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The diagnostic management of suspected pulmonary embolism

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General introduction



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A diagnostic algorithm based on helical CT has gained widespread interest due to the common availability of helical CT. These algorithms have however often been implemented without appropriate assessment in clinical practice¹¹.

Another step forward was the development of clinical prediction rules and D-dimer tests in the nineties. They're advantageous because of the possibility of limiting the requirement for objective diagnostic tests such as ventilation-perfusion scintigraphy or helical CT. Clinical prediction rules categorize patients with a clinical suspicion of pulmonary embolism into a low, intermediate and high pre-test probability of pulmonary embolism. Although implicit clinical assessment empirically has been shown to be reasonably accurate, the advantage of a clinical prediction rule is the rapid bedside stratification of likelihood of PE by a more standardized approach.

D-dimers are degradation products of cross-linked fibrin that are released when a thrombus is degraded by fibrinolysis. D-dimer tests are rapid and widely available tests with high sensitivity and negative predictive value (97-100%). However, D-dimer tests are not specific (specificity of approximately 35 - 45%) due to enhanced fibrinolysis in several other conditions (malignancy, infection, high age, postoperative state, pregnancy).

Several studies have demonstrated that it is safe to exclude pulmonary embolism in patients with a low pre-test probability of pulmonary embolism combined with a normal D-dimer test¹²⁻¹⁴. Using such an approach, more invasive radiological imaging tests are obviated in 15-47% of patients suspected of PE.

An overview of the diagnostic tools available to diagnose or exclude pulmonary embolism in patients with clinically suspected PE is given in Chapter 2.

Aims of the studies and outline of the thesis

Several questions remain regarding the clinical utility of the combination of a clinical prediction rule and D-dimer as well as regarding helical CT. A retrospective analysis suggested that the clinical utility of the Wells score could be further increased by using two, instead of three categories of clinical probability, dichotomising patients either into 'unlikely' or 'likely' to have pulmonary embolism. However, no large, prospective studies have been carried out to evaluate this dichotomization. Furthermore, it is currently unknown whether the diagnosis of pulmonary embolism can be excluded, and anticoagulant treatment withheld, on the basis of a negative helical CT alone, without performing additional tests.

Our **first aim** was to investigate whether patients with a clinical suspicion of PE could be safely left untreated on the basis of a clinical decision rule indicating 'PE unlikely' combined with a normal D-dimer test. Our **second aim** was to evaluate whether helical CT could be used as a sole test to exclude PE in patients with a clinical suspicion of PE with either a clinical decision rule indicating 'PE likely' or an abnormal D-dimer test in patients indicated as 'PE unlikely'. To answer these questions, the Christopher-study was designed, a prospective management-study performed in 12 hospitals in the Netherlands between November 2002 and September 2004. It evaluated a diagnostic algorithm of sequential application of clinical decision rule, D-dimer tests and helical CT. The results of the Christopher-study are described in Chapter 3.

Due to the non-specificity of clinical signs and symptoms of PE, only 20-30% of patients with clinically suspected PE do have the disease. Ideally, a simple non-invasive test without radiation exposure and with low costs excludes a diagnosis of PE in the 70-80% of patients with a clinical suspicion of PE who do not have the disease. Excluding PE by non-invasive tests has been simplified by the introduction of the Wells clinical decision rules and quantitative D-dimer assays. These tests use fixed cut-off levels, i.e. a score of 4 to categorize patients into 'PE unlikely' or 'PE likely' and a cut-off level of 500 ng/ml to categorize a D-dimer test as 'normal' or 'abnormal'. Our **third aim** was to analyse whether the cut-off levels of the clinical decision rule as well as the D-dimer test could be varied to increase the clinical utility in excluding pulmonary embolism (Chapter 4).

The safety of excluding PE on the basis of a normal helical CT has been the subject of debate over the past years since the accuracy of CT has been reported to be only 70%. The reason for the low accuracy is believed to be the limited reliability of detecting small emboli in subsegmental arteries. The advent of multi-row detector CT (MDCT) is thought to increase the detection rate at the subsegmental artery level. In the Christopher-study, we used single (SDCT)- as well as multi-row detector systems and therefore, our **fourth aim** was to analyse whether the prevalence of subsegmental PE differed between the two CT systems (Chapter 5).

Patients diagnosed with PE are treated with oral anticoagulants for a period of at least three months. Despite treatment, some patients experience a recurrent thrombo-embolic

event, while others experience side effects from treatment, i.e. major or minor bleeding events. Our **fifth aim** was to evaluate within the Christopher-study the natural course of hemodynamically stable patients diagnosed with PE and to assess the incidences of recurrent venous thrombo-embolism, bleeding and mortality. Our **sixth aim** was to identify risk factors for these events as well as the time course of these events (Chapter 6).

In many diagnostic studies of pulmonary embolism, patients with a clinical suspicion of PE are eligible, without discriminating patients with or without a prior history of PE. No study has reported on the safety of withholding anticoagulant therapy on the basis of normal diagnostic tests in patients with a clinical suspicion of recurrent PE. The consequences of misdiagnosis of recurrent PE are major. Incorrectly concluding that recurrent PE is present exposes the patient to prolonged - and often life-long- anticoagulation with its attendant costs, inconvenience, and bleeding risks. Incorrectly concluding that recurrent PE is absent puts the patient at high risk of ongoing PE, which may be fatal. Our **seventh aim** was to analyse the safety of the diagnostic algorithm used in the Christopher-study to exclude clinically suspected recurrent PE in patients with a history of PE (Chapter 7).

Patients diagnosed with a first episode of pulmonary embolism are usually treated for six months with anticoagulant therapy. It is unknown whether all pulmonary clots have resolved by the end of treatment. Our **eighth aim** was to review the literature to establish evidence concerning rate of resolution of pulmonary clots six months after diagnosis of PE (Chapter 8).

Pregnancy is a common exclusion criterion for studies on diagnostic tests in patients with a suspicion of PE. It is generally thought that helical CT exposes the fetus to more radiation exposure than VQ scintigraphy. Our **ninth aim** was to investigate whether fetal radiation exposure is indeed higher in helical CT compared to VQ scintigraphy (Chapter 9). Moreover, our **tenth aim** was to scrutinize the literature in order to evaluate the evidence concerning performance of diagnostic tests in pregnancy for a clinical suspicion of DVT and PE (Chapter 10).

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