Pulmonary embolism: advances in diagnosis and prognosis
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Summary
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This thesis focuses on the diagnosis and prognosis of pulmonary embolism (PE). In the first part, studies are described in which we further optimized the diagnostic workup of patients with suspected PE. The second part of the thesis focuses on the prognosis of patients with proven PE, while in the third part, focus lies on the diagnosis and prognosis of PE in specific patient populations.

Part I – Diagnosis of pulmonary embolism

Chapter 2 gives an overview of the current diagnostic methods to rule out or confirm PE, along with information on epidemiology and risk factors for PE. In chapter 3, the safety and clinical utility of a recently introduced clinical decision rule (CDR), the simplified Wells rule was validated in an independent large cohort of patients with suspected PE. Although the simplified and the original Wells rule are composed of the same clinical variable, in the simplified rule, all items carry the same weight instead of different weights. This facilitates computation of the score: if none or one of the items is present, a normal D-dimer test can exclude the diagnosis. This retrospective validation study showed that the proportion of patients categorized as PE “unlikely” is similar using the original Wells rule and the simplified version (78% and 70%, respectively). The prevalence of PE was 13% and 12%, respectively, for patients with an “unlikely” result. Also, the two CDRs were similar in the proportion of patients in whom PE could be excluded based on PE “unlikely” and a normal D-dimer test result: 28% using the original and 26% using the simplified Wells rule, respectively. None of these patients experienced venous thromboembolism (VTE) during a three-month follow-up, and therefore it was concluded that the simplified Wells rule appeared to be safe and clinically useful.

Prospective validation of the simplified rule was the next step, and was carried out in chapter 4. In this chapter, four recently introduced or widely used CDRs were prospectively compared for the exclusion of PE, in combination with D-dimer testing. A “black box” study design was used, in which the variables of four CDRs (the Wells rule, the simplified Wells rule, the revised Geneva score and the simplified revised Geneva score) were collected, together with the D-dimer test result. A computer program calculated the outcome of each CDR and, in combination with the D-dimer test result, indicated whether PE could be excluded directly, or if a CT-scan should be performed to exclude or confirm the diagnosis. The number of patients categorized as “PE unlikely” ranged from 62% (simplified Wells rule) to 72% (Wells rule), but the prevalence of PE in the “unlikely” group was similar with all four CDRs (13%-16%). Combined with a normal D-dimer test, the CDRs excluded PE in similar proportions of patients: 22-24%. The total failure rates of the CDR-D-dimer combinations were similar (n=1, 0.5% to 0.6%, upper 95% CI 2.9% to 3.1%). Despite discordances between the CDRs in 30% of patients, PE was missed in none of the patients with a normal D-dimer level. Hence, it was concluded that the Wells rule, the revised Geneva score, the simplified Wells rule as well as the simplified revised Geneva score show similar safety and clinical utility for excluding PE when combined
with a D-dimer test. Furthermore, with this prospective validation, the more straightforward simplified decision rules are ready for use in clinical practice.

In Chapter 5a and 5b, the results are described of two questionnaire based studies on the implementation of CDRs and D-dimer testing, and the influence of D-dimer knowledge on clinical probability assessment. The results of the first study indicated that physicians do not use the guidelines for diagnosis of PE consistently. Furthermore, the knowledge of an abnormal D-dimer test result before seeing the patient leads to a higher CDR score (using the Wells rule). This was confirmed in the second study, in which six hypothetical case-descriptions of patients with suspected PE were presented to 150 physicians in the Netherlands. Knowledge of the D-dimer result not only resulted in more “likely” results, but conversely, knowledge of a normal D-dimer resulted in more “unlikely” results. Both variations could have direct clinical consequences, such as unnecessary imaging testing or inappropriate exclusion of the diagnosis, which emphasizes the importance of first examining the patient before taking note of the D-dimer test result.

In chapter 6, a new age-dependent cut-off for the D-dimer test was derived and validated. In older patients, the D-dimer test has reduced specificity and is therefore less useful in ruling out PE. Applying an age-dependent cut-off in patients with an “unlikely” clinical probability for PE, calculated as (age x 10 µg/L) for patients above 50 years, considerably increased the proportion of patients in whom PE could be excluded without further imaging testing, without reducing safety. In the total population, the number of patients in whom additional testing could be avoided increased up to 18%, while it doubled among patients >70 years: 16% when the conventional cut-off value was used compared to 33% when the age-dependent cut-off value was used.

