Diagnosis and Management of Pulmonary Embolism

Abstract

Pulmonary embolism (PE) is a condition characterised by an obstruction of the pulmonary arterial system by one or more emboli. Advanced clinical practitioners are often faced with ruling out a diagnosis of PE in patients with nonspecific symptoms such as dyspnoea and pleuritic chest pain, which can be fairly mild and therefore a diagnosis of PE easily missed. PE's can be a challenge to diagnose, especially in the elderly since it can be difficult to differentiate their symptoms from other less serious illnesses. Widely used scoring tools are helpful to score a patients probability of having a PE. The Wells' score is the most widely used pre-test clinical probability indicator of PE utilised in the UK, which scores the patient's probability of having a PE based on their risk factors. The D dimer test is a relatively simple investigation to rule out venous thromboembolism but can be raised for various reasons other than PE. Computed tomography pulmonary angiography (CTPA) is regarded as the gold standard imaging modality for investigation of acute PE but VQ scans be used as an alternative imaging technique for diagnosing PE in those where CTPA is contraindicated. Thrombolysis is underutilised in clinical practice due to the fear of adverse bleeding events. Patients without a massive or sub-massive PE are treated with anticoagulant therapy, usually commencing with subcutaneous low molecular weight heparin and switching over to a direct oral anticoagulant (DOACs). There has been a shift away from treatment with warfarin for prevention and treatment of VTE over the last decade.

Key words

Pulmonary embolism, VTE; DOACs; D Dimer; VQ scan; CTPA; warfarin; ACP's

Introduction

In the authors' experience, patients often present with non-specific symptoms which makes diagnosis of a PE difficult. In addition, the assessment and diagnosis of PE can vary across specialities and clinicians. In this case-based discussion the authors will critically analyse and discuss the evidence around diagnosis and management of PE.

Definition and symptoms

Pulmonary embolism is a condition characterised by an obstruction of the pulmonary arterial system by one or more emboli (National Institute of Health and Care Excellence (NICE), 2015). Advanced clinical practitioners are often faced with ruling out a diagnosis of PE in patients with nonspecific symptoms such as dyspnoea and pleuritic chest pain which can be fairly mild and therefore a diagnosis of PE easily missed (Geersing et al, 2012). In addition, patients may also present with symptoms such as haemoptysis, fever and tachycardia (European Lung Foundation, 2019). Pulmonary embolism can be a challenge to diagnose especially in the elderly since it can be difficult to differentiate their symptoms from other less serious illnesses (Ma and Wang et al, 2017).

Globally venous thromboembolism (VTE) causes a death every six seconds and is recognised as the number one cause of preventable deaths in hospitals (Thrombosis UK, 2019). In the United Kingdom (UK) up to 55 per cent of VTE cases occur during or following hospitalisation (Thrombosis UK, 2019).

Risk factors

Risk factors for pulmonary embolism include pregnancy, cancer, obesity, previous deep vein thrombosis or PE, varicose veins, recent surgery, hospitalisation and immobilisation or lower limb trauma within the previous twelve weeks (NICE, 2015). An assessment of the clinical probability of PE should be the first step in assessment of a patient suspected to have a PE. Family history of VTE has also been identified as a risk factor for patients developing VTE (Kelly et al, 2018). Therefore, patients with a family history of VTE presenting to the emergency department (ED) with symptoms such as chest pain and dyspnoea should be considered for VTE (Kelly et al, 2018).

Wells' scoring system

The Wells' score (Wells et al, 1997) is the most widely used pre-test clinical probability indicator of PE utilised in the UK which scores the patient's probability of having a PE based on their risk factors (Kline, 2017). The nine component Wells' score for deep vein thrombosis (DVT) was originally developed by Wells et al. in 1997 followed by a seven-component risk assessment score for PE in 1998. The two-tier score is divided into PE likely; a score of more than four points, or PE unlikely; a score of four points

or less (Kline, 2017, NICE, 2015). The Wells score has been shown to be accurate in predicting PE in hospitalised patients (Posadas-Martinez et al, 2013). Furthermore, the Wells score has been found to be more effective in predicting PE than the Geneva score, another risk assessment tool (Ma et al, 2016). However, this study was only a small single centre study and should therefore be replicated in a large multicentre environment to increase validity of the results. Regardless, the Wells score is utilised as the preferred method of predicting PE risk by clinicians in the UK.

