



WHY WE NEED A MULTI-DISCIPLINARY TEAM FOR THE MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE)

Case Presentation: A 55-year-old gentleman recently referred to my care from the Emergency Department with pleuritic chest pains after a long-haul flight. He was diagnosed with bilateral sub-segmental pulmonary arterial emboli. Echocardiography excluded right ventricular dysfunction. Past medical history was remarkable for an arterial thrombotic stroke manifesting as a right hemi-paresis in 2012, from which he had made an excellent functional recovery. He was compliant to aspirin, lipid-lowering and anti-hypertensive therapy. He was also diagnosed at that time with essential thrombocythemia; platelet counts remained normal with pegylated interferon. Duplex venous scanning of both lower limbs reported an extensive thrombus burden extending above the knee on the left side. Vascular surgical input was requested to determine if urgent mechanical catheter-based thrombectomy would be of benefit. Essential thrombocythemia is a rare haematological malignancy with overall good survival but predisposes to moderate to high risk of developing arterial or venous thrombosis lifelong. Discussion with his haematologist affirmed the decision for lifelong anti-coagulation. Patient education on the risks of future travel, the risk benefit ratio and surveillance of indefinite anti-coagulation is now necessary. This case illustrates the complexity of venous thrombo-embolic disease and why a multi-disciplinary approach is integral to optimising his short term and longer-term outcomes.

Venous thromboembolism (VTE) constitutes the 3rd leading cardiovascular diagnosis after myocardial infarction and strokes. The effective management of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) requires early confirmation of clinically suspected disease, which is reliant on both clinicians and the public having a high awareness of these disorders.

Contemporary gold standard management of acute VTE events, especially in the case of hemodynamic instability, should involve a pulmonary embolism response team (PERT). The PERT mobilizes expertise from various disciplines to evaluate the risks and benefits of various therapeutic options and to determine the optimal treatment choice. For instance, the immediate decision to administer thrombolysis or use mechanical thrombectomy is strongly influenced by co-morbidity concerns to be considered. The optimal structure of the PERT will depend on the available expertise at the institution and could comprise emergency medicine, interventional and noninterventional cardiology, interventional radiology, vascular surgery, hematology, and pharmacy, Figure 1. Each member has a crucial role in the PERT. The initial steps in acute PE care, such as diagnosis and risk stratification, are often managed by emergency medicine specialists, although acute PE may also be diagnosed after a patient has been admitted. Then, either critical care, respiratory medicine or cardiology provide an initial PERT consultation and gather relevant patient information. Endovascular procedures, such as catheter embolectomy, if warranted, are usually provided by interventional cardiology or radiology or vascular surgery. The hematologist on the team can provide expertise in anticoagulation selection and, if appropriate, guide on duration

of treatment and conduct a thrombophilia evaluation, if indicated. Finally, a clinical pharmacist ensures that dosing of different drugs, such as thrombolytics and anticoagulants, are appropriate and adequate.



Figure. The composition of the Pulmonary Embolism Response Team (PERT)

Following in-hospital treatment, patients need close outpatient follow-up. The purpose of post-discharge anticoagulation is the prevention of recurrent thrombosis, embolization, and death, the risk of which is greatest in the first 3-6 months following the diagnosis. The important issues for outpatient management include monitoring the tolerability of the selected anticoagulant, hypercoagulability/malignancy screening, and surveillance for symptoms suggestive of chronic thromboembolic pulmonary hypertension. Cancer patients constitute a special high-risk group for VTE and recurrent VTE. This population has a four times higher risk of thrombosis compared to the general population. The need for thromboprophylaxis is evaluated by means of score systems, the Khorana risk score (KRS) being one of the most validated. Risk factors for VTE are previous VTE, distant metastasis, recent surgery, and antineoplastic therapy (anti-angiogenic therapy, immunotherapy, use of protein kinase inhibitors).

In summary, managing VTE is best managed using a multi-disciplinary approach because of its complex nature and the need for different specialists to collaborate at each stage on the diagnosis, acute and chronic treatment, prevention, patient education and long term care. This approach ensures that the patient receives the most comprehensive and individualized care possible.

QUIZ

Question 1:

What is the primary benefit of using pharmaco-mechanical catheter-directed thrombolysis (PCDT) in the treatment of iliofemoral deep vein thrombosis (DVT)?

- A) It reduces the risk of pulmonary embolism
- B) It is more cost-effective than anticoagulant therapy
- C) It improves quality of life and reduces the severity of post-thrombotic syndrome
- D) It eliminates the need for anticoagulant therapy

Question 2:

According to the 2019 European Society of Cardiology (ESC) Guidelines, which factor is NOT used in the risk stratification of patients with pulmonary embolism?

- A) Hemodynamic data
- B) Imaging analysis of the right ventricle
- C) Status of cardiac biomarkers
- D) Patient's age and gender

Answer is available on our website:

<http://www.harleystreet.sg/quiz - answers/medbulletin-dec-2023/>

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THE HARLEY STREET
HEART & VASCULAR CENTRE

INTRODUCTION

Greetings from the Harley Street Heart and Vascular Centre! To keep our primary care colleagues up-to-date with the latest advances in the management of patients with cardiovascular diseases, we have prepared four interesting articles written by our Harley Street Specialists. The theme of the current newsletter is on thromboembolism which can be challenging for clinicians to both diagnose and manage optimally.

Dr Pinakin Parekh gives an overview of the diagnosis and management of acute pulmonary embolism. His article outlines what clinicians should be looking out for, what early assessment should involve and and cites the current European Society of Cardiology guidelines. Dr Reginald Liew provides a follow-up article on the same theme by giving an update on the current use of direct oral anticoagulants in the treatment of venous thromboembolism. Dr Michael MacDonald's article is on the less well understood condition of chronic thromboembolic pulmonary hypertension and right heart failure, which can sometimes occur following acute pulmonary embolism and lead to significant morbidity and mortality. Finally, Dr Rohit Khurana describes and interesting case of a patient presenting with an acute pulmonary embolism and highlights why a multi-disciplinary approach, including emergency physicians, vascular specialists, haematologists as well as cardiologists, is sometimes required for optimal management of patients, both in the acute and chronic phases.

As usual, the newsletter ends with a short quiz aimed to test your clinical judgement and acumen. The answer to the quiz will be posted on our website (<https://www.harleystreet.sg/medbulletin/>).

We hope these articles will be useful to your daily practice and help challenge and improve your management of patients with cardiovascular disease. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

From The Harley Street Heart and Vascular Centre



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PULMONARY EMBOLISM – DIFFERENTIATING THE STABLE VERSUS UNSTABLE PATIENT

Once pulmonary embolism has been diagnosed in a patient, the key next steps are to determine the severity of its presentation. This impacts decision making with regards to patient disposition (ambulatory management, general ward admission or high dependency/intensive care unit monitoring) as well as reperfusion therapy consideration beyond just anticoagulation. Reperfusion therapies included systemic thrombolysis, catheter directed therapies (local thrombolysis vs mechanical embolectomy) or surgical embolectomy.

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA ^b	Elevated cardiac troponin levels ^c
High		+	(+) ^d	+	(+)
Intermediate	Intermediate–high	–	++	+	+
	Intermediate–low	–	++	One (or none) positive	
Low		–	–	–	Assessment optional; if assessed, negative

Figure 1.

The 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of acute pulmonary embolism provides a structured algorithm in risk stratifying patients (Figure 1). Patients are categorized into 4 groups based on hemodynamic data, imaging analysis of the right ventricle and the status of cardiac biomarkers. They are classified as high risk, intermediate high risk, intermediate low risk and low risk.

Hemodynamic instability in the form of cardiac arrest or obstructive shock (systolic BP < 90mmHg or systolic BP drop > 40mmHg for > 15 minutes) not attributable to other reasons such as sepsis, hypovolemia, cardiac arrhythmia denotes a high-risk patient.

Right ventricular dilatation (RV to LV ratio > 1.0) on either a CT pulmonary angiogram or a transthoracic echocardiogram together with elevated cardiac biomarkers (Trop T, NT-pro BNP) prognosticates patients to the intermediate high risk category.

The simplified Pulmonary Embolism Severity Index (sPESI) is used to further dichotomise an intermediate low risk patient from a low risk patient (Figure 2).

Based on these profiles, treatment strategies can be appropriately tailored for patients (Figure 3). Intermediate high risk patients are a clinical challenge because they can deteriorate rapidly following an initial anticoagulation therapy. It is important to identify 'normotensive' shock subset of patients (e.g persistent tachycardia, increasing lactate) who are compensating in the early stages. Early reperfusion therapy would be a consideration for them.

Systemic thrombolysis is currently the default recommendation in high risk patients unless they have contraindications. There has been a great interest in catheter based therapies to avoid the risk associated with systemic thrombolysis and also to reduce the clot burden quicker. The current registry and cohort data have shown favorable outcomes and multiple randomized control trials are currently in progress to validate this new paradigm in pulmonary embolism management for unstable patients.

Criteria of the simplified Pulmonary Embolism Severity Index (sPESI), which enables estimation of the risk of 30-day mortality after diagnosis of PE (5)

Parameter	Score
– Age (if >80 years)	1
– Active tumor disease	1
– Chronic cardiopulmonary disease	1
– Heart rate >100/min	1
– Systolic blood pressure <100 mm Hg	1
– SaO ₂ <90%	1
0 points = low (30-day mortality 1%)	
≥ 1 point = high (30-day mortality 10.9%)	

Figure 2.

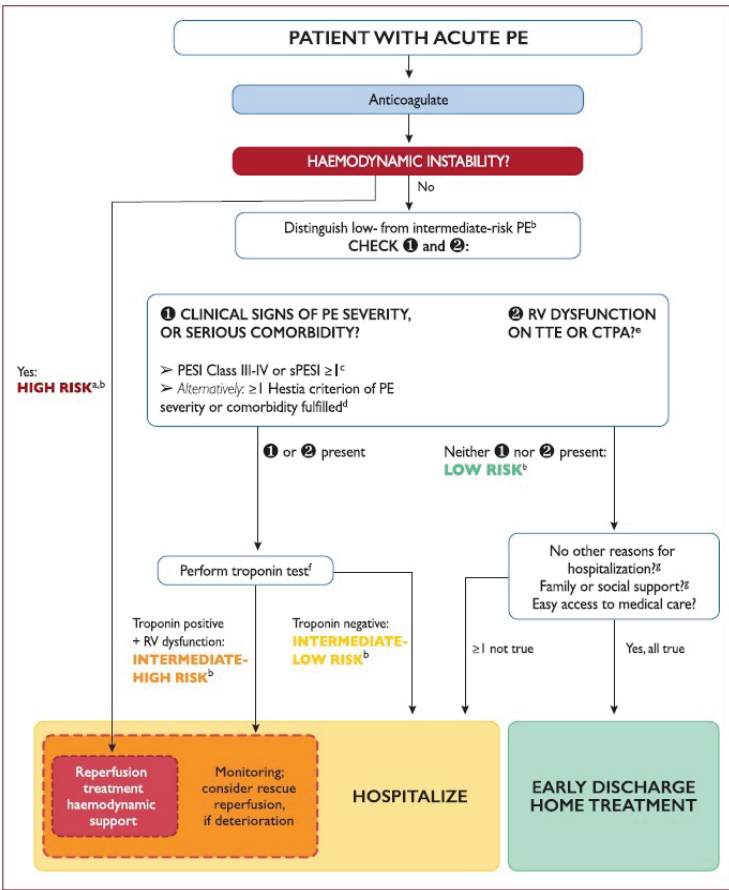


Figure 3.

UPDATES ON THE USE OF ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease affecting approximately 1-2 in 1,000 adults per year. The incidence of PE has increased significantly with the increasing use of computed tomography pulmonary angiography (CTPA) due to the widespread availability of the test and its diagnostic accuracy. Most pulmonary emboli are believed to originate from the proximal deep veins of the leg, even though only 25-50% of patients with PE have clinically evident DVT. Up to 50% of first-time pulmonary emboli are "unprovoked" or idiopathic- these patients have a high risk of VTE recurrence, estimated at 30% over 5 years [1]. VTE in the remaining patients tend to be associated with risk factors such as active malignancy, surgery (especially orthopedic), trauma, immobility, and estrogen use/pregnancy. This group has a very low risk of VTE recurrence (<3 per 100 patient-years) if the precipitating risk factor is resolved. For most patients, a combination of risk factors (both identifiable and unidentifiable) likely contributes to VTE events.

Anticoagulation is the mainstay of the treatment of acute VTE. Direct oral anticoagulants (DOAC), which are easier to use than conventional anticoagulants, have been compared with conventional anticoagulation in several randomized clinical trials including >11,000 patients with acute PE and shown to be as effective and at least as safe as conventional anticoagulation in patients with PE without hemodynamic compromise [1]. DOACs should not be used in pregnant or breastfeeding women or in those with significant renal or liver dysfunction or in patients with high-risk antiphospholipid syndrome.

