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Review Article

Pulmonary embolism prophylaxis and treatment: What's right, what's wrong, and the future

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ABSTRACT

Recognition of the importance of effective pulmonary embolism treatment and prophylaxis has improved inpatient care in many settings. Recommended drug treatment and prophylaxis of acute pulmonary embolism have changed little over the past 10 years. However, new information has emerged, which when combined with early pharmacology studies of unfractionated heparin and low molecular weight heparin, clearly shows important deficits in current practice that, if remedied, could reduce risk and likely save lives. These involve ensuring improved bioavailability of low molecular weight heparin prophylaxis dosing by abandoning once-daily dosing, adopting weight- or weight-category based dosing, and dosing twice daily or by continuous infusion in critically ill patients. For pulmonary embolism treatment, failure to recognize that presenting patients often have subnormal perfusion resulting in unpredictable bioavailability of subcutaneous anticoagulant has meant undertreatment, and delay in reaching a therapeutic anticoagulant level, assuredly resulting in failure of timely improvement as well as recurrent thromboembolism. Intravenous anticoagulant should be rapidly adopted as first treatment for acute pulmonary embolism until normal hemodynamic values are restored and cutaneous perfusion returns. Treatments under development include clinical investigation of intensive care unit (ICU) patients receiving intravenous low molecular weight heparin prophylaxis, weight-based, targeting an anticoagulant level in anti-Xa units that is both effective and safe. The same would be useful for pulmonary embolism treatment, although return to initial anticoagulation with unfractionated heparin is more easily monitored by activated partial thromboplastin time (aPTT) and is an easy standard of care to adopt. Pulmonary embolism clot removal is being accomplished by suction thrombectomy and catheter-directed lysis, each with its own different procedural characteristics. Whether either confers benefit compared to conscientiously administered intravenous anticoagulation cannot be shown in ongoing studies using subcutaneous treatment in control patients with subnormal perfusion. Factor XI/XIa inhibition is another treatment approach being studied. Another approach to lytic therapy under study, administering an inhibitor of alpha-2-antiplasmin, may cause less bleeding than tissue plasminogen activators.

Introduction

For over 50 years, beta-lactam antibiotics have been known to have the property of requiring a sufficient blood or tissue level for therapeutic effect for a duration of time. Yet they have been dosed intermittently by bolus with blood levels allowed to decay below therapeutic, rather than by continuous intravenous (iv) infusion. Now, after multiple clinical trials and meta-analyses, without firm proof that continuous infusion of beta-lactam antimicrobials provides longer survival, yet with convincing proof that it cures infections better than intermittent dosing, hospital practice is changing to continuous infusions for beta-lactams.[1]

There are three important lessons here for physicians who treat or seek to prevent venous thromboembolism (VTE), pulmonary embolism (PE) or deep vein thrombosis (DVT). First, best medical practice for patients takes into account drug effects in patients, including pharmacokinetics, rather than ignoring pharmacokinetics and embracing dosing convenience used in early clinical trial protocols. Second, drugs with targeted effects, like antimicrobials and anticoagulants, are not the keys to extended life—they are instead specific interventions on their targets and that effect, rather than survival of patients with complex medical, genetic, social, and behavioral backgrounds, is the proper outcome measure for clinical trials. Last, many physicians are willing to pay attention to the first two lessons and improve their practice, improving upon past

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inferior practice that was based on early, often marketing-influenced protocols.

In this review, regarding PE, we describe what is going well, what is not, and what the future may hold.

What's going right with pulmonary embolism

There is increasing awareness of PE and DVT risk for inpatients, with measurement and reporting of frequency of incidence and prophylaxis use. For example, a report from Chinese hospitals surveying a patient sample from 2016 to 2017 who suffered thromboembolism within 6 weeks after hospitalization found only 31 % of patients received any prophylaxis, and only 5 % of medical and 8 % of surgical patients received appropriate prophylaxis.[2] Multiple country-wide activities to improve prophylaxis ensued. By 2020, implementation of a computerized clinical decision support system, resulting from heightened awareness, resulted in a 50 % reduction in clinical venous thromboembolism (VTE) in the intervention group *vs.* usual care, in a large referral center-of-excellence hospital.[3] At baseline in 2019, proper prophylaxis in medical and surgical patients was applied in 23 %; in the intervention group in 2020, the rate rose to 35 %. In the standard care group, the rate rose to just 27 %. Even with an average length of stay of just 8 days, there was an impact on inpatient-diagnosed VTE before discharge: a rate of 1 % in the intervention group that used prophylaxis in 35 % of patients, compared to an inpatient VTE rate of 2 % with standard care and 27 % prophylaxis use. While not statistically significant ($P = 0.18$) in this small pilot study at one medical center, these data foreshadow the patient benefit to be gained as a very large country's inpatient centers focus on preventing VTE and its complications.[3]

