Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism
van Es, Josien

Citation for published version (APA):
van Es, J. (2013). Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 16

Summary and perspectives

J. van Es
S. Middeldorp
P.W. Kamphuisen
Summary

This thesis focuses on the diagnosis, treatment and prognosis of pulmonary embolism (PE). In the first part, studies are described in which we further aimed to optimize the diagnostic workup of patients with suspected PE. The second part of the thesis focuses on the treatment and prognosis of patients with established PE.

In chapter 2, the safety and clinical utility of a new cut-off level for the D-dimer in patients above 50 years (age x 10 µg/L) was evaluated, combined with the original Wells score and the Revised Geneva score, and also with the recently introduced simplified version of the Wells score and revised Geneva score (RGS). The simplified Wells and simplified RGS are composed of the same clinical variables as the original version, but in the simplified rules, all items carry the same weight instead of different weights. In this retrospective validation study the diagnostic yield for excluding PE with the age-adjusted cut-off appeared to be highest in combination with the original Wells rule, i.e. 14.5% compared to 13.5% with the simplified Wells and 13.8% with both original and simplified RGS, although the differences were not statistically significant. The failure rates were similar for all clinical decision rules (2 patients, approximately 2.5%, 95% CI 0-8%).

In patients with a malignancy, the performance of these four clinical decision rules was compared in chapter 3. Direct comparison of four different clinical decision rules in patients with malignancy and suspected PE suggests that the simplified Wells score might have a higher sensitivity (94%, 95% CI 81-98) compared to the other three clinical decision rules (Wells score 65% (95% CI 48-95%), RGS 74% (95% CI 57-84%), simplified RGS 76% (95% CI 60-88%), respectively) (p<0.05). This did not translate in a higher number of patients in whom PE could be excluded without the need of computed tomography- (CT-scan), probably due to the low number of patients with a normal D-dimer result.

CT-scanning has become the standard test in the diagnostic work-up of patients with suspected PE. However, especially among young patients, concerns have been raised regarding the risk of cancer following radiation exposure with CTPA. Especially among young women, the lifetime attributable risk of cancer incidence is considerable, particularly the risk of breast cancer. Therefore, they may benefit from an alternative diagnostic modality, which is described in chapter 4. Perfusion scanning combined with chest X-ray result (X/Q) according to the PISAPED criteria seems an adequate alternative, but has never been validated. We therefore directly compared this strategy
with CT-scan in patients aged < 50 years with suspected PE. In patients younger than 50 years of age with a high risk of PE (likely Wells score or elevated D-dimer level), the accuracy of X/Q according to the PISAPED criteria was prospectively evaluated, in order to avoid CT-scanning and thereby the radiation exposure. In seven hospitals in the Netherlands and Belgium, 76 consecutive patients were included and X/Q-scans were analyzed by two trained nuclear physicians. The prevalence of PE in the patients was 33%. The interobserver agreement was high (κ=0.89). After consensus reading, 21 patients (28%) were categorized as ‘PE present’, 54 (71%) as ‘PE absent’, and two (2.6%) as ‘non-diagnostic’. In 17 patients (22%) there was a discrepancy between the CPTA and the X/Q. The PPV and NPV were 71.4 (95% CI 50-86) and 83.0 (95% CI 71-91), respectively. Consequently, the diagnostic accuracy of X/Q according to PISAPED criteria seems limited in our cohort.

