect on long-term mortality, functional impairment, residual right ventricular (RV) dysfunction, and the incidence of chronic thromboembolic pulmonary hypertension.

An important feature of PEITHO-3 is the stringent definition of intermediate-high-risk PE as an inclusion criterion. Instead on relying exclusively on imaging (evidence of RV dysfunction) and biochemical (circulating levels of elevated laboratory biomarkers) criteria, which possess a high sensitivity but low specificity to predict cardiorespiratory decompensation or death [27,33], additional baseline clinical predictors of early life-threatening events are required for inclusion: an initial systolic blood pressure ≤ 110 mm Hg, respiratory rate > 20 breaths/min (or, as a surrogate, an arterial oxygen saturation < 90 % on room air), or history of chronic heart failure. In a post hoc analysis of the first PEITHO trial, the presence of at least one of these criteria defined an enriched patient population (53 % of the total number of patients included), in which the incidence of the composite clinical outcome was 11.2 % in the control group as opposed to as low as 3.7 % in the thrombolysis group [61].

A similary advanced concept for defining intermediate-high-risk PE and, with it, identifying the 'true' candidates for reperfusion treatment has been adopted in the Higher-Risk Pulmonary Embolism Thrombolysis trial (HI-PEITHO; ClinicalTrials.gov Identifier: NCT04790370). HI-PEITHO is an ongoing multinational controlled randomised adaptive-design multicentre parallel-group comparison trial [62]. Its primary objective is to assess whether ultrasound-assisted catheter-directed thrombolysis plus anticoagulation is associated with a reduction in the composite outcome of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed PE recurrence compared to anticoagulation alone. Allocation to the treatment arms is open-label, but the composite primary efficacy outcome and safety outcomes are adjudicated by a blinded critical events committee. Besides the 'standard' confirmation of intermediate-high-risk PE [14], patients need to fulfil at least two of the following clinical criteria indicating an elevated risk of early death and/or imminent hemodynamic collapse: 1) heart rate ≥ 100 beats per minute; 2) systolic blood pressure ≤ 110 mm Hg; 3) respiratory rate > 20/min and/or oxygen saturation on pulse oximetry (SpO_2) < 90 % (or partial arterial oxygen pressure < 60 mm Hg) at rest while breathing room air. HI-PEITHO also assesses the impact of the tested reperfusion treatment on a broad

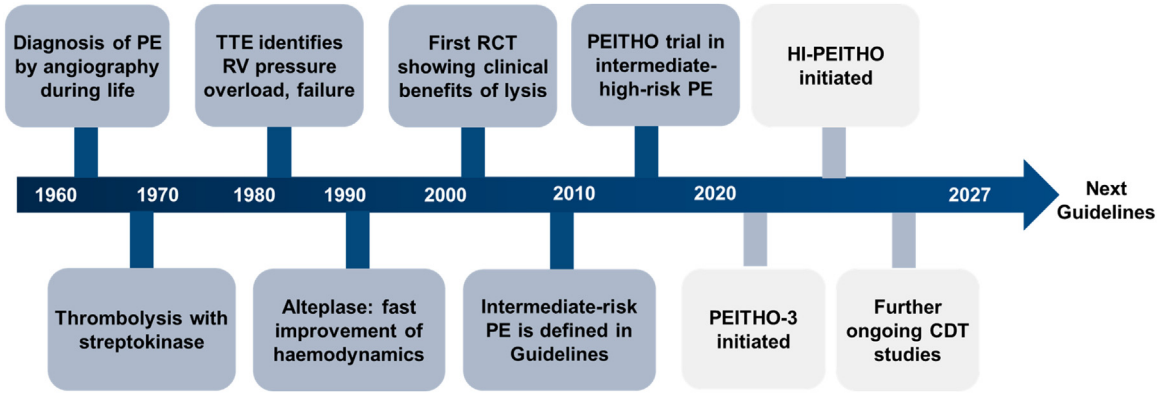

Fig. 2. Key milestones in the historical evolution of the management of intermediate-high-risk pulmonary embolism: focus on reperfusion treatment.
CDT: catheter-directed treatment; PE: pulmonary embolism; PEITHO: Pulmonary Embolism International Thrombolysis study; RCT: randomised controlled trial; TTE: transthoracic echocardiogram.

spectrum of functional and patient-reported outcomes, including various quality of life indicators, as well as on the utilization of health care resources.

6. Conclusions and outlook

Pulmonary embolism poses a substantial acute and chronic burden on patients, healthcare systems, and societies in many parts of the world [63-65]. The progressive reduction of in-hospital case fatality over the past two decades has been challenged by increasing annual incidence and hospitalisation rates as well as numbers of acute PE survivors necessitating chronic care [43,66-69]. Despite these facts, PE has long remained in the shadow of more common cardiovascular syndromes such as myocardial infarction and stroke. In the past, three landmarks were the approval of the thrombolytic agent alteplase in 1990, the introduction of low molecular weight heparins at the turn of the millennium, and the launch of direct oral anticoagulants in 2010. Today, PE-focused technological progress and research is one of the most rapidly advancing fields in cardiovascular medicine. Innovative pharmacomechanical or purely mechanical modalities of reperfusion treatment promise high efficacy combined with superior safety compared to older thrombolytic regimens. Adequately powered randomised controlled trials are finally underway to inform future guidelines (Fig. 2). Substantial progress is also being made in post-PE care, increasingly focusing on patient-related outcome measures and the patients' quality of life.

With his pioneering work, which focused on antithrombotic and reperfusion treatment but also extended to the entire spectrum of acute PE diagnosis and management, Guy Meyer has contributed like few others to advancing the field. His gentle character and his wise, diplomatic and democratic (inclusive) approach to communication and problem solving, combined with his determination and scientific rigour, allowed him to build a broad, sustainable collaborative research network with colleagues worldwide. In doing so, Guy has left an enduring legacy for the next generations of physicians and researchers in France, Europe, and the world.

Declaration of competing interest

SVK reports personal lecture/advisory fees and research grants to his institution from Bayer AG, Boston Scientific, Daiichi-Sankyo, LumiraDx, Penumbra, and Inari Medical. OS reports research grants from Boeringher Ingelheim; and personal fees from Boston Scientific and Inari Medical. SZG reports no conflict of interest related to this work. NM reports personal lecture/advisory fees and research grants from Bristol-Myers Squibb, Pfizer, Boston Scientific and Inari Medical.

CRediT authorship contribution statement

Stavros V. Konstantinides: Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **Olivier Sanchez:** Conceptualization, Writing – review & editing. **Samuel Z. Goldhaber:** Conceptualization, Writing – original draft, Writing – review & editing. **Nicolas Meneveau:** Conceptualization, Writing – review & editing.

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