How long should patients be treated with DOAC for VTE?

Patients with acute VTE should receive anticoagulant therapy for at least 3 months to reduce the risks of further embolization, thrombus extension and early recurrence of VTE. The decision to stop treatment at 3 months or continue indefinitely depends on whether the reduced risk of recurrent VTE with continued anticoagulation therapy outweighs the increased risk of bleeding. In patients with a clear provoking factor, the long-term risk of VTE recurrence is low and anticoagulation therapy can usually be stopped after 3 months. If the PE was very large and produced hemodynamic effects on the right heart or if the patient has persistent residual symptoms, treatment may be extended to 6 months. In patients with persistent provoking factors such as active cancer or a positive thrombophilia screen or who have had previous episodes of unprovoked VTE, the long-term risk of recurrence is high and anticoagulation therapy is recommended long term.

Which is the best DOAC to use?

It is still not known whether a particular DOAC is preferable for the treatment of VTE over the others. The choice of agent is guided by pharmacologic properties and patient characteristics and preferences (e.g., concomitant interacting medications and patient preference for once-daily or twice-daily medication). The benefits of using apixaban and rivaroxaban are that low-molecular-weight heparin (LMWH) does not need to be administered before starting, whereas LMWH should be administered for 5 to 10 days before the initiation of dabigatran or edoxaban (Figure). Ongoing randomized trials are assessing apixaban compared with rivaroxaban for the initial treatment in patients with VTE (NCT03266783) and various doses of these drugs for extended treatment of such patients (NCT03285438).

Is COVID-19 associated with an increased risk for venous thromboembolism (VTE)?

The incidence of VTE in COVID-19 patients depends on the patient population but appears to be high. In a meta-analysis of 66 observational studies, the overall prevalence of VTE in hospitalized patients varied between 9.5 to 40% (depending on whether a screening ultrasound scan was performed) and was approximately 22.7% in intensive-care-unit (ICU) patients [2]. As D-dimer levels tend to be increased in patients with COVID-19, they are less useful in the diagnosis of VTE. Clinical judgement and additional tests such as ultrasound leg scans and CTPA should be performed in patients in whom VTE is suspected.

As rivaroxaban and apixaban have a significant drug interaction with ritonavir, a component of the antiviral PAXLOVID, combined use of these drugs may increase the risk of bleeding. If patients are already on these drugs for other indications, e.g. atrial fibrillation, the dose may need to be lowered during the 5-day treatment period with PAXLOVID. Warfarin can be co-administered with PAXLOVID but patients require close monitoring during the treatment period, LMWH or unfractionated heparin in hospitalized critically ill patients is preferred because of the shorter half-life and fewer drug-drug interactions compared with DOACs.

Summary points:

- DOACs are the mainstay of treatment for patients with stable venous thromboembolism who can be managed in an outpatient setting and have been shown to be effective in major randomized clinical trials.
- Most patients should be treated with DOACs for 3-6 months, depending on the presence of any clear provoking factors
- COVID-19 infection is associated with a higher risk of VTE. Stable patients can be managed with DOAC or warfarin but potential interactions with PAXLOVID should be considered.

[1] Antithrombotic Management of Venous Thromboembolism: JACC Focus Seminar. Renner and Barnes. J Am Coll Cardiol. 2020 Nov, 76 (18) 2142–2154.

[2] Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Nopp et al. Res Pract Thromb Haemost. 2020 Oct 13;4(7):1178–1191.