The new cut-off value also seemed promising for patients with malignancy and suspected PE, as was shown in chapter 7. In this chapter, we examined potential explanations for the lower performance of the CDR-D-dimer combination for the exclusion of PE among patients with malignancy. The study showed not only that both the Wells rule and the D-dimer test are less diagnostic in patients with cancer, also the individual variables in the Wells rule are less diagnostic in cancer patients than in non-cancer patients with suspected PE. Elevating the D-dimer cut-off value for cancer patients to 700 µg/L or using the age-dependent cut-off approach yielded a modest absolute increase in clinical utility of 5%.

The safety of the CDR-D-dimer combination to exclude the diagnosis is currently only validated and used in hospital setting, where a quantitative D-dimer test is used. Excluding the diagnosis outside the hospital, in primary care, could further optimize the diagnostic strategy for PE. Chapter 8 describes a scenario-analysis for a diagnostic strategy consisting of the Wells rule combined with a point-of-care D-dimer test for the exclusion of PE. The test characteristics of two point-of-care D-dimer tests, the SimpliRed test and the Simplify test, were applied to data from a large cohort of outpatients. This analysis showed that theoretically, the Wells rule could
be combined with a point-of-care D-dimer test to safely exclude PE in primary care. However, to endorse safety, the cut-off of the Wells rule had to be lowered, which resulted in only a modest clinical efficiency of the CDR-D-dimer combination: exclusion of the diagnosis was possible in 24% and 12% of patients for the two D-dimer test, respectively.

With the introduction of multi-detector row CT (MDCT), sensitivity to diagnose PE has greatly improved. Although several clinical management studies have shown that a normal MDCT-scan alone is sufficient to exclude the diagnosis, it has remained debatable whether this is also true in the subgroup of patients with a “high” pre-test probability for PE. Chapter 9 focuses on this dilemma: using data from a large management study it shows that CT-scanning indeed safely excluded the diagnosis in the general population (failure rate of 1.1%, 95% CI, 0.6-1.9%). However, if a high clinical suspicion was combined with a normal CT, the failure rate was 5.3% (95% CI, 1.8-14.4%). Fortunately, the number of patients with this combination was very low (approximately 1 of 20 patients with a normal CT). If it occurs, the physician could consider additional testing, albeit that at present it is unclear which method should be used.

Furthermore, with the advent of newer generations MDCT scans it is conceivable that the number of patients in whom only isolated small peripheral emboli are seen, increases, with several unknown clinical consequences. In chapter 10, a ‘low’-end CT scan (4-slice MDCT) and a ‘high’-end CT scan (64-slice MDCT) were compared for differences in detection patterns. Although prevalence of PE was equal in both cohorts (22% and 24%, respectively), there was a trend towards more subsegmental PE with 64-slice CT: in 2 of 26 patients with PE in the 4-slice cohort the embolism was subsegmental, compared to 5 of 24 patients in the 64-slice cohort. Also, in this multi-reader setting, the number of inconclusive examinations was 10%, which is much higher compared to reports from clinical management studies: 2-3%. Hence, it was concluded that diagnosis of PE with MDCT could be less straightforward than generally assumed.

Because of the risk of cancer following CT-scan radiation exposure, particularly the risk of breast cancer among young women, young patients might benefit from a strategy in which CT-scanning is avoided. In chapter 11, an alternative diagnostic strategy was proposed and retrospectively evaluated among women younger than 50 years with suspected PE, consisting of a clinical decision rule, D-dimer testing, and the combination of a chest X-ray and perfusion scintigraphy. The strategy, evaluated in two modest populations of young women with suspected PE, seemed promising to reliably exclude or confirm the diagnosis and CT-scan could theoretically be avoided in 60% to 83% of women. Prospective evaluation of this “X/Q” combination in a larger population of young patients is currently awaited.

Part II – Prognosis of pulmonary embolism

In the first chapter of the second part of this thesis, chapter 12, the literature was reviewed for the advantages and disadvantages of thrombolytic therapy in patients in whom PE has been
diagnosed. The prognosis of patients with PE may vary, and risk stratification should be used to identify patients with an increased risk of adverse outcome. Right ventricular dysfunction is an independent predictor of death and clinical deterioration, but assessment has (logistical) limitations when echocardiography is used. In **chapter 13**, CT-measured right ventricular overload was studied. In this prospective study totalling 457 patients with CT-proven PE, a right to left ventricle dimension rate $\geq 0.9$ on CT-scan had 92% sensitivity for RVD compared to the reference standard echocardiography. RVD at MDCT was an independent predictor for in-hospital death or deterioration (odds ratio 2.7; 95% CI, 1.2-6.4). However, the positive predictive value was only 15%, and does not justify treatment upgrading in all patients who have RVD on MDCT. Conversely, however, the negative predictive value of RVD for death due to PE was 100%, which means that patients without RVD have a very low risk of in-hospital adverse outcome and could candidate for home-treatment.