D Dimer test

The D dimer test is a useful and relatively simple investigation to rule out venous thromboembolism. Fibrin D dimer is a degradation product of cross-linked fibrin which increases in the presence of VTE (Goldhaber and Bounameux, 2012). It is extremely sensitive of more than 95 per cent (Goldhaber and Bounameux, 2012). However, the D dimer is not specific enough to diagnose a PE in isolation since it can be elevated in a range of other conditions such as pregnancy, peripheral vascular disease, cancer and inflammatory diseases (BTS, 2003).

D dimer concentration also increases with age and therefore it's specificity for PE decreases (Douma et al., 2010). This has prompted numerous researchers to investigate whether an age adjusted D dimer should be used as a method to exclude PE rather than the standard cut off value of 500 used commonly in most laboratories in the UK (Kline, 2017, Douma et al., 2010). It has been suggested that an age adjusted D dimer would be more specific in diagnosing PE in older adults reducing the number of patients investigated for PE and potentially reducing costs and harm to patient's (Dutton et al., 2018). However, the exact age cut off figure has yet to be decided. There have been many studies that have measured D dimer assays as ten times the patients age, in those aged over 50 years which have supported the age adjusted D dimer as a safe method to exclude PE in those assessed as low or moderate probability (Penaloza et al 2012, Douma et al, 2010). In these studies, a higher percentage of older adults had a normal D dimer concentration when the adjusted D dimer assay was utilised, reducing the need for further harmful investigations. In contrast, a more recent study investigated whether five times the patients age would be a more appropriate target range (Dutton et al, 2018). However,

Sensitivity: Internal

this study was a small-scale study and therefore further large-scale randomised control trials are required to investigate this further.

The British Thoracic Society (BTS) (2003) guidelines advise that a D dimer should only be checked once probability of PE has been assessed. Furthermore, they suggest that the D dimer should not be performed in those with a high probability of PE, these patients should proceed straight to imaging (BTS, 2003). This is also supported by the American College of Physicians since a negative D dimer in a patient with a high probability of PE should not remove the need for imaging (McCarthy, 2015).

In the authors' experience, many clinicians will often request a D dimer for a patient without first assessing the Wells score and therefore risk assessing the patient for the likelihood of a PE. Obviously, the D dimer is often found to be elevated in older patients which prompts further investigation with imaging.

CTPA

Studies have shown that clinicians will often request computed tomography pulmonary angiography (CTPA) for patients deemed low risk, leading to exposure to hazardous radiation, increasing the risk of breast cancer especially in those aged under 40 years, in addition to the risk of contrast induced nephropathy (Ma and Wang et al, 2017, McCarthy, 2015; Takach Lapner and Kearon, 2013). According to Ma and Wang (2017) they established that only 10-15% of elderly patients were confirmed to have a PE following a CT scan, demonstrating the amount of unnecessary CTPA's performed especially on older people.

CTPA is regarded as the gold standard imaging modality for investigation of acute PE but should be undertaken after the assessment of probability of PE (BTS, 2003). Studies have shown that a combination of risk assessment, D dimer testing and CTPA is the most preferred diagnostic method for diagnosis of a pulmonary embolism (Gao et al, 2018). CTPA remains far superior to alternative imaging modalities such as the ventilation perfusion scan (VQ) as demonstrated in the literature (Anderson et al, 2007). Furthermore, CTPA has been shown to detect more pulmonary emboli than the VQ scans (Van Es et al, 2015).