It is well known that the diagnostic accuracy of a test can vary with the strength of clinical suspicion. In that case, previously reported accuracy estimates may not be generalizable to all subgroups. In chapter 5, we tested the accuracy of the D-dimer test in patients with suspected PE who scored zero, one or two items of the Wells score. We used data of 723 patients with suspected PE, of which 177 (24%) patients had zero items on the Wells score, 300 (41%) had one item positive, and 136 (19%) had two items positive, including the subjective item of "PE more likely than an alternative diagnosis". The estimated sensitivity for the D-dimer test at the 500 µg/L positivity threshold was similar in the three subgroups whereas the specificity differed significantly, at 0.49, 0.30 and 0.16 respectively. Hence, we conclude that the diagnostic accuracy of D-dimer testing varies significantly across subgroups defined by the Wells score. As a next step, we aimed to develop a new clinical decision rule in chapter 6 that incorporates Wells items and a D-dimer test result. We used 723 patients for a derivation cohort and a separate validation dataset of 2784 patients with suspected PE. After building a logistic regression model with the D-dimer result and Wells items, three Wells items were identified as significantly adding information to D-dimer: two clinical items (haemoptysis and clinical signs of deep venous thrombosis) and the subjective item (PE more likely than an alternative diagnosis). Based on the most frequent combinations, we identified two groups: (1) none of these items positive (41%), and (2) the subjective item or one of the clinical items positive (59%). We investigated the accuracy of this new rule with different cut-off values of the D-dimer test. The safety of this new clinical decision rule needs to be evaluated in future management studies.
In chapter 7, we prospectively studied whether alternative diagnoses observed on CT-scan, ordered for PE, have either diagnostic or therapeutic consequences in 203 consecutive patients with suspected PE. A total of 39 patients (19%) were diagnosed with PE and 61 (30%) had no abnormality on CT-scan. Findings supporting an alternative diagnosis were detected in 88 (43%) patients. However, in only 18 patients, a new and conclusive alternative diagnosis for the complaints was made based on the outcome of the CT-scan. Overall, findings supporting alternative diagnoses had therapeutic consequences in 10 (5%) patients. Incidental findings (nodules/lymph nodes) requiring diagnostic procedures were present in 17 (8%) patients. Although in patients undergoing CT-scan for suspected PE, findings supporting alternative diagnoses were found in almost half of the patients, in only few patients this had therapeutic consequences. Besides, the proportion of incidental findings was in the same range. CT-scan should therefore only be used to find or exclude PE, but not to establish an alternative diagnosis.

We measured prothrombin fragment 1+2 (F1+2) levels in urine and plasma in patients with venous thromboembolism (VTE) and myocardial infarction (MI), and in healthy controls in chapter 8. In this pilot study we showed that in patients with acute VTE plasma levels of F1+2 are elevated, and that F1+2 levels in the urine are increased, but to a lesser extent than in plasma. F1+2 levels in both urine and plasma were similar between patients with acute MI and healthy controls. These results show that F1+2 levels of the VTE patients are marginally increased in the urine. This was, however, not significantly different compared to healthy controls.

**PART II – TREATMENT AND PROGNOSIS OF PULMONARY EMBOLISM**

In the first chapters of the second part of the thesis, chapter 9 and chapter 10 review the current treatment regimens for PE and VTE, respectively, discussing the new anticoagulants, duration of treatment and treatment in special patient groups, such as patients with renal failure, obesity or thrombophilia.

Although these chapters describe that standard treatment with anticoagulant therapy is known to effectively treat PE, little is known about the rate of clot resolution. This is of importance, because nowadays repeat CT-scans are often ordered after six months of anticoagulant treatment without solid evidence for clinical relevance. In chapter 11, 374 consecutive patients with PE confirmed by CT-scan (n=264) or perfusion scintigraphy (n=83) underwent a repeat scan after three weeks of anticoagulant...
treatment. Overall, complete clot resolution occurred in 41% of the patients, while in 12%, no resolution occurred. Clot resolution was higher with CT-scan (44%) compared to perfusion scintigraphy (31%). This implies that clot resolution occurs early after PE in the majority of patients and suggests that normalization measured with CT-scan may be greater compared to perfusion scintigraphy.

In chapter 12, we assessed residual pulmonary thrombosis on a repeat CT-scan after six months of anticoagulant treatment in 141 patients with PE. The scans were analyzed independently by two different radiologists, who calculated the obstruction index using the scoring system of Qanadli. We also evaluated the relation between the presence of residual thrombosis and recurrent VTE in a 2-year follow-up, in this prospective, multicenter study. After six months of treatment, seven patients (5%; 95% CI 2-10%) had residual thrombosis in at least a segmental pulmonary artery. In another 14 patients (10%; 95% CI 6-16%), non-occlusive post-thrombotic webs or strictures were found. During follow-up, 13 (9.2%) patients experienced recurrent VTE. None of the patients with residual PE developed recurrent VTE.

With the introduction of improved imaging techniques, more isolated subsegmental PE has been detected, whereas the clinical significance of subsegmental PE is unclear. Chapter 13 investigated the clinical outcome during three months follow-up of patients with subsegmental PE compared to more proximal PE (segmental and central PE), and to patients in whom PE was excluded. Subsegmental PE was confirmed in 116 of 748 (16%) patients with PE and these patients had an increased risk of mortality compared to patients in whom PE was ruled out and a similar mortality risk as those with more proximally located PE.

The influence of the duration of complaints before CT-scanning on the D-dimer level and the prognosis of patients is described in chapter 14, which aimed to assess the impact of diagnostic delay on the safety of excluding PE with the use of a clinical decision rule and D-dimer testing. Diagnostic delay (complaints present for at least 7 days) was present in approximately 19% of the patients. D-dimer testing yielded a high sensitivity rate, and the failure rate of an unlikely clinical probability and normal D-dimer test was 0.5% in patients with and without diagnostic delay. Hence, delay in confirming PE was associated with a more central PE location, but does not appear to impact the risk of recurrent VTE or mortality.

In chapter 15 the quality of life of 109 patients with PE was investigated by a generic and a disease-specific questionnaire (PEmb-QoL). Quality of life assessed with the generic questionnaire was higher in patients with PE compared to patients with COPD and congestive heart failure, comparable to patients with acute myocardial infarction, and worse compared to the general Dutch population.
Chapter 16

Future perspectives

The cornerstones of the diagnostic management of patients with suspected PE are clinical decision rules, D-dimer assays and imaging tests. In the last decade several large management studies support a standardized strategy consisting of these three diagnostic modalities to optimize safety and cost-effectiveness. Still, challenges remain and need attention to further optimize the strategy. First, the diagnosis is established on CT-scan in only 20-30% of the patients with suspected PE. Despite the many advantages of CT-scan, the concomitant radiation and iodine contrast exposure are important limitations of this imaging modality. Therefore, further optimizing the diagnostic work-up of PE is still needed. Besides, because inappropriate use of an algorithm could increase recurrence of VTE, it is important that the available strategies are adhered to and that these are used only in patients with suspected PE. Besides, since the signs and symptoms of PE overlap with other potentially dangerous cardio-pulmonary diseases, it is of importance to assess a fast and simple diagnostic work-up, which all physicians can assess appropriately, in or out of office hours. The use of an alternative clinical decision rule which is easier to remember and to apply, could increase the implementation of clinical probability assessment in a clinical setting.

Second, future studies should further focus on optimization of the strategy for subgroups of patients in whom the clinical utility of current strategies 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 (data of the ADJUST study are expected soon), it can be applied in a clinical setting and would improve the clinical utility of the strategy for elderly patients. With regard to the treatment of PE, new oral anticoagulant drugs have the potential to simplify treatment. So far, the results from large clinical trials have shown efficacy and safety for the prophylaxis and treatment of VTE. These new anticoagulants are now available.

Although treatment with both the conventional and new anticoagulants is very effective in patients with confirmed PE, the rate of clot resolution is less well studied. Patients with residual thrombosis in the pulmonary arteries are at risk of developing recurrent PE or chronic thromboembolic pulmonary hypertension. We found that the amount of residual thrombosis in the pulmonary arteries is less than always assumed. Further large prospective studies, which focus on the association between residual thrombosis and recurrent venous thromboembolism or chronic thromboembolic pulmonary hypertension, as well as on the risk factors for developing these sequels of PE, are welcome.