Standard treatment with anticoagulant medication is known to effectively treat PE, although little is known about the rate of clot resolution and the performance of CT compared to perfusion scintigraphy for its measurement. The two modalities were compared in **chapter 14**, where 165 consecutive patients with PE confirmed by CT (n=127) or perfusion scintigraphy (n=38) were followed up for three weeks at which time a repeat scan was performed. The study showed greater thrombus resolution with CT-scan (45%) compared to perfusion scintigraphy (29%) after three weeks of conventional anticoagulant treatment. This implies that clot resolution occurs early after PE and suggests that normalization measured with CT-scan may be greater compared to what is known from earlier studies with perfusion scintigraphy.

**Part III – Pulmonary embolism in specific patient populations**

In the third part of the thesis, two studies are described on VTE and its complications in specific patient populations. In **chapter 15**, we assessed the prevalence of asymptomatic (incidental) VTE on staging CT-scans of 838 patients with cancer, and the therapeutic implications of these thrombi. The prevalence of incidental VTE was 2.5% (95% CI, 1.6-3.8); 1.3% had PE or DVT and 1.1% had abdominal vein thrombosis. Although this prevalence was relatively low and most patients with PE or DVT were treated, none of the patients with thrombosis in other locations received anticoagulants. Further research is necessary to understand the natural history of these thrombi, in order to develop adequate guidelines.

In **chapter 16**, the prevalence of chronic PE among 48 patients with Klippel-Trenaunay Syndrome (KTS) from the Dutch KTS-cohort was assessed. Patients with this congenital malformation syndrome with vascular malformations are known to have an increased risk of developing VTE, and continuous thrombi formation without treatment might results in long term sequelae such as chronic PE or chronic thromboembolic pulmonary hypertension. Although a large proportion of KTS-patients had a history of VTE (17%; 95% CI, 8.7-30%), the prevalence of chronic PE was 4.2% (95% CI, 1.2-14%) and therefore appeared less alarming than assumed. Although based on these data the indication for screening for chronic
thromboembolic pulmonary hypertension seems limited, awareness for this adverse outcome remains appropriate, especially among patients presenting with shortness of breath and a history of VTE.

**Future perspectives**

With the current diagnostic algorithm consisting of clinical probability assessment, D-dimer testing followed by imaging if necessary, a well-validated, safe and efficient diagnostic strategy is available for the management of patients with suspected pulmonary embolism. However, several challenges remain and need attention to further optimize the strategy. First of all, because inappropriate use of an algorithm could increase recurrence of VTE, it is important that the available strategies are adhered to and that they are used as they are intended. This can be facilitated by using the simplified clinical decision rules, since they are easier to remember and to apply. This could increase implementation of clinical probability assessment in a clinical setting. Second, future studies could focus on optimization of the strategy for subgroups of patients in whom the clinical utility is low, for instance, patients with suspected recurrent PE, inpatients, patients with malignancy and older patients. Once the age-dependent D-dimer cut-off value is prospectively validated, it can be applied in a clinical setting and would improve the clinical utility of the strategy for elderly patients and patients with cancer. Despite the many advantages of CT scanning over other imaging modalities, the concomitant radiation and iodine contrast exposure are important limitations of the test. Further studies are necessary to validate alternative strategies for young patients and patients with renal impairment in order to avoid CT-scanning.

With regard to the treatment and prognosis of PE, more studies are desired to investigate risk stratification tools in order to identify patients with a high risk of adverse outcome. It has been generally accepted that patients who are hemodynamically instable should receive thrombolytic therapy. Therefore, in current clinical practice risk stratification is particularly required in patients who are hemodynamically stable. Unfortunately, at the moment few studies have focused on risk stratification in this group of patients alone. The optimal stratification tool is able to identify a small group of patients with a high risk of adverse outcome. Importantly, the test should be easy to implement in a clinical setting and work-up. Future studies should focus on the identification of such an instrument. Subsequently, the benefit of thrombolytic therapy in normotensive patients with PE should be evaluated.

Although treatment with anticoagulants is very effective in patients with confirmed PE, the rate of clot resolution is less well studied. Patients with PE are at risk of developing recurrent PE or chronic thromboembolic pulmonary hypertension. Currently, it is not well known which patients will develop these sequelae, and why. Further studies on risk factors for developing recurrent VTE or chronic thromboembolic pulmonary hypertension are very welcome, as well as studies which focus on the optimal duration of treatment for patients with VTE.