VQ scans

VQ scans be used as an alternative imaging technique for diagnosing PE in those where CTPA is contraindicated such as those with chronic kidney disease, the elderly and pregnant ladies (Grippi and Elias et al, 2015). A VQ scan is a nuclear medicine scan that uses radioactive material to examine ventilation and perfusion of the lungs (Jong, 2018). During the first part of the scan radioactive material is inhaled and the ventilation of the lungs is analysed then during the second part radioactive material is injected into a vein and the perfusion of the lungs is studied (Jong, 2018).

VQ scan should not be used in those who are critically ill, obese or have underlying pulmonary disease since the test involves the patient lying supine and can take significantly longer than a CTPA (Jong, 2018). Furthermore, CTPA would be preferable to a VQ scan in a patient who may be suitable for an embolectomy as it allows mapping of the location and extent of clot burden in the pulmonary arteries, which a VQ scan does not (Jong, 2018). However, an additional limitation of the VQ scan is the high percentage of non-diagnostic tests which can be up to 50 per cent (Van Es et al, 2015). The clinician would then be faced with the decision whether to further investigate with a CTPA if PE was still clinically a possible diagnosis, increasing the risks to the patient and subjecting the patient to additional investigations. However, since the VQ scan actually exposes the patient to a significantly lower dose of radiation with no side effects is in its favour and therefore a safer alternative to CTPA is pregnancy and younger patients (Van Es et al, 2015).

The overuse of investigations such as D dimer testing and computed tomography scanning has been shown to not actually improve patient outcomes but rather increase the risk of harm to the patient and expense to the hospital trust and the NHS as an organisation (McCarthy, 2015, Raja et al, 2015). CTPA remains the gold standard imaging modality to diagnose a PE despite the risks. However, an assessment of those risks should be calculated by the clinician and a VQ scan considered if the risks deemed too high. This would be with the knowledge that a VQ scan has a lower specificity than the CTPA.

Sub-segmental PE

There appears to be a lack of consensus in clinical practice on whether a sub-segmental PE should be treated with anticogulants. It has been suggested that

treatment should only be commenced for sub-segmental PE if the patient has symptoms, an elevated D dimer, risk factors for VTE or previous VTE (Kline, 2017).

Thrombolysis

European guidelines advise that in clinically unstable patients presenting with a sub massive or massive PE on admission and, in the absence of any contraindications, thrombolysis is indicated (Konstantinides et al, 2014). Thrombolysis is however under utilised in clinical practice due to the fear of adverse bleeding events (Zuin et al, 2018). The optimal therapeutic window for administration of thrombolysis has not yet been established (Zuin et al, 2018). A review of the data from 374 patients over a seven-year period deemed high risk of PE concluded that thrombolysis administered within 8.5 hours from onset of symptoms may be associated with a reduction in the 30 day cardiovascular mortality in high risk patients. However due to the small population size, further large scale randomised controlled studies are required to evaluate this further (Zuin et al, 2018).

Anticoagulants

Patients without a massive or submassive PE are treated with anticoagulant therapy usually commencing with subcutaneous low molecular weight heparin and switching over to a direct oral anticoagulant (DOACs). There has been a shift away from treatment with warfarin for prevention and treatment of VTE over the last decade, which was previously the only oral anticoagulant approved for prevention and treatment of VTE (Rosovscky and Merli, 2017). In contrast to warfarin, the newer oral anticoagulants only inhibit one component in the clotting cascade. Dabigatran affects prothrombin, factor II and Edoxaban, Rivaroxaban and Apixaban affect factor Xa (Rosovsky and Merli, 2017). In addition to increased safety with the DOACS, the patient requires no monitoring with these drugs in comparison to warfarin which requires regular blood tests and monitoring of international normalised ratio (INR) level (Rosovsky and Merli, 2017). Warfarin also has many other limitations; it is has many interactions with other medications and foods and has a narrow therapeutic window which increases the risk of bleeding and can therefore cause catastrophic bleeding in patients who are not compliant with their treatment or in those patients whom maintaining a steady stable INR is difficult (e medicines compendium, 2017).

A meta-analysis which systematically reviewed ten clinical trials comparing the DOACs with standard VTE treatment of parenteral anticoagulants and vitamin K antagonists, found that DOACs were associated with less recurrent VTEs, fewer major and fatal bleeds and reduced mortality (Gomez-Outes et al, 2015).

