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EDITORIAL

A major leap in the diagnosis of pulmonary embolism

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Souhami's Textbook of Medicine states that '*The characteristic symptom of pulmonary embolism is sudden breathlessness. Lateral, usually basal pleuritic chest pain and haemoptysis, consisting of frank red blood without sputum, develop some time after the onset of breathlessness. In addition to respiratory symptoms, there may be pain or swelling of the leg, suggesting deep vein thrombosis. (...) The respiratory rate is usually raised and if infarction has taken place, there may be a pleural rub and a small pleural effusion. The most important cardiovascular sign is tachycardia. Within a few hours of pulmonary infarction fever is the rule*'.[1] Harrison's Principles of Internal Medicine is somewhat more cautious than the above-presented straightforward clinical presentation of pulmonary embolism.[2] The chapter on pulmonary embolism stresses that all of the mentioned symptoms and signs may occur, but that quite often the presentation can be highly atypical, with only one of the mentioned symptoms present, or that history and physical examination may be '*deceptively normal*' in a patient with pulmonary embolism. In fact, the notion that the clinical diagnosis of pulmonary embolism may be very difficult, and the confusion that may occur with many other clinical entities, such as myocardial infarction, pneumonia, pleuritis, or pericarditis, was already expounded decades ago in the clinical handbooks 'Bedside Medicine' by the famous Dutch internist Snapper and the 'Netherlands Textbook of Internal Medicine' by Formijne *et al.*[3,4] Indeed, most clinicians will appreciate that the manifestation of pulmonary embolism may be difficult, in some cases highly atypical, at times misleading, and sometimes leading to considerable confusion and delay of the proper diagnosis.

However, even if the clinical suspicion of pulmonary embolism has been properly raised, confirmation of this diagnosis may also pose some problems. Confirmation of a clinical suspicion of pulmonary embolism has indeed been found indispensable, as more than 70% of the patients with clinically suspected pulmonary embolism do not have this diagnosis and would be unnecessarily exposed to anticoagulant treatment if no additional accurate tests were done.[5] Accurate diagnostic tests have long been hampered by disadvantages, such as the invasiveness of the 'gold standard' test, i.e. pulmonary angiography, or limited availability, difficulty in interpretation and serious important inter-observer variability of other tests, such as perfusion scintigraphy. Recently, new diagnostic modalities for the diagnosis of pulmonary embolism have been introduced. First, spiral computed tomography has emerged as a relatively simple, generally accessible, and accurate test for the diagnosis of pulmonary embolism.[6] Secondly, measurement of plasma D-dimer levels have been shown to have a very high sensitivity for venous thrombotic disease (including pulmonary embolism).[7,8] This means that the negative predictive value of low levels of D-dimer for the absence of pulmonary embolism is strong, particularly if the pre-test likelihood of the diagnosis is low. Lastly, clinical decision guidelines, based on an incisive analysis of databases of signs and symptoms of large numbers of patients with and without pulmonary embolism, have been evaluated and were found to be able to discriminate between patients with a high, intermediate, and low risk of pulmonary embolism. The clinical decision guideline generally used is the Wells score, which identifies groups with a low risk of pulmonary embolism (3.4%), a moderate risk of pulmonary embolism (27.8%), and a high-risk group (78.4% pulmonary embolism).[9] A subsequent analysis revealed that dichotomisation of the groups (i.e. high risk or low risk) further increased the clinical utility of this score.[10]

The Dutch multicentre Christopher study group has recently combined these three new diagnostic modalities and the resulting management strategy was evaluated in a large clinical trial in patients with clinically suspected pulmonary embolism.[11] First, patients were classified as having low or high risk of pulmonary embolism based on the Wells score. In patients with a low score, a D-dimer

test was carried out. If this test was normal, pulmonary embolism was considered to be excluded, no further diagnostic tests for pulmonary embolism were carried out, and the patients were not treated with anticoagulants. Of the total study population of 3306 patients, 2206 patients (67%) had a low Wells score and of these patients 1057 (48%) had a normal D-dimer. At three-month follow-up, there were no fatal events, four nonfatal pulmonary embolisms and one deep vein thrombosis. If we consider this as an acceptable outcome (which most clinicians probably will), it means that in 32% of patients with clinically suspected pulmonary embolism this diagnosis can be safely rejected on the basis of history, physical examination, and a simple laboratory test. In patients with a low Wells score but a positive D-dimer and in all patients with a high Wells score a spiral computed tomography scan was performed. In these 2199 patients (50 patients did not undergo a CT scan), pulmonary embolism was present in 674 patients (31%), absent in 1505 patients (68%), and inconclusive in 20 patients (1%). Patients with proven pulmonary embolism were treated with anticoagulants whereas patients in whom the diagnosis was rejected or those with an inconclusive scan did not receive antithrombotic treatment. At three-month follow-up there were 21 nonfatal events (7 (recurrent) pulmonary embolism, and 14 deep vein thrombosis) and 18 patients with fatal pulmonary embolism. Importantly, the incidence of fatal and nonfatal pulmonary embolism was 0.5 and 0.2%, respectively, in patients with a CT scan excluding pulmonary embolism. Taken together, the algorithm as studied by the Christopher group represents a serious simplification of the diagnostic management of pulmonary embolism with a clinical efficacy and safety that equals previously evaluated and more complex diagnostic strategies. The proposed management strategy is highly feasible in most clinical centres and will presumably quickly find its place in routine patient evaluation for suspected pulmonary embolism.

