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The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 12

General Discussion and summary

The studies described in this thesis aim to improve both the diagnostic strategy in patients with suspected pulmonary embolism as well as the therapeutic management in patients with proven acute pulmonary embolism. **Chapter 1** consists of a general introduction and overview of the presented studies. **Chapter 2** gives an overview of the currently available diagnostic strategies for clinically suspected acute pulmonary embolism and the treatment of acute pulmonary embolism. The different clinical decision rules, the D-dimer test and the different imaging tests will be discussed. Furthermore, the current situation concerning the treatment of acute pulmonary embolism including risk stratification, the possibility of outpatient treatment, indications for thrombolysis, the available anticoagulants and the optimal duration of treatment will be addressed.

Part I: Diagnostic management in suspected pulmonary embolism

Chapter 3 discusses the results of a systematic review and patient-level meta-analysis on the efficiency and safety of the exclusion of pulmonary embolism based on a Wells score combined with D-dimer testing. This is the most applied diagnostic strategy to exclude pulmonary embolism without an imaging test worldwide. The results of this study confirm results of earlier studies that proved the efficiency and safety of this strategy for the total group of patients. What this study adds, is the confirmation of the safety of the strategy in different clinically relevant subgroups: inpatients, patients with cancer, chronic obstructive pulmonary disease and venous thromboembolism in their medical history and patients who present themselves late to the clinician. In all groups, the risk of a venous thromboembolism was less than 3 % during 3 months after the initial exclusion of pulmonary embolism based on the Wells score and a D-dimer test. Also, it was shown that the use of an age-adjusted D-dimer threshold (calculated by multiplying the patients age by ten for patients over 50 years of age) instead of the fixed threshold of 500 µg/L fot the total group leads to an increase of patients in whom pulmonary embolism could be ruled out without an imaging test from 28% to 33%. Finally, it is mentioned that the profits of the application of the age-adjusted D-dimer threshold differs between subgroups, being logically the highest in the older patients.

In **chapter 4**, the safety of exclusion of pulmonary embolism based on a normal CTPA is examined. For most patients, the safety of a normal CTPA is undisputed, but in patients with a high pre-test probability, this remains controversial in literature. To clarify this issue, the results of 4 earlier studies on the safety and efficiency of the diagnostic management of suspected pulmonary embolism were combined. This study confirmed that in the total group of patients, the risk of venous thromboembolism after a normal CTPA is very low: 2.0% during the first 3 months. In specific patient groups however, the risk of venous thromboembolism is higher, despite a normal CTPA: this concerns patiens with a very high pre-test probability (Wells score >6), patients with complaints of deep venous thrombosis and patients with a malignancy.

It is difficult to determine whether and to which extent this higher risk is caused by missed diagnoses of venous thromboembolism at presentation of by newly developed venous thromboembolism in the period thereafter. A strategy to diminish the risk of venous thromboembolism is also unclear.

The following two chapters set out two studies that investigated improvement of the diagnostic process in suspected pulmonary embolism. In **chapter 5** the possibility of applying a higher D-dimer threshold in patients with a low pre-test probability was examined, using the combined results of two earlier studies. Instead of the dichotomous algorithm, the trichotomous algorithm based on the Wells score was used. In patients with a low pre-test probability of PE, based on a Wells score of <2 points, a D-dimer threshold of <1000 µg/L was used; in patients with a moderate pre-test probability, based on a Wells score of 2-6 points, the D-dimer threshold was <500 µg/L and only in patienst with a high risk on PE based on a Wells score of >6 points, a CTPA was performed directly. The results show that this strategy leads to improved efficiency in the diagnostic process: the percentage of patients in whom PE could be excluded without a CTPA rises from 26% to 36%. The number of missed diagnoses of PE seems to be small, though it requires a prospective validation study to confirm this.

Chapter 6 shows the results of the YEARS study: a prospective validation study of a highly simplified diagnostic algorithm for suspected PE. In the YEARS algorithm, the Wells score was replaced by three YEARS items: clinical signs of deep veen thrombosis, hemopthysis and whether the treating clinician thinks pulmonary embolism is the most probable diagnosis. These items are scored, and subsequently a D-dimer test is performed in all patients. When no YEARS item is present and the D-dimer result is <1000 µg/L, PE is excluded without the use of CTPA. In patients with one or more YEARS items, the D-dimer threshold is set at <500 µg/L to be able to exclude PE without a CTPA. This algorithm wat tested prospectively in the YEARS study in 3465 patients. Results reveal that this algorithm can be applied safely: the risk of venous thromboembolism after exclusion of PE was only 0.61%. Benefits of the YEARS algorithm are the simplified procedure: there are only three items to score and in all patients a D-dimer test can be performed instead of only those with an unlikely pre-test probabilty. The main benefit, however, is the 14% increase of the the number of patients who can be managed safely without a CTPA in comparison with the standard algorithm, 48% versus 34% respectively.

Part II: Treatment of acute pulmonary embolism

In the treatment of pumonary embolism and deep venous thrombosis, one of the most important developments of the past years is the introduction of the direct oral anticoagulants. These oral drugs directly inhibit thrombine (factor IIa) or factor Xa. Their largest benefit is a more stable famockinetic and farmacodynamic profile, which makes routine evaluation of the anticoagulant effect, as in vitamin K antagonists, not required.

Also, several studies report lower risks of bleeding complications. **Chapter 7** describes a meta-analysis of individual studies of the direct oral anticoagulants for the treatment of acute PE and deep venous thrombosis. The results confirm that direct oral anticoagulants are equally effective in the prevention of recurrent venous thromboembolism with a relative risk of 0.88 (95% confidence interval 0.74-1.05). Also, this meta-analysis confirms the indication of a lower risk of bleeding complications when direct oral anticoagulants are used: the relative risk of major bleeding is 0.60 (95% confidence interval 0.41-0.88). It should be emphasized, however, that the absolute risks of both recurrent venous thromboembolism and major bleeding are small, and therefore so are the differences between absolute risks.

In **chapter 8**, a very specific recommendation from the Dutch Guideline on Diagnostics, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention Arterial Thrombosis is evaluated. In general, it is costumary to advise anticoagulant treatment for indefinite duration to all patients who have had a second venous thromboembolism. However, the guideline also advises to consider limited duration of treatment of twelve months in patients in whom the second thromboembolism appeared more than one year after the cessation of anticoagulant treatment for the first event. There was solely indirect evidence fort his recommendation. This chapter reveals the outcomes of the application of this specific recommendation in the Leiden Universitry Medical Centre. Of 131 patients with second venous thromboembolism more than one year after stopping anticoagulant treatment, 77 patients were treated for a limited duration. After stopping anticoagulant treatment, the incidence of venous thromboembolism was 9.4 per 100 patientyears (95% confidence interval 6.1-14), and the risk seems even higher in patients with an idiopathic second venous thromboembolism and lower in those with a provoked venous thromboembolism. Although this is an observational study, it is highly probable that this high risk of recurrent venous thromboembolism exceeds the risk of continuing anticoagulant treatment, mainly bleeding complications. Therefore, this study does not support the recommendation of the Dutch Guideline.

The three chapters that follow adress the treatment of cancer-associated venous thromboembolism. In **chapter 9**, a cohort study is described which evaluates the safety of stopping anticoagulant treatment in cancer-assiciated venous thromboembolism in patients cured from cancer. Out of 358 included patients with cancer-associated venous thromboembolism, anticoagulant treatment could be discontinued in 68 patients after they were cured from their malignancy. The risk of recurrent venous thromboembolism in this group was low with an incidence of 3.2 per 100 patientyears (95% confidence interval 1.5-5.9). Notable in this study is the observation that in 7 out of the 10 patients with recurrent venous thromboembolism, a recurrence of the malignancy was observed at the same moment or shortly after the diagnosis of recurrent venous thromboembolism. These results support the current guideline to discontinue anticoagulant treat-

ment for cancer-associated venous thromboembolism in patients cured from cancer. **Chapter 10** outlines a meta-analysis of the use of direct oral anticoagulants voor cancer-associated venous thromboembolism. The method of this study is identical to the study described in chapter 7, but in this chapter the focus was on cancer-associated venous thromboembolism only. A total of 19,060 patients were included in the five separate studies, of which 973 were known to have an active malignancy. The risks of recurrent venous thromboembolism and bleeding complications were relatively high, compared to patients without cancer, which is in accordance with current literature. The relative risk for recurrent venous thromboembolism for direct oral anticoagulants compared to vitamin K antagonists was 0.66 (95% confidence interval 0.38-1.2) and the risk for major and clinically relevant bleeding 0.94 (95% confidence interval 0.70-1.3). It must be mentioned that little information was provided about the nature and dissemination of the cancer as well as anti-cancer treatment. Furthermore, the treatment in the control arm of this study, vitamin K antagonists, is not the treatment of first choice in cancer-associated venous thromboembolism. For these reasons, the results of this study should be interpreted cautiously. The results may serve as a strong stimulant to investigate direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism, which is currently underway.

Chapter 11 finally focuses on coincidental diagnosed pulmonary embolism, generally referred to as incidental pulmonary embolism. This is a relatively new clinical presentation predominantly seen in cancer patients, due to the relatively high risk of venous thromboembolism and by the frequent performance of high quality CT-scanning in these patients. Based on observational, often small studies it is recommended to treat incidental pulmonary embolism in the same way as clinically suspected pulmonary embolism. This chapter aimed to collect as much data as possible out of the individual observational studies in order to find the best available evidence on the treatment of incidental pulmonary embolism. Information concerning a total of 926 patients out of 11 different studies was collected. The most important results include a comparable risk of recurrent venous thromboembolism in patients treated with low molecular weight heparins compared to vitamin K antagonists: 6.2% vs 6.4% during 6 months after the diagnosis. The risk in 53 patients who were not treated with anticoagulant treatment, for which the reason was unknown, was 12%. The risk of major bleeding was considerably higher in patients treated with vitamine K antagonists: 13% versus 3.9% in the group treated with low molecular weight heparins. Despite several important limitations due to study design, these results suggest that anticoagulant treatment lowers the risk of recurrent venous thromboembolism and that low molecular weight heparins are favourable over vitamin K antagonists. Both conclusions support the recommendations of current guidelines.

Perspective for the future

A diagnostic algorithm such as the YEARS algorithm allows clinicians to exclude pulmonary embolism in patients in which they suspect pulmonary embolism, without the use of potentially harmfull CTPA. For the future, it remains a challenge to further diminish the need for CTPA. It does not seem to be very likely however that any more profit can be achieved from alterations in the clinical decision rule or D-dimer thresholds.

Perhaps, in the future CTPA can be replaced by alternative imaging such as an MRI scan, to overcome concerns on radiation exposure. For now, the low sensitivity and high risk of inconclusive results are the most important limitations of MRI scanning for suspected PE. Another challenge for the future is the suspicion of pulmonary embolism in pregnant women. This is a relatively common clinical challenge, in which the risk of radiation exposure for the unborn child forms an extra concern and argument to make an effort to reduce the use of CTPA. Untill now, no diagnostic strategy was validated to exclude pulmonary embolism in pregnant women without an imaging test, emphasizing the urgent need for a prospective study of an algorhitm such as the YEARS algorhitm in this group.

The introduction of the direct oral anticoagulant poses several important unanswered questions concerning the optimal treatment of acute pulmonary embolism. These drugs have now become the treatment of choice for the majority of patients with acute pulmonary embolism. In cancer patients, the efficacy and safety of these drugs is being investigated. Also, the low risk of bleeding complications has influence on the risk-benefit ratio of extending anticoagulant treatment. Therefore, the introduction of these drugs may have consequences for the choices on the duration of treatment. Clinicians and patients will tend to continuing anticoagulant treatment indefinitely, also for a first episode of venous thromboembolism, due to the lower bleeding risks. This will have important consequences and will lead to higher health care costs and over-treatment, since many patients never develop a recurrent venous thromboembolism. Furthermore, it is interesting whether the risk of a recurrent event evolves over time: does anticoagulant treatment prevent a recurrence only during therapy, or does the risk decline over time, which creates a possibility to stop anitocagulant treatment later on?

In incidental pulmonary embolism, the advantage of anticoagulant treatment remains unclear. Indirect evidence, as in this thesis, suggests a lower risk of recurrent venous thromboembolism when treated, and therefore a benefit for patients. Cancer patients, however, are also known to have a considerably higher risk of bleeding complications during anticoagulant treatment. A definite answer to this question requires a randomized trial directly comparing no or only very short duration of treatment to indefinite duration of treatment, but such a trial will probably never be performed.