However, the DOACS have an important limitation, warfarin can easily be reversed with vitamin K in the event of an overdose, but there is currently not a standard reversal agent for the DOACs available except for Dabigatran (NICE, 2019). The DOACs do have another advantage over warfarin in that they have a shorter half-life, as once the last dose has been taken the drug will be out of their circulation after 12 to 24 hours in contrast to warfarin which can take up to seven days meaning that they are generally a safer type of drug than warfarin (NICE, 2019). Unfortunately, since the DOACs are renally excreted they cannot be used in patients who have severe renal impairment (NICE, 2019).

Rivaroxaban tends to be the drug of choice for treatment and prevention of recurrent VTE in the authors local trust. Usually Rivaroxaban is administered orally at a dose of 15mg twice daily for 21 days then 20mg once daily thereafter (Einstein Investigators, 2010). This is supported by NICE guidance who recommend treatment of DVT and PE and prevention of recurrence of VTE with Rivaroxaban (NICE, 2013). The exact duration of treatment is not specified but must be continued for at least three months for those with transient risk factors such as trauma but potentially longer duration for those with more permanent risk factors or unprovoked DVT or PE (NICE, 2013). A large randomised control trial which was shown by the manufacturers to demonstrate the effectiveness of Rivaroxaban was the Einstein PE study (NICE, 2013). This study demonstrated that Rivaroxaban is as effective for prevention of recurrent DVT and PE compared with LMWH and warfarin therapy with the added advantage of significantly less bleeding (Einstein Investigators, 2012). This study demonstrates that a single DOAC was as effective as combination treatment with LMWH and warfarin which is likely to improve patient concordance and improve patient outcomes (Einstein Investigators, 2012). Rivaroxaban does have to be taken with food and as yet does not have a reversal agent but does still offer a safer alternative to warfarin (Rivovsky and Merli, 2017). There are potential reversal agents likely to be available in the future but these are currently still undergoing clinical trials.

The DOACS have not yet been compared to each other in clinical trials but clearly offer a safer and effective treatment and prevention of recurrent VTEs than previous conventional treatments such as warfarin. Rivaroxaban is the recommended DOAC to treat and prevent recurrence of VTE but further research in the long-term effects of Rivaroxaban are required (NICE, 2013).

VTE risk assessment

In addition to the assessment and management of patients presenting to hospital with symptoms of VTE another vital role of the advanced clinical practitioner is assessment and prevention of VTE in those patients admitted to hospital as an elective admission or with symptoms of another disease process. The authors have experience of completing these risk assessments and advanced clinical practitioners are often the role models in the medical team by ensuring these risk assessments are completed correctly and in a timely manner. NICE (2018a) advocate that all medical, surgical and trauma patients should have their VTE and bleeding risk assessed using a recognised national tool as soon as possible after admission to hospital. Furthermore, those patients assessed as at risk of VTE and not at increased risk of bleeding should be offered VTE prophylaxis (NICE, 2018a). If assessed as requiring pharmacological VTE prophylaxis then this should be administered within 14 hours of admission (NICE, 2018b).

NICE (2018b) also advocate reassessment if the patient's condition changes which in the authors experience is poorly performed. For example, a patient may present with a possible GI bleed and has been risk assessed that pharmacological VTE prophylaxis would not be appropriate. However, if that patient has later been found to not have a GI bleed and there is no other reason not to receive VTE prophylaxis, and they are not reassessed then they could potentially develop a hospital acquired VTE. Therefore, risk assessment is important on admission and reassessment if their condition changes. Although a mandatory requirement, VTE risk assessment can go uncompleted and may not be completed correctly. The National VTE risk assessment tool is recommended as the assessment tool to be used nationwide. However, there are concerns that this tool has not been evaluated against other tools to assess its efficacy and accuracy (NICE, 2018b). It is widely recognised that further research is needed in this area.