There is increasing interest in diagnosing, not missing, PE as the cause of dyspnea, syncope and near-syncope, and vague chest discomfort, reflected in Emergency Department physicians promoting their own interests in the disease. The same is occurring in cardiologists, interventional radiologists, hematologists, general internists, clinical pharmacists, and of course pulmonary and ICU physicians. The heightened awareness, interest, and involvement of so many different hospital staff members makes failure to consider PE in patients far less likely. However, there can be negative consequences also, discussed below.

Treatment of PE has become protocolized, uniform, in many health systems, which can have the benefit of guiding inexperienced clinicians into a "consensus" treatment path rather than fostering opportunity for odd personal treatment preferences and mistakes in calculating dosages. But here also can be negative consequences, since patient care must often be individualized. Also, some health professionals simply know more than those determining the protocol, and input of the former may be pushed aside and their treatment plans for individuals challenged or even rejected.

Recognition has become wider that some patients will not recover fully after PE treatment and should be followed longer-term for repairable impairments. While previously patients were generally divided into 3 groups, full recovery, partial recovery, and chronic thromboembolic pulmonary hypertension (now often called CTEPH), the criteria for diagnosing CTEPH have changed somewhat, with a mean pulmonary artery pressure (mPAP) of 20 mm Hg replacing 25 mm Hg, and pulmonary vascular resistance (PVR) criterion reduced to 2.0 Wood units, resulting in many more patients being diagnosed with CTEPH.[4] Also, multiple physician groups are proposing their own favored approach to the partial-recovery group, and pharma companies are eager to promote and have their drugs intervene in the enlarging group, which may benefit some patients and stop ongoing impairment. Procedures are also being further developed and refined to alleviate some of the pulmonary hypertension that results in patient dyspnea.

Last, a wide spectrum of new treatments to benefit patients with PE are being explored. These include drugs: using low molecular weight heparin (LMWH) by continuous iv infusion rather than subcutaneous (sc) depot dosing with its accompanying unpredictable bioavailability, new anticoagulants that focus on factor XI/XIa, and new drug approaches to acute clot lysis. Each seeks to achieve the promise of reducing thrombus with lower bleeding risk. New catheter-based techniques with good convenience and reduced bleeding risk, which might reduce the risks of residual clot and only partial recovery from PE, are also being explored. There is more than one product involved in each initiative, improving the chance that even if one should fail due to unsuitability or human error, other candidates may succeed. Some of these approaches are described below.

Thus, there are many aspects of PE that are going right!

What's going wrong with pulmonary embolism

While heightened suspicion for and diagnostic recognition of PE is generally satisfactory, journals, medical meetings, and the professional societies that sponsor them seem to be regularly pushed to "innovate" with new approaches, not proven superior, that may delay and confuse. "Overburdening physicians with algorithms that drive clinical decision-making is becoming more and more customary", wrote two PE experts in a *JAMA* editorial[5] about a new many-step PE diagnostic algorithm JAMA was excited to publish in December 2021 but performed no better than usual clinical evaluation followed by age-adjusted D-dimer evaluation, before diagnostic imaging, if warranted.

A setting where algorithms can unnecessarily complicate and even negatively impact clinical care occurs when electronic medical record or other hospital policies require adherence to obtaining a "score" before providing PE/DVT prophylaxis. Scores with names such as Geneva, Padua, and Caprini, can serve the good purpose of reminding clinicians of their inpatients' PE/DVT risk. In some settings where prophylaxis is not understood as necessary, or a patient is at high bleeding risk, such scores can be helpful in decision-making. But the alternative approach we find superior, the approach many hospitals require regarding vaccinating staff as influenza season approaches, is "do it unless contraindicated". Prophylaxis very rarely causes harm unless a patient is prone to bleeding or heparin-induced thrombocytopenia (HIT). The impression that instead following a generalized score leading to a decision of "prophylaxis not needed" is a superior approach has not been tested. Inpatient PE/DVT prophylaxis is inexpensive and thoughtful consideration in each patient of prophylaxis unless contraindicated, which is the sort of patient-focused care to which all physicians should aspire.

