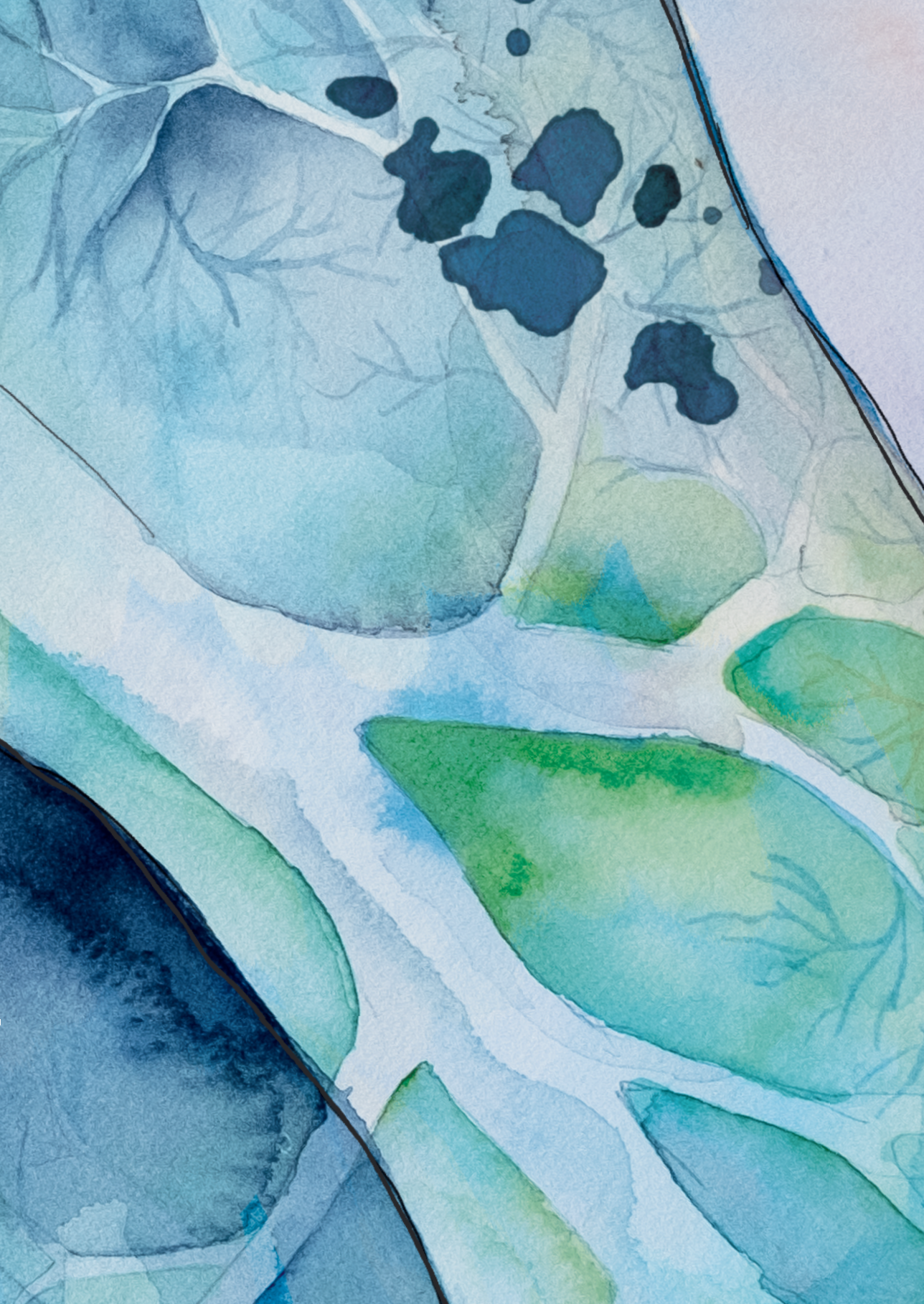
The diagnostic management of suspected pulmonary embolism in special patient populations

Stals, M.A.M.



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General discussion and summary

GENERAL DISCUSSION AND SUMMARY

In this thesis, we described studies focusing on the non-invasive diagnostic management of patients with suspected PE and studies reporting on venous thrombotic complications in patients with COVID-19. **Chapter 1** provides a general introduction of the diagnosis of pulmonary embolism (PE) and an overview of the presented studies.

Part 1: The diagnostic management of suspected acute pulmonary embolism

Chapter 2 describes the challenges of diagnosing PE in patients with cancer, elderly patients and patients with renal insufficiency, three patient subgroups at particular high-risk for venous thromboembolism (VTE).[1,2] One of the key points of this paper was to review the available evidence on applying diagnostic strategies with adapted D-dimer thresholds in these patient subgroups, since D-dimer levels are known to be frequently elevated, even in the absence of thrombosis.[3-6] Based on the limited available data, diagnostic strategies for ruling out PE starting with clinical decision rules (CDRs) and D-dimer testing seem clinically useful in these specific patient categories as well. Although the yield of the CDR/D-dimer combination in reducing chest imaging is lower, efficiency could likely be increased by applying strategies with adapted D-dimer thresholds.

Chapter 3 presents the results of a large systematic review and individual patient data meta-analysis on the safety and efficiency of the most widely used diagnostic strategies for ruling out pulmonary embolism across clinically relevant patient subgroups (defined by sex, age, cancer, and previous venous thromboembolism (VTE)). Strategies under evaluation were the Wells and revised Geneva scores combined with fixed and adapted D-dimer thresholds, and the YEARS algorithm. For this study, individual patient data from 20 553 patients were available. Results showed that, across all strategies, efficiency was highest in patients younger than 40 years and gradually decreased with age, with the lowest efficiency in patients above 80 years and patients with cancer. Furthermore, efficiency increased considerably in the subgroups when adapted D-dimer thresholds were applied, