Improving efficiency of the diagnostic management of pulmonary embolism

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Chapter 11

General discussion and future perspectives

This thesis contains different studies that are focused on improving the diagnostic management of patients with suspected acute pulmonary embolism (PE). Chapter 1 contains a general introduction on the condition 'acute pulmonary embolism' and its current diagnostic management.

PART I: THE DIAGNOSTIC MANAGEMENT OF SUSPECTED PULMONARY EMBOLISM DURING PREGNANCY

Chapter 2 provides an overview on the use of clinical prediction rules and D-dimer tests in the diagnostic work-up of suspected pulmonary embolism during pregnancy. The most often used clinical prediction rule in the non-pregnant setting is the Wells score, which consists of seven clinical items. Pregnant women were excluded in the main clinical derivation and validation studies of the Wells score. Therefore, this clinical prediction score is not validated for this specific population. In the 1990s, several studies have shown that D-dimer levels physiologically increase steadily during pregnancy, making this test less useful to rule out venous thrombo-embolism (lower specificity). During the first trimester of pregnancy, 50-100% of all patients have D-dimer levels less than the most used threshold of 500 ng/mL, and 0-76% of all patients during the third trimester. Different studies investigated an alternative D-dimer threshold during pregnancy, but suggested new threshold varied among the studies and were never prospectively (externally) validated.

There are contradicting recommendations in different international guidelines for the use of clinical decision rules and D-dimer testing for the diagnostic work-up of suspected PE during pregnancy. Even so, the majority of guidelines clearly indicates that only imaging tests – CT-scan or ventilation perfusion scintigraphy – are currently available to safely exclude or confirm this diagnosis during pregnancy.

Chapter 3 is a systematic review and meta-analysis of the safety, efficiency and the maternal and fetal radiation exposure of two different imaging modalities that are widely used to confirm or rule out PE were compared, i.e. ventilation perfusion scan and the CT-scan. The pooled number of false negative scans was 0.0% (95%CI 0-0.04) for ventilation perfusion scan and 0.0% (95%CI 0.0-0.16) for CTPA, showing comparable sensitivity. The pooled rate of non-diagnostic results with ventilation perfusion scan and CT-scan were 14% (95%CI 10-18) and 12% (95%CI 8-17) respectively, which was unexpectedly high for CT. The maternal and fetal radiation exposure was well below the safety threshold for both imaging modalities, although they could not be compared given the lack of high quality data. Notably, none of the included studies in this meta-analysis have used state-of-the-art imaging techniques as currently used in clinical practice. Hence, our pooled estimates are likely outdated and contemporary CT and VQ sequences involve less radiation exposure and less non-diagnostic

tests. In conclusion, this meta-analysis demonstrates that both imaging modalities are safe and can be applied to use to rule out PE during pregnancy.

The results of a multinational, multicenter, prospective diagnostic management study for suspected PE during pregnancy are presented in chapter 4. The YEARS algorithm was validated in this study in a pregnant population. The YEARS algorithm was adapted for pregnancy; all patients with clinical signs of deep venous thrombosis were referred for ultrasonography of the symptomatic leg, and if DVT was confirmed, treatment with anticoagulants was initiated without further CTPA imaging. The YEARS algorithm consists of assessment of three clinical items; haemoptysis, clinical signs of deep venous thrombosis and PE the most likely diagnosis, in combination with D-dimer measurement. A total number of 498 patients were included in 17 different hospitals in the Netherlands, France and Ireland. The PE-prevalence was 4.0% (20/498) with a 3-month VTE failure rate was 0.21% (95%CI 0.0-1.2) with one patient who developed a popliteal DVT after twelve weeks of follow-up. CTPA could be avoided in 40% (95%CI 35-44) of all patients. Subgroup analysis demonstrated that 65% of all patients could be managed without CTPA during the first trimester compared to 32% of patients in the third trimester. The conclusion of this study is that the pregnancy adapted YEARS algorithm safely ruled out PE in pregnant patients across all three trimesters. This study is the largest management study ever performed in the setting of pregnant patients with suspected PE, and its results will certainly change clinical practice since potential harmful imaging was avoided in a large proportion of patients.

PART II: THE DIAGNOSTIC MANAGEMENT OF SUSPECTED PE IN NON-PREGNANT PATIENTS

Part II of this thesis encompasses analyses on the diagnostic management of suspected PE in non-pregnant patients. In current clinical practice, different diagnostic algorithms for confirming or excluding PE are used indiscriminately in women and men. Men and women can present with different clinical presentations for acute PE and there are also sex-specific risk factors for venous thrombo-embolism such as use of estrogens in female patients. Three different diagnostic algorithms for acute PE, the Wells rule with fixed D-dimer threshold, the Wells rule with age-adjusted D-dimer cut-off (calculated as age x 10) and the YEARS algorithm, were compared in chapter 5 for safety and efficiency between men and women. Individual patient data were obtained from seven prospective studies that enrolled consecutive adult patients with suspected PE. The pooled prevalence of PE was lower in women (18.7%) than in men (25.7%) for an odds ratio of 0.69 (0.62-0.76). The overall efficiency was higher in women with an OR of 1.11 (95%CI 1.02-1.2) when data from the studies were pooled. The failure rate was comparable for men and women for all different algorithms,

so the investigated pre-imaging diagnostic algorithms are more efficient for women with a similar failure rate.

In the next chapters, we investigated if combinations of different strategies could improve their efficiency by further reducing the number of required CT-scans in the diagnostic work-up for patients with suspected PE even further. Chapter 6 describes a study of the combination of the YEARS algorithm with the age-adjusted D-dimer cut-off. In this analysis, four hypothetical scenarios were analysed to investigate if this combination could improve the efficiency further without compromising safety. Only one scenario proved to be more efficient than the YEARS algorithm alone. . In 847 of the 2017 patients of 50 years and older with at least 1 YEARS item, a CTPA was not necessary to exclude PE using the combination of YEARS and the age-adjusted D-dimer cut-off, compared to 752 of the 2017 patients using the YEARS algorithm alone for an absolute difference of 4.7% (95%CI 1.7-7.7). This improvement in efficiency came at the cost of a higher failure rate of 0.75% (95% CI 0.49-1.13). Due to this safety issue, we concluded that there is no added value of implementing the age-adjusted D-dimer cut-off in the YEARS algorithm in the studied patients.

Another strategy to simplify the diagnostic work-up for suspected PE is the Pulmonary Embolism rule out criteria (PERC-rule). This rule consists of seven clinical items. When all items are absent, no further diagnostic tests are required to exclude the diagnosis of PE. In chapter 7 we investigated whether the PERC rule could be used in combination with the YEARS algorithm. A total of 250 out of 1316 patients were PERC negative. The combination of these two strategies reduced the number of required CT-scans with 57 scans (4.3%, 95%CI 0.52-8.1), although eleven patients with PE would have been missed. These missed diagnoses were mostly seen in patients with at least one YEARS-item. The absolute 0.98% increase of the failure rate of the algorithm forces us to conclude that the combination of the YEARS algorithm with the age-adjusted D-dimer cut-off is not safe.

Chapter 8 describes a comparison of total visit time in the emergency department for patients with suspected PE with two different diagnostic algorithms, the YEARS algorithm and the conventional diagnostic strategy with the Wells rule and fixed D-dimer threshold. This was compared on different time points during the diagnostic process, and estimated associated costs of the emergency department visit were calculated. The hypothesis that the YEARS algorithm would be faster due to simultaneous assessment of the three YEARS items and the D-dimer measurement was confirmed in this analysis: the YEARS algorithm was associated with a significantly shorter emergency department visit time of ~60 minutes. Consequently, treatment with anticoagulants was initiated 53 minutes faster using the YEARS algorithm than the conventional algorithm. The estimated costs were reduced with 123 euros per visit for YEARS. Thus, YEARS was shown to be associated with a shorter visit time than the conventional diagnostic strategy, leading to faster start of treatment in case of confirmed PE and savings on emergency department sources.

Chapter 9 describes an evaluation of the added value of chest X-ray in the diagnostic work-up of suspected PE. Currently, almost all patients with suspected PE are referred for chest X-ray and many also for CTPA. However, this is not in accordance with recommendations of in international guidelines, in which the use of chest X-ray is not recommended at all. Reasons why a chest X-ray is often used in clinical practise are its wide availability, the fast execution, the low radiation exposure and the low costs. The aim of this study was to investigate whether chest X-ray provides incremental diagnostic value to the YEARS criteria that is used for selecting patients with CTPA. Further, we aimed to assess differences in chest X-ray results between patients with confirmed PE and patients with PE ruled out. Our results demonstrated that chest X-ray examinations were more frequently abnormal in patients with confirmed PE than in those with PE ruled out, 36% versus 26% respectively (OR 1.60, 95%CI 1.18-2.18). The most frequent chest X-ray abnormalities were 'consolidation' in both patient groups. Only the finding of a rib fracture or pneumothorax, which were present in only 6 out of 1473 patients (0.4%), significantly lowered the post-test probability of PE to an extent that CTPA could have been avoided. The conclusion of this analysis was that the incremental value of chest X-ray in the diagnostic work-up of patients with suspected PE is limited and our data do not support routine chest X-ray in all patients with suspected PE, especially not in patients with an established indication for CT-scan.

Chapter 10 evaluated the prevalence of subsegmental pulmonary embolism – small emboli in the subsegmental vessels – in the YEARS study compared to the Christopher study, where the conventional diagnostic strategy was used. Over the past years, the rate of identified isolated subsegmental pulmonary embolism has doubled with advances in technology, although the clinical relevance of these small emboli is debated and the indication for anticoagulation is questionable in selected patients. A total number of 2291 patients from the YEARS cohort were compared to 3306 patients from the Christopher study. The prevalence of PE was 12% in the YEARS patients (278/2291) with 28 patients diagnosed with isolated subsegmental PE (10% of all PE diagnoses), compared to a prevalence of 20% (676/3306) in the Christopher study with 110 patients with isolated subsegmental PE (16% of all PE diagnoses) for an absolute difference of 6.2% (95% confidence interval 1.4-10). We concluded that application of the YEARS algorithm was associated with a lower prevalence of subsegmental PE, most likely due to the lower sensitivity of YEARS for smaller more distal emboli due to the higher D-dimer threshold without a compromising safety of the diagnostic work-up. These findings indirectly lend support to the hypothesis that some of the isolated subsegmental PE cases may safely remain untreated.

FUTURE PERSPECTIVES

The diagnostic management of patients with suspected acute PE has greatly evolved over the last decades. Diagnostic algorithms with combinations of clinical decision rules and D-dimer tests have significantly and safely decreased the number of required imaging tests to confirm or exclude PE. An important benefit of this reduction is a decrease in CT-associated complications and costs.

The Artemis study demonstrated that the pregnancy adapted YEARS algorithm was safe to use in pregnant patients with suspected PE during all trimesters in a Western European population. Further validation in external cohorts of pregnant women in different continents and for different D-dimer assays than used on the Artemis study will support wide application of the algorithm. Moreover, the algorithm may be further improved. The levels of D-dimer will rise during pregnancy. It is interesting to investigate whether higher D-dimer thresholds than 1000 ng/ml can be used safely during the second and third trimester of pregnancy, to further increase the efficiency of the pregnancy adapted YEARS algorithm and reduce the number or required imaging tests. The very low prevalence of PE among the patients in the Artemis study as well as other studies would support such an approach. The first step would be to evaluate and compare the D-dimer levels during the three different trimesters in patients in whom PE is excluded and in patients with confirmed PE. When new D-dimer thresholds can be established, these should be validated in a new study before it may be applied in clinical practice.

Further research in other patient subgroups who are often excluded from trials -or were only present in small numbers- is necessary, such as elderly patients, inpatients and patients with active cancer. As in pregnant women, D-dimer levels are higher in these groups than in patients without such comorbidities . Hence, further increase of the D-dimer threshold could potentially decrease the use of CTPA in this subgroup too.

The emergency departments of hospitals are crowding with the aging population and the threshold to test for presence of PE has decreased over the past years. Another step to increase the efficiency of the diagnostic management of patients with suspected acute PE is to investigate whether general practitioners could also apply YEARS. If this practice would prove safe, the number of unnecessary referrals and health care costs would decrease in addition to the number of imaging tests ordered.

A final option to improve the specificity of the diagnostic algorithms for suspected PE would be to develop advanced models that allow a personalized D-dimer threshold for each individual patient. The main limitation of such models would be that scores can no longer be easily calculated nor remembered. Prospective management studies evaluating the safety (sensitivity) of such algorithms should therefore also focus on applicability in daily practice.

Lastly, future studies should also investigate the role of the magnetic resonance imaging (MRI) in diagnosing PE, since MRI does not involve use of radiation. Especially the non-

contrast enhanced MR direct thrombus imaging (MRDTI) technique is of particular interest. MRDTI is currently not validated to rule out VTE, but results of ongoing studies with this very purpose are expected shortly. MRI techniques in general could be especially beneficial for patients with a relative contra-indication to CTPA, such as those with contrast allergies or severe renal failure. Up till now, technical issues have prevented the extensive spread introduction of MRI in the work-up of suspected PE.