If patients are deemed too high risk of bleeding to receive pharmacological prophylaxis, they can be offered mechanical prophylaxis in the form of compression stockings, however, there needs to be further assessment of the patient before these can be applied (NICE, 2018b). Unfortunately, anti-embolism stockings cannot be offered to patients with peripheral arterial disease, local tissue damage, extensive oedema or peripheral neuropathy (NICE, 2018b). The decisions not to provide patient's with VTE prophylaxis must be clearly documented and explained to the patient (NICE, 2018b).

Advanced clinical practitioners are expected to autonomously clinically assess a patient admitted with non-specific symptoms such as pleuritic chest pain and dyspnoea. They should follow local and national guidance on assessing probability of PE, performing D dimer if indicated and then deciding if imaging is required. Assessment of patients with possible diagnosis of PE is often done poorly in practice and diagnosis can be difficult due to the often-non-specific symptoms patient's present with. Advanced clinical practitioners are best placed to promote the evidence-based practice and therefore carefully assess each patient and perform only the most appropriate and clinically indicated investigations. The authors are now confident in the processes to follow in diagnosing and managing patients suspected of, and diagnosed with a PE. However, they also recognise that due to the difficulty in diagnosis there may be times further advice from a senior colleague to ensure the correct management for the patient. There is a requirement to move away from subjecting patients to needless and invasive investigations which are not clinically indicated, can cause patients harm and increase costs to the NHS.

References

Anderson, D.R., Kahn, S.R., Rodger, M.A., Kovacs, M.J., Morris, T., Hirsch, A., Lang, E., Stiell, I., Kovacs, G., Dreyer, J., Dennie, C., Cartier, Y., Barnes, D., Burton, E., Pleasance, S., Skedgel, C., O'Rouke, K. and Wells, P.S. (2007) 'Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial', *JAMA,* 298(923), pp. 2743-2753. doi:10.1001/jama.298.23.2743

British Thoracic Society (BTS) (2003) *British Thoracic Society guidelines for the management of suspected acute pulmonary embolism.* Available at: https://www.brit-thoracic.org.uk (Accessed: 15 January 2019).

Douma, R.A., Le Gal, G., Sohne, M., Righini, M., Kamphuisen, P.W., Perrier, A., Kruip, M.J.H.A., Bounameux, H., Buller, H. R. and Roy, P.M. (2010) 'Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts*', British Medical Journal (BMJ),* 340(c1475), doi: https://doi.org/10.1136/bmj.c1475

Dutton, J., Dachsel, M. and Crane, R. (2018) 'Can the use of an age-adjusted D-dimer cut-off value help in our diagnosis of suspected pulmonary embolism?', *Clinical Medicine,* 18(4), pp. 293-296. doi: 10.7861/clinmedicine.18-4-293

Einstein Investigators. (2010) 'Oral Rivaroxaban for symptomatic venous thromboembolism', *The New England Journal of Medicine,* 363, pp. 2499-2510. doi:10.1056/NEJMoa1007903

Einstein PE Investigators. (2012) 'Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism,' *New England Journal of Medicine,* 366, pp. 1287-1297. doi:10.1056/NEJMoa1113572

E Medicines Compendium (EMC) (2017) *Warfarin 1mg tablets.* Available at: https://www.medicines.org.uk (Accessed: 20 February 2019).

European Lung Foundation (2019) *Pulmonary Vascular disease.* Available at: https://www.europeanlung.org (Accessed: 17 February 2019).

Gao, H., Liu, H. and Li, Y. (2018) 'Value of d dimer levels for the diagnosis of pulmonary embolism: An analysis of 32 cases with computed tomography pulmonary angiography', *Experimental and Therapeutic Medicine,* 16(2), pp. 1554-1560. https://doi.org/10.3892/etm.2018.6314

Geersing, G.J., Erkens, P.M.G., Lucassen, W.A.M., Buller, H.R., Cate, H., Hoes, A.W., Moons, K.G.M., Prins, M.H., Oudega, R., Van Weert, H.C.P.M. and Stoffers, H.E.J.H, (2012) 'Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study', *British Medical Journal (BMJ),* 345(e6564), doi: https://doi.org/10.1136/bmj.e6564