Which additional lessons can be learned from this landmark trial for the diagnosis of pulmonary embolism? First, even the most sophisticated diagnostic algorithm is not 100% perfect. The presence of pulmonary embolism, sometimes even fatal, in patients who were thought to be free of this disease based on the diagnostic steps in this strategy was rare but did occur, which is in line with previous studies.[12] In fact, one may view this as the premium that must be paid for the large number of patients who do not require extensive additional testing or who would have unjustly received anticoagulant treatment in the absence of pulmonary embolism. In the last group alone, the number of complications that might be expected from this inappropriate over-use of anticoagulation is likely to outweigh the burden of patients in this study that had an undetected pulmonary embolism.

A complicating factor may be that the interpretation of a spiral CT scan for pulmonary embolism, which is crucial for the diagnosis in more than two thirds of the patient population, may be difficult and can only be performed by experienced radiologists. In fact, previous studies have shown that proper radiological adjudication of especially subsegmental and distal emboli may be difficult, although the interobserver variability is still acceptable.[13] Also in the Christopher study a small number of CT scans were judged as inconclusive. On the other hand, the use of the CT scan in the diagnostic algorithm carries the advantage that if pulmonary embolism is not present, an alternative diagnosis can be made on the basis of the scan result, which was often not possible with previous imaging modalities for pulmonary embolism, such as angiography or scintigraphy.[14]

Another factor that needs to be stressed is that the diagnostic algorithm can only be applied as it was evaluated in the study. This means that D-dimer has only proven to be valuable in patients with a low probability of disease and only for the exclusion of thrombotic disease. D-dimer has no role whatsoever in patients with a high suspicion of pulmonary embolism or as a marker to select patients who might have pulmonary embolism based on a positive result. Unfortunately, the subtle intricacies of the operator characteristics of D-dimer are easily forgotten in clinical practice, and abuse and misinterpretation of this test is a real threat for the accurate diagnosis of pulmonary embolism in many clinical settings.

Lastly, and importantly, the Christopher trial is one of the largest, if not the largest, trial in more than 3500 patients with suspected pulmonary embolism. The study was a multicentre enterprise, undertaken in 12 academic and nonacademic centres in the Netherlands without any form of external financial support. The investigators need to be commended for this enormous effort and their determination to complete this very important study, which is indeed likely to change the diagnostic management of patients with a clinical suspicion of pulmonary embolism.

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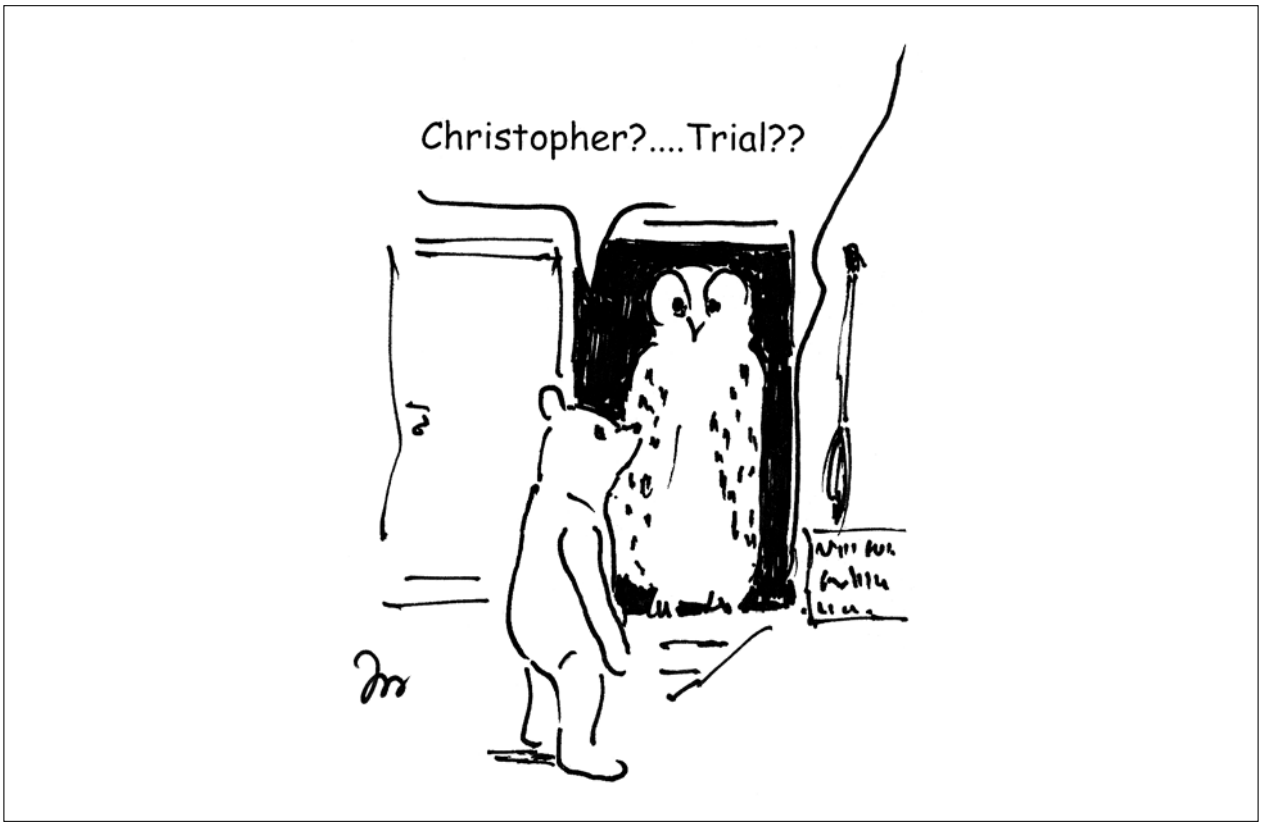

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