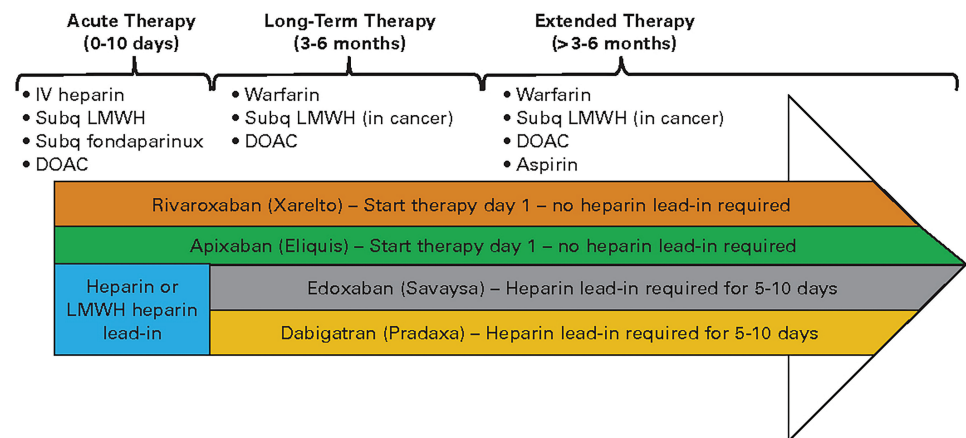
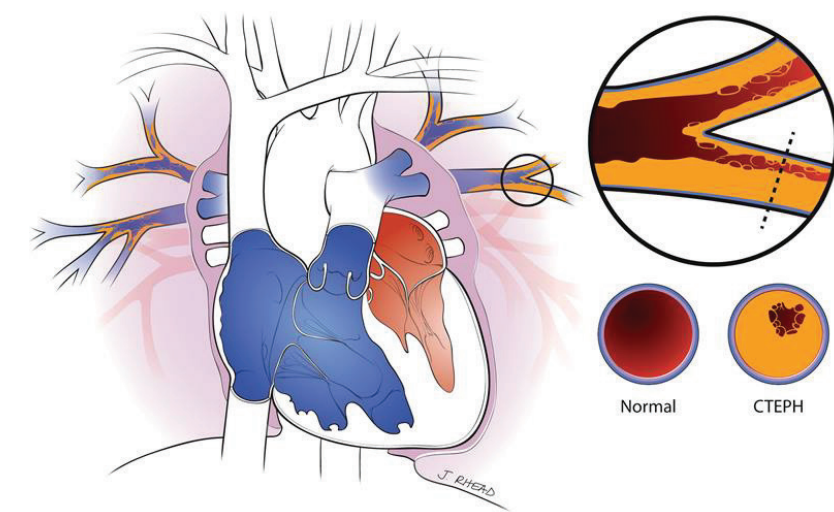


Figure- Initiation of Direct Oral anticoagulation in patients with venous thromboembolism

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION AND CHRONIC RIGHT HEART FAILURE



Early diagnosis and intervention are crucial to prevent the progression of right heart failure. Pulmonary endarterectomy (PEA) is considered the gold standard treatment for suitable candidates, significantly improving symptoms and survival rates. Balloon pulmonary angioplasty (BPA) and medical therapy with pulmonary arterial hypertension (PAH)-targeted drugs are alternative treatments for patients ineligible for PEA.

In conclusion, CTEPH is a complex disease that necessitates a multidisciplinary approach for optimal management. Early diagnosis and appropriate therapeutic interventions are crucial to halt the progression of right heart failure. The evolving landscape of medical and surgical treatments, along with an enhanced understanding of the disease mechanisms, offers hope for improved quality of life and better prognostic outcomes for patients with CTEPH and chronic right heart failure.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a debilitating condition characterized by the obstruction of pulmonary arteries due to unresolved thromboemboli, leading to an increase in pulmonary vascular resistance and ultimately, right heart failure. CTEPH is not an uncommon sequelae post pulmonary embolism (PE); the prevalence varies across studies with estimates ranging from 0.1% to as high as 5% or even 10% in cases of recurrent pulmonary embolism. Specifically, it's noted that about 1% to 5% of PE survivors may develop CTEPH, with certain studies suggesting a prevalence of 3-4% post acute PE, and up to 10% following recurrent pulmonary embolism. This article aims to shed light on the underlying pathophysiology linking CTEPH to chronic right heart failure, diagnostic challenges, and current therapeutic approaches.

The pathophysiology of CTEPH and chronic right heart failure is intertwined. Persistent obstruction of pulmonary arteries by thromboemboli elevates pulmonary artery pressure and resistance. The right ventricle compensates initially through hypertrophy, but with ongoing pressure overload, it eventually dilates and fails. The resultant right heart failure manifests with symptoms such as fatigue, exertional dyspnea, and peripheral edema.

Diagnosing CTEPH is challenging due to its nonspecific symptoms and requires a high index of suspicion, especially in patients with a history of venous thromboembolism (VTE). A combination of clinical examination, echocardiography, ventilation/perfusion (V/Q) scintigraphy, and right heart catheterization is often employed to confirm the diagnosis.

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