Diagnostic strategy for excluding pulmonary embolism in primary care
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SUMMARY

DIAGNOSTIC STRATEGY
FOR EXCLUDING PULMONARY EMBOLISM
IN PRIMARY CARE
**Chapter 1:** Pulmonary embolism (PE) remains a frequently missed and delayed diagnosis. In patients with symptoms suggestive of pulmonary embolism the primary care doctor cannot do anything but refer to secondary care. Both history and physical examination are neither specific nor sensitive for PE. In secondary care only 10-20% of these referred patients are diagnosed with pulmonary embolism. Several management studies in secondary care have demonstrated that PE can be excluded safely in patients with low clinical probability as assessed with a clinical decision rule or with the unstructured clinical estimate (‘gestalt’) combined with a normal D-dimer test result. The introduction of easy to use rapid point of care (POC) D-dimer tests might facilitate using a similar strategy to exclude PE safely in a primary care setting, thereby avoiding unnecessary referrals.

**Chapter 2** described a scenario-analysis that calculated the expected results of a diagnostic strategy consisting of the Wells clinical decision rule (CDR) combined with a point of care D-dimer test. Data of 2701 outpatients from a large prospective management study performed in secondary care were analysed. We used test characteristics of two qualitative point of care D-dimer tests, the SimpliRed test and the Simplify test. Patients were divided into groups according to their individual Wells CDR scores with different cutoff values. Within each group PE was excluded in patients with the combination of a Wells CDR below the cutoff value and a negative D-dimer test result. Combining the prevalence of PE in each group with the sensitivity and specificity of the D-dimer test we calculated the theoretical failure-rate and the efficiency of the combined strategy in each clinical probability group.

Efficiency was defined as the proportion of all study patients, in whom PE was excluded (and thus would not need referral) based on a Wells CDR below various cutoff values and a negative D-dimer test. The failure rate was defined as the proportion of patients in whom PE was excluded based on a Wells CDR below various cutoff values and a negative D-dimer test, with symptomatic and proven VTE during 3 months follow-up. In scenario 1 (SimpliRed-D-dimer sensitivity 85%, specificity 74%) PE was excluded safely in 23.8% of patients but only by lowering the cutoff value of the Wells rule below 2 (failure rate: 1.4%, 95% CI 0.6-2.6%). In scenario 2 (Simplify-D-
dimer sensitivity 87%, specificity 62%) PE was excluded safely in 12.4% of patients provided that the Wells-cutoff value was set at 0 (failure rate: 0.9%, 95% CI 0.2-2.6%). We concluded that a diagnostic strategy using the Wells CDR combined with a qualitative point of care D-dimer test can be used safely in primary care albeit with only moderate efficiency.

Chapter 3 described a meta-analysis that compared sensitivity and specificity of gestalt (physicians’ unstructured estimate) and different clinical decision rules and assessed their failure rate and efficiency when used in combination with D-dimer testing. We included 52 studies. Meta-analysis was performed on studies investigating gestalt (n=15; sensitivity 0.85/specificity 0.51), Wells-rule at cutoff <2 (n=19;0.84/0.58), Wells-rule at cutoff ≤ 4 (n=11;0.60/0.80), Geneva-rule (n=5;0.84/0.50) and revised Geneva-rule (n=4;0.91/0.37). Increasing prevalence of PE was associated with higher sensitivity and lower specificity for all rules and gestalt. Gestalt, Wells-rule at cutoff <2 and the Geneva-rules had a similar and high sensitivity for detecting pulmonary embolism. None of them however was sensitive enough to exclude pulmonary embolism on its own. The specificity of gestalt and the revised Geneva was considerably lower thereby generating more false-positives and more unnecessary computerised tomography-scanning. Therefore we advocate physicians to use a standardized decision rule instead of gestalt. Overall PE-failure rate of gestalt and all decision rules combined with (quantitative or qualitative) D-dimer testing was 0.7% (95% CI 0.5-1.0%) enabling safe exclusion of PE in 35% of patients. Combining a decision rule or gestalt with a D-dimer test seemed safe for all strategies except for combining the less sensitive Wells-rule at cut-off ≤ 4 with the less sensitive qualitative D-dimer test (failure rate 1.7%,95% CI 1.0-2.8%). We concluded that because both sensitivity and specificity of gestalt and all rules are highly dependent on the prevalence of PE in the study-population the choice of the decision rule and the D-dimer test must be different for physicians working in different settings.