Goldhaber, S.Z. and Bounameux, H. (2012) 'Pulmonary embolism and deep vein thrombosis', *The Lancet,* 379, pp. 1835-1846. doi:10.1016/S0140- 6736(11)61904-1

Gomez-Outes, A., Lecumberri, R., Suarez-Gea, M.L., Terleira-Fernanadez, A.I., Monreal, M. and Vargas-Castrillon, E. (2015) 'Case Fatality Rates of Recurrent Thromboembolism and Bleeding in Patients Receiving Direct Oral Anticoagulants for the Initial and Extended Treatment of Venous Thromboembolism: A Systematic Review', *Journal of Cardiovascular Pharmacology and Therapeutics,* 20(5), pp. 490-500. https://doi.org/10.1177/1074248415575154

Grippi, M.A., Elias, J.A., Fishman, J.A., Kotloff, R.M., Pack, A.I. and Senior, R.M. (2015) *Fishman's Pulmonary Diseases and Disorders.* 5th edn. Volume One. USA: McGraw-Hill Education.

Jong, I. (2018) Inside Radiology. *VQ Scan.* Available at: https://www.insideradiology.com.au/vq-scan/ (Accessed: 20 February 2019).

Kelly, C., Agy, C., Carlson, M., Steenblik, J., Bledscoe, J., Hartsell, S. and Madsen, T. (2018) 'Family history of venous thromboembolism predicts the diagnosis of acute pulmonary embolism in the emergency department', *The American Journal of Emergency Medicine,* 36(9), pp.1550-1554. https://doi.org/10.1016/j.ajem.2018.01.023

Kline, J. A. (2017) 'Diagnosis and Exclusion of Pulmonary Embolism', *Thrombosis Research,* 163, pp. 207-220. https://doi.org/10.1016/j.thromres.2017.06.002

Konstantinidies, S.V., Torbicki, A., Agnelli, G., Danchin, N., Fitzmaurice, D., Galie, N., Gibbs, J.S., Huisman, M.V., Humbert, M., Kucher, N., Lang, I., Lankeit, M., Lekakis, J., Maack, C., Mayer, E., Meneveau, N., Perrier, A., Pruszczyk, P., Rasmussan, L.H., Schindler, T.H., Svitil, P., Vonk Noordegraaf, A., Zamorano, J.L., Zompatori, M. and Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). (2014) '2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism', *European Heart Journal,* 35(43), pp. 3069a-3069k. doi: 10.1093/eurheartj/ehu283

Ma,Y., Wang, Y., Liu, D., Ning, Z., An, M., Wu, Q. and Lin, Y. (2017) 'A safe strategy to rule out pulmonary embolism: The combination of the wells score and d-dimer test: One prospective study', *Thrombosis Research,* 156, pp. 160-162. doi:10.1016/j.thromres.2017.06.018

Ma, Y., Huang, J., Wang, Y., Wu, T., Cai, D., Liu, Y., Wu, Q., Hui, J. and Shi, Y. (2016) 'Comparison of the Wells score with the revised Geneva score for assessing pretest probability of pulmonary embolism in hospitalized elderly patients', *European Journal of Internal Medicine*, 36, pp. 18-19. https://doi.org/10.1016/j.ejim.2016.09.003

McCarthy, M. (2015) 'CT and D-dimer testing are overused in patients with suspected pulmonary embolism, US college says', *British Medical Journal (BMJ),* 351, doi: https://doi.org/10.1136/bmj.h5261

National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries. (2015) *Pulmonary embolism.* Available at: https://cks.nice.org.uk/pulmonary-embolism (Accessed: 6 January 2019).

National Institute for Health and Care Excellence (NICE) (2018a) *Rivaroxaban for treating pulmonary embolism) Quality Standard [QS3] Venous thromboembolism in adults: reducing the risk in hospital.* Available at: http://www.nice.org.uk (Accessed: 6 January 2019).

National Institute for Health and Care Excellence (NICE) (2013) *Rivaroxaban for treating pulmonary embolism and preventing recurrence of venous thromboembolism*. Available at: https://www.nice.org.uk (Accessed: 20 February 2019).

National Institute for Health and Care Excellence (NICE) (2018b) *Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.* Available at: http://www.nice.org.uk (Accessed: 6 January 2019).

National Institute for Health and Care Excellence (NICE) (2019) *Warfarin Sodium.* Available at: https://bnf.nice.org.uk/drug/warfarin-sodium.html (Accessed 20 February 2019).

Penaloza, A., Roy, P.M., Kline, J., Verschuren, F., Le Gal, G., Quentin-Georget, S., Delvau, N. and Thys, F. (2012) 'Performance of age-adjusted D-dimer cut-off to rule out pulmonary embolism', *Journal of Thrombosis and Haemostasis,* 10(7), pp. 1291-1296. **https://doi.org/10.1111/j.1538-7836.2012.04769.x**

Posadas-Martinez, M.L., Vazquez, F.J., Giunta, D.H., Waisman, G.D., Bernaldo De Quiros, F.G. and Gandara, E. (2013) 'Performance of the Wells score in patients with suspected pulmonary embolism during hospitalization: A delayed-type cross sectional study in a community hospital', *Thrombosis Research,* 133(2), pp. 177-181. https://doi.org/10.1016/j.thromres.2013.11.018

Raja, A.S., Greenberg, J.O., Qaseem, A., Denberg, T.D., Fitterman, N. and Schuur, J.D. (2015) 'Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines committee of the American College of Physicians', *Annals of International Medicine,* 163(9), pp.701-711. doi:10.7326/M14-1772.

Rosovsky, R. and Merli, G. (2017) 'Anticoagulation in Pulmonary Embolism: Update in the Age of Direct Oral Anticoagulants', *Techniques in Vascular and Interventional Radiology,* 20(3), pp. 141-151. https://doi.org/10.1053/j.tvir.2017.07.003

Takach Lapner, S. and Kearon, C. (2013) 'Diagnosis and management of pulmonary embolism', *British Medical Journal (BMJ),* 346. doi: https://doi.org/10.1136/bmj.f757

Thrombosis UK (2019) *Thrombosis Statistics.* Available at: https://www.thrombosisuk.org/thrombosis-statistics.php (Accessed: 17 February 2019).

Van Es, J., Douma, R.A., Hezemans, R.E.L., Peneloza, A., Motte, S., Erkens, P.G.M., Durian, M.F., Van Eck-Smit, B.L.F. and Kamphuisen, P.W. (2015) 'Accuracy of X-ray with perfusion scan in young patients with suspected pulmonary embolism', *Thrombosis Research,* 136(2), pp. 221-224. https://doi.org/10.1016/j.thromres.2015.05.018

Wells, P.S., Anderson, D.R., Bormanis, J., Guy, F., Mitchell, M., Gray, L., Clement, C., Robinson, K.S. and Lewandowski, B. (1997). 'Value of assessment of pretest probability of deep-vein thrombosis in clinical management', *The Lancet,* 350(9094), pp.1795-1798. doi: 10.1016/S0140-6736(97)08140-3

Wells, P.S., Ginsberg, J.S., Anderson, D.R., Kearon, C., Gent, M., Turpie, A.G., Bormanis, J., Weitz, J., Chamberlain, M., Bowie, D., Barnes, D. and Hirsh, J., (1998) 'Use of a clinical model for safe management of patients with suspected pulmonary embolism', *Annals of Internal Medicine,* 129(12), pp. 997–1005. doi: 10.7326/0003-4819-129-12-199812150-00002

Zuin, M., Rigatelli, G., Carraro, M., Pastore, G., Lanza, D., Zonzin, P., Zuliani, G. and Roncon, L. (2018) 'Systemic thrombolysis in haemodynamically unstable pulmonary embolism: The earlier the better?' *Thrombosis Research,* 173, pp. 117-123. https://doi.org/10.1016/j.thromres.2018.11.029