Another innovation of dubious value in settings where PE expertise already exists is the "PERT", the Pulmonary Embolism Response Team. Whereas a single noninvasive cardiology consultant or emergency physician can decide whether to invite an interventional cardiologist to intervene in a patient with acute coronary syndrome, somehow it has been declared to require "emergency medicine physicians, cardiologists, pulmonologists, hematologists, interventional radiologists, pharmacists, acute medicine physicians, vascular medicine physicians, vascular surgeons, cardiac surgeons and critical care physicians"[6] to serve on a PERT to properly manage a sick acute PE patient. However, the expertise assembled at a particular time will depend upon who is on-call at the time and clearly cannot be equivalent at all times. Imposing this type of decision-making upon already PE-capable consultants can delay and overly complicate patient management when evidence, about catheter interventions for example, remains unclear. Involving more people unavoidably involves their biases and financial interests, which do not necessarily benefit the sick PE patient. PERT began at the Massachusetts General Hospital, a Harvard University hospital, only in 2012. It is odd that this hospital did not think it was handling acute PE at the highest possible level with so much consultation available that it was made mandatory with PERT. But for some hospitals without or with limited PE expertise, PERT can of course be useful in some patients, as described just above.

Older practitioners know that, in the past, treatment of acute suspected or proven PE or DVT was with weight-adjusted continuously

infused unfractionated heparin (UFH) because the resulting anticoagulant level in blood was patient weight dependent and short-lived unless maintained by constant infusion. It was also shown that ensuring the anticoagulant level attained the therapeutic threshold more quickly improved clinical outcome. This report[7] compared different iv and sc UFH fixed-dose regimens, without considering patients, measuring aPTT, and used 24 h as a convenient cut-off for exceeding or failing to exceed the desired aPTT boundary. Whatever the initial bolus of UFH used, rapid titration to exceed the lower aPTT boundary resulted in significantly fewer recurrences. This approach was also proven to provide superior protection to standard care at the time.[8]

Weight-adjusted sc UFH prophylaxis was never tested; 5000 U sc every 12 or 8 h was compared to nothing or placebo. Similarly, PE prophylaxis is now often implemented with a once daily fixed, not weight-adjusted, sc dose of a LMWH, or sometimes twice or three times daily not weight-adjusted UFH sc dose if renal function is impaired, since LMWH elimination is nearly solely renal. Fixed-dose sc UFH was long ago proven superior to placebo for PE/DVT prevention in surgical patients. The fixed-dose once-daily LMWH regimen arose from clinical trials decades ago comparing with placebo[9] or UFH given more frequently, e.g., twice daily. What many modern practitioners do not know is that LMWH anticoagulant target peak blood levels for prophylaxis are in the range of 0.20–0.40 anti-Xa U/ml,[10] approximately 4 h after sc injection. But with once daily dosing, those levels often drop below therapeutic and become undetectable long before 24 h elapse. Moreover, without being weight-based, it ensures inadequate levels for much of the 24-hour period for obese patients and higher risk of bleeding for lean patients with a bleeding risk factor.

LMWH sc once-daily dosing and fixed dosing regardless of patient weight are less than scientific and jeopardize effective prophylaxis especially in high-risk patients, those with trauma, in ICU, and postoperative. Many published studies have shown this for different LMWHs. Enoxaparin 40 mg (4000 U) injected the evening before surgery showed peak anti-Xa blood levels 3–5 h later from 0.10 to 0.55 U/ml, with the lowest levels in patients with highest weight.[11] Forty mg of a different LMWH showed peak anti-Xa levels from 0.28 to 0.13 U/ml in patients weighing 50 kg and 104 kg respectively, but 50 U/kg of the same LMWH provided peak anti-Xa levels of 0.18 to 0.20 U/ml for patients weighing 55 and 90 kg, respectively. These results, repeated for multiple LMWHs, prove the reliability of bioavailability for LMWH prophylaxis dosed sc by weight during normal hemodynamics.[12]

Published LMWH data long ago showed blood levels fall below measurable levels during many hours of the dosing interval when administered once daily sc for prophylaxis.[12,13] In healthy volunteers with normal kidney function, when receiving a fixed dose of 40 mg enoxaparin sc, anti-Xa levels fall below 0.10 U/ml long before 24 h elapse depending upon patient weight. Even when the LMWH tinzaparin, dosed by patient weight, is given to healthy volunteers at the approved dose of 75 U/kg once daily, “normal-weight” participants’ mean anti-Xa level dropped below 0.10 U/ml at 10 h, and that of “heavy-weight” participants at 13 h. For the remainder of the 24 h period, there was little to no bioavailable prophylactic anticoagulant present.[14]

Furthermore, with once-daily fixed dose sc LMWH, in addition to subtherapeutic blood levels worsening with increasing patient weight and beyond 10–16 h in patients at thrombosis risk, ICU patients have been shown to have highly unpredictable bioavailability. ICU patients have unpredictable perfusion of their subcutaneous tissue. The subcutaneous anticoagulant, entering capillaries and lymphatics, often finds increased intrathoracic pressure from continuous positive airway pressure (CPAP) or positive end expiratory pressure (PEEP) impairing venous and thoracic duct return to the right heart. In 2002, experts in the Netherlands had shown that average bioavailability of sc fixed-dose LMWH is far reduced in ICU patients receiving vasopressor.[15] In ward patients, the mean anti-Xa peak blood level at 4 h was 0.30 U/ml, with 16 % of patients (1 SD) having levels below 0.20 U/ml. For patients in ICU receiving vasopressor, mean anti-Xa peak blood level at 4 h was 0.08 U/ml, with 16 % of patients (1 SD) having levels below 0.02 U/ml. Moreover, for ICU patients not receiving vasopressor, although the 4 h mean level was similar to the ward level, 0.26 U/ml, 16 % of patients (1 SD) had levels below 0.14 U/ml. The variability of bioavailability of sc LMWH in ICU patients, including those not receiving vasopressor, was enormous.

Recently, Belgian ICU physicians studied blood anticoagulant levels in ICU patients receiving once-daily, fixed (not weight-adjusted) sc LMWH prophylaxis, adjusted for kidney function, and compared with the pharmacokinetic effect of a 4-h LMWH infusion.[16] These modern results confirm very unpredictable bioavailability. In the new study from Belgium, a re-plotting of patient individual data from ICU patients receiving no vasopressor once again showed the unpredictable bioavailability in vasopressor’s absence in a fully modern ICU. In this study, for the group of patients randomized to sc administration, 15 patients receiving vasopressor, 15 not, the mean peak anti-Xa level 4 h after injection was 0.20 U/ml. But 16 % (1 SD) had levels of 0.10 anti-Xa U/ml or below, and prophylaxis blood levels decreased from there over the remaining 20 h before the next injection.[16]

While some clinicians might point to average blood levels and those within 1 standard deviation (SD) as satisfactory, it is important to remember that in hospital medicine, we treat individual patients, rather than averages. Cardiologists choose coronary artery stent diameters based on a specific lesion diameter. ICU physicians titrate respiratory rate, tidal volume, vasopressor, heart rate inhibitor drug, and insulin infusions based on the parameters of the patient in front of them. Having 50 % of patients above or below the mean value and having 16 % of patients above 1 SD and 16 % below, particularly if the SDs are wide, should not be acceptable if the treatment can be easily improved, such as by adjusting for weight and more frequent dosing.

This is of special and greatest concern in high-risk patients, such as those immobilized by trauma and those in the ICU. In the USA, trauma ICU care has already embraced sc LMWH pharmacokinetic information regarding duration of action and patient weight dependence. Trauma experts now recommend dosing by weight class (30 mg q 12 h for 50–60 kg, 40 mg q 12 h for 61–99 kg, 50 mg q 12 h for ≥100 kg), checking anti-Xa levels to ensure peak values of 0.2–0.4 anti-Xa U/ml, a level intended to intensively reduce PE/DVT risk in trauma patients for whom blood loss may already be an established fact.[17,18] With traumatic brain injury, the approach is more cautious.

As mentioned, VTE treatment for hospitalized patients, whether by UFH, LMWH, or fondaparinux, iv (UFH or rarely LMWH) or sc (LMWH and fondaparinux), is always dosed by weight or weight category. Sc LMWH PE treatment is usually, but not always, dosed q 12 h. Before testing in PE patients, the LMWH tinzaparin was tested at 175 anti-Xa U q 24 h and found noninferior to iv heparin for DVT,[19] which does not require urgent effective anticoagulation. When once-daily weight-based-dosed sc tinzaparin treatment of PE was found noninferior to UFH treatment later in a clinical trial, 50 % of tinzaparin patients had at least 18 h of iv UFH first (95 % CI was up to 24 h).[20] Recent pharmacokinetic studies during coronavirus disease 2019 (COVID-19) in a European ICU of twice-daily weight- and renal function-adjusted treatment-intended LMWH showed, after 2 days of sc dosing every 12 h (4 doses), that a quarter of patients had blood anti-Xa anticoagulant levels much higher than necessary, risking bleeding, and 20 % had anti-Xa blood levels subtherapeutic by 8–9 h after sc injection, 3–4 h before the next dose was due.[21] Personally inspecting the figure depicting blood anti-Xa levels in these modern ICU patients in this open-access publication is enlightening for physicians considering future sc anticoagulant treatment in ICU patients.

As distressing as this information is, equally distressing is to see it dismissed by alleged ICU experts stating, “Risks and benefits of dosing LMWH according to drug levels have not been studied”.[22] Of course they have,[18,23-27] as have drug levels of UFH before them. In 1983, the *New England Journal of Medicine* published a study of dosing UFH by adjusting doses to reach protocol-required aPTTs *vs.* fixed dosing for prophylaxis

in high-VTE-risk hip replacement patients and found efficacy superiority, without increased bleeding, when the dosing was adjusted to raise the aPTT to the target, 31.5–36 s.[23] Superior efficacy of having the aPTT reach a therapeutic level, rather than be subtherapeutic, was likewise proven decades ago in a study described above.[8] Physicians caring for patients must remain aware that not everything printed in a prominent medical journal is true.

For the medical emergency of acute PE treatment, iv UFH, iv LMWH or another anticoagulant if HIT forbids heparin use and the blood level can be monitored, is the proper treatment to rapidly achieve an anticoagulant effect that can be measured and adjusted if necessary. There are studies, case series, and case reports describing iv LMWH use.[20-22,28] Once the initial dosing is complete, an entirely stable patient, with normal blood pressure, heart rate, urine output, and without findings of right ventricular compromise (elevated troponin or brain natriuretic peptide [BNP], enlarged right ventricle on computed tomography [CT] scan or echocardiogram, reflux of upper extremity-injected contrast into the inferior vena cava by high pressure in the right atrium) can be transitioned to sc LMWH or even one of the tested direct oral anticoagulants with regulatory approval, rivaroxaban with food twice daily or apixaban twice daily. But it is the rare patient who will meet these stringent requirements early—for the majority of patients, continued iv anticoagulant with blood level monitoring is the safest course until true hemodynamic normality supervenes.

What's new with pulmonary embolism

There are exciting developments in treatment and prevention of PE. ICU clinician investigators are studying how to administer prophylaxis with a weight-based bolus followed by constant infusion of weight-based LMWH to provide safe but likely highly effective anticoagulant blood levels. With anti-Xa levels measurements available to these physicians, they can also do the same, in time, for LMWH treatment of PE. The advantage of LMWH over UFH in these patients is reduced risk of HIT, a concern with prolonged heparin dosing such as prophylaxis with long duration ICU stay. But for so many hospitals without anti-Xa blood level results readily available, learning how to dose prophylaxis with iv UFH by bolus and continuous infusion is an ongoing and important unfulfilled need.

For acute PE treatment in patients with marked renal insufficiency, the LMWH dose is halved or UFH is used instead. Weight-based continuous intravenous LMWH after a bolus is a promising way to relieve the large and important bioavailability problems of LMWH dosed sc as it was in its first protocols >30 years ago, in patients who had already received many hours of carefully titrated UFH.

Another very promising advance is suction thrombectomy. Using a catheter placed sequentially in each pulmonary artery hilum, strong negative pressure is then briefly applied to suck out multiple clots and accompanying blood.[29] After pushing the blood through a sterile filter that retains the clots, the sterile blood is then sterilely re-infused and the procedure is repeated. In this approach, no targeting of clot is routinely needed because clot that responds to suction will be mobilized into the catheter from its location despite right ventricular systole. There is no infusion of thrombolytic drug that risks local or distant, such as central nervous system hemorrhage. The catheters are made with no abrasive surface that could injure the pulmonary artery. After approximately 60 min of total intervention, including suction on one hilum, then the other, the catheter is withdrawn.

In contrast, catheters infusing thrombolytic drugs locally are left in place for hours near the pulmonary artery hilum or both hila for bilateral clots. A recent randomized clinical trial compared local thrombolytic infusion to local thrombolytic infusion augmented by a catheter that also delivered ultrasound waves. In each group, the catheters were in place approximately 14 h. Patients were moved to the ICU after catheter placement and alteplase infusion start in the interventional radiology department. An average of 20 mg total alteplase was infused in each treatment group. The outcomes were similar between the two group, with no superiority shown. Both reduced the thrombus score revealed by CT pulmonary angiogram after the procedure, the primary outcome, by a similar amount. Neither was associated with excess bleeding.[30]

We need to discern whether and to what extent suction thrombectomy's benefit or catheter-directed lysis is superior to careful and adequate patient anticoagulation with supportive care. But the ongoing clinical trials will make that decision difficult, because they administer sc LMWH as control arm anticoagulation, perhaps even once daily, which can easily underdose, promoting treatment failure, severe critical illness, and death, and easily overdose in these intermediate and high-intermediate risk patients, promoting bleeding risk. Measuring anticoagulant levels to ensure the control group patients are properly anticoagulated is not in the protocols, though measurements and adjustments were a requirement of the excellent original PEITHO study comparing anticoagulant to thrombolytic treatment. The control treatment in these studies, without measuring anti-Xa blood levels in the control group patients while giving iv UFH to the suction thrombectomy or catheter-directed thrombolysis patients, cannot help inform us whether the newer treatments are superior to proper anticoagulation and supportive treatment.

Yet another approach to DVT and PE seeks to lyse the clot *in situ* with theorized lower risk than traditional thrombolytic drugs like tissue plasminogen activator (r-tPA) (alteplase) or tenecteplase. These traditional lytic drugs can activate plasminogen throughout the body, even when intentionally administered *in situ* through a catheter, as described above, at the lowest possible dose. The most feared consequence is bleeding at an occult site in the brain, where studies in apparently normal persons have shown an astonishingly high prevalence of silent brain microbleeds, 20 %, in apparently healthy persons over age 60 years, 33 % for those over age 80 years.[31] Activating plasminogen is intended to dissolve a lung or leg clot, leading to dissolving an occult brain clot and intracerebral hemorrhage is the risk with traditional lytic drugs. A new approach instead uses an inhibiting antibody to alpha-2 antiplasmin. Alpha-2 antiplasmin, made by the liver, binds to fibrin clots on their lysine amino acids, blocking plasmin's sole method for lysis of the clot, at lysine residues. The hope is that inhibiting this inhibition of circulating plasmin with a manufactured antibody at lower or higher dose, compared to placebo, will allow lysis of the leg, lung, or coronary artery clot with a reduced risk of distant brain occult microbleeds.

Another anticoagulant approach uses different approaches to inhibiting factor XI or XIa, activated factor XI, as anticoagulant therapy intended to confer lower bleeding risk. Factor XI propagates clot in the lumen by the "intrinsic pathway". Persons born with factor XI deficiency do not experience excessive bleeding. There are small molecule and other inhibiting approaches being tried in clinical studies. How well these will work in the total absence of even low, prophylaxis-type levels of conventional anticoagulant is uncertain.

Last, with regard to preventing post-PE complications: This is being studied but in a roundabout way. Prolonged *vs.* usual duration full anticoagulation after PE for high-risk patients is an intuitive approach but the outcome, CTEPH, is relatively rare (about 4 % two years after a first symptomatic PE)[32] that there is little interest in starting such a study. Genetic analyses of patients with CTEPH are beginning to identify what patients may be at risk, but what to do to reduce a CTEPH outcome is uncertain. The treatment of CTEPH is mostly limited to specialized centers, where surgical pulmonary thromboendarterectomy improves patient performance at acceptable risk. Some centers are increasingly employing pulmonary artery catheter angioplasty, a delicate procedure that can open pulmonary artery narrowings and webs without surgery, most often after a series of catheter angioplasty sessions.

None of the uncertainties regarding preventing lasting complications from PE have prevented ambitious physicians from establishing consensus groups dictating a comprehensive guide for optimal follow-up after

PE. Included are how and when to resume sporting activities, including numerical ranges in minutes listed for moderate-intensity and for vigorous sporting activity.[33] Unfortunately, supportive evidence for benefit from adhering to these specified regimens is not available.

Conclusions

There is much going well with PE prevention and treatment, too much going wrong, and there are promising developments to help our patients now and in the future. This field would be helped by clinicians incorporating pharmacokinetic evidence in their anticoagulant use and by clinician investigators adhering to study designs of integrity that will change practice, have explanatory power, or both. How the future unfolds will determine if we can improve relief of patients suffering PE and prevent disability and postpone death in them and those at PE risk.

CRediT authorship contribution statement

Bruce L Davidson: Writing–review & editing, Writing–original draft, Visualization. **Nicolas De Schryver:** Writing–review & editing, Writing–original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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