All studies included in the meta-analysis were performed in a secondary care setting. However in many countries the primary care doc-
In Chapter 4 the results of a prospective diagnostic validation study performed in primary care to validate the Wells PE CDR combined with D-dimer testing were described (AMUSE-2: Amsterdam Maastricht Utrecht Study on thrombo Embolism). The study evaluated the safety of excluding PE using the Wells rule (either with cutoff ≤ 4 points or <2 points) with a qualitative point of care D-dimer test (Clearview Simplify). We included 598 adult patients (mean age 48 years, 71% women) with suspected PE. Primary care doctors scored the seven variables of the Wells rule and performed the D-dimer test. Regardless of the results of the Wells rule and D-dimer test primary care doctors were asked to refer all patients to secondary care for reference testing. The diagnosis of pulmonary embolism was confirmed or refuted based on a composite reference standard, including three months of follow up. A total of 73 patients had a diagnosis of venous thrombo-embolism (prevalence PE 12.2%). If a Wells cutoff score of ≤ 4 points was combined with a negative D-dimer test result then 272 patients would not have been referred for diagnostic testing and in 4 of them PE would have been missed: failure rate 1.5% (95% CI 0.4-3.7%). The efficiency of this strategy was 45.5% (272/598). If a Wells cutoff score of <2 points was combined with a negative D-dimer test result then 168 patients would not have been referred for diagnostic testing and in 2 of them PE would have been missed: failure rate 1.2% (95% CI 0.1-4.2%) with an efficiency of 28.1% (168/598). We concluded that a Wells cutoff score of ≤ 4 combined with a negative qualitative point of care D-dimer test can safely and efficiently exclude pulmonary embolism in primary care.

Chapter 5 reported the most common alternative diagnoses (after excluding pulmonary embolism) in patients in whom the primary care doctor suspected pulmonary embolism. This study was a secondary analysis of the AMUSE-2 study as described in Chapter 4. After medical history and physical examination all patients were referred to secondary care and diagnosed according to local hospital protocols. Patients were followed-up for three months. After these 3
months, primary care doctors were asked to document the final diagnosis for each patient. In order to analyse the association between the clinical probability of PE (as assessed by Wells score and result of D-dimer) and the severity of the final diagnosis, we divided the alternative diagnoses in two categories: clinical serious diseases, leading to immediate medical treatment and clinical less serious diseases not leading to any other treatment than supportive care (e.g. painkilling in case of musculoskeletal pain). The most frequent alternative diagnoses after excluding pulmonary embolism were: nonspecific thoracic pain/dyspnoea (43%), pneumonia (13%) and myalgia (12%). Patients with a Wells score > 4 points or a positive point of care D-dimer test were more likely to have a clinical serious disease (OR 2.1; 95% CI 1.4-3.1). Especially pneumonia was strongly associated with a high probability of PE (OR 2.7; 95% CI 1.6-4.8).

After excluding pulmonary embolism in patients with an unlikely Wells decision rule and a negative D-dimer test, the primary care doctor still has to differentiate between clinically relevant (= serious) and clinically non-relevant (= less serious) diseases accounting for the presented symptoms. Chapter 6 described the additional value of CRP-testing in these patients. This study was a secondary analysis of the AMUSE-2 study as described in Chapter 4. We included 191 patients, referred to secondary care for reference testing, with an unlikely Wells decision rule and a negative point of care D-dimer test. Alternative diagnoses were divided in clinically relevant diseases and clinically non-relevant diseases. CRP-test results were missing in 60 of 191 study-patients (31%) due to the fact that the CRP-test was ordered at the discretion of the attending physician in secondary care. We imputed the CRP-test result in these 60 patients. With the constructed ROC-curve the optimal cutoff value of the CRP-test was determined and appeared to be 10mg/l. Doctors in secondary care diagnosed 44 of the 191 patients (23%) with a clinically relevant disease including 4 patients with pulmonary embolism (failure of the negative Wells PE rule/negative D-dimer test-strategy). In 116 of 191 patients (61%) the CRP-value was below 10mg/l. Twelve of those 116 patients (10%) had a clinically relevant disease, including one patient with pulmonary embolism. Two of these 12 patients needed admission to
hospital. From the remaining 75 patients with a CRP ≥ 10mg/l, 32 patients had a clinically relevant disease (43%) of whom 15 (20%) were admitted to hospital. We concluded that the primary care doctor might be able to further manage the patient in whom he excluded pulmonary embolism with the use of a (point of care) CRP-test to reduce the risk of having a clinically relevant alternative disease in patients with a CRP < 10mg/l. This strategy needs further evaluation before implementation.

Chapter 7 looked at the accuracy of multi-detector computed tomography with expert opinion as reference standard in diagnosing pulmonary embolism. Computed tomography pulmonary angiography (CTPA) is currently the preferred diagnostic test in secondary care in patients having a high clinical probability or a positive D-dimer test. The negative predictive value (NPV) for symptomatic venous thromboembolism in 3 months following a CTPA without signs for embolism in this population approaches 99%. However, in the diagnosis of pulmonary embolism using CTPA two major concerns remain. Firstly, with the introduction of multi-detector CT the prevalence of (sub) segmental emboli increased but the clinical implications of these small clots are uncertain. Secondly, we are not well informed about the number of false-positive CT-scans due to the lack of a gold standard. Data from the AMUSE-2 study as described in Chapter 4 were used. We included 79 patients who underwent CT pulmonary angiography. CT-scan reading by the local radiologist in daily care was retrospectively compared with expert reading as reference standard. In 5 of 30 patients (17%) diagnosed locally with PE the experts could not confirm the diagnosis. In 11 of 49 patients (22%), originally diagnosed as being negative for PE, the expert radiologists disagreed. The experts diagnosed 17 of 32 PE-patients (53%) with a central or lobar pulmonary embolism. All these 17 patients were diagnosed with pulmonary embolism by the local radiologist as well. The experts diagnosed 15 patients with either segmental or subsegmental PE. In 7 of these 15 patients (47%) the local radiologist refuted PE. None of these 7 patients with a false negative diagnosis (and
hence not treated with anticoagulants) suffered from venous thromboembolism sequelae during the three months follow-up. We concluded that the accuracy of the CT-scan using the expert radiologist as reference standard is not optimal. On the one hand this study showed at least 10% false-positives exposing patients to treatment unnecessarily. On the other hand small emboli seemed to be missed although the clinical implications of this finding are yet unknown.

In the discussion Chapter 8, a 35 year old woman suspected of pulmonary embolism presented in primary care. We described the difficulties the primary care doctor experiences in dealing with suspected pulmonary embolism patients. We followed the patient in the application of the diagnostic strategy using the Wells rule and the D-dimer test. It is of paramount importance to first examine the patient and assess the clinical probability before applying the D-dimer test. Doctors need to apply a standardized rule in stead of gestalt (empirical clinical judgement of the physician). Although doctors using gestalt are well able to correctly identify PE-patients at high risk for pulmonary embolism, they do this at the expense of more non-PE-patients incorrectly identified at high risk. The advantages and disadvantages of qualitative versus quantitative D-dimer testing in primary care were described. Finally, we discussed the problems to be expected with implementation of this diagnostic strategy. Implementation of the strategy using the Wells rule and the D-dimer test might lead to an increase in testing for PE in primary care. This will not influence the safety of the strategy but might increase the number of unnecessary referrals to secondary care. This stresses the importance of the application of a D-dimer test with a high specificity in primary care. To ascertain whether the validated strategy will actually be used by physicians, will change or direct physicians’ decisions and will improve patient outcomes, an impact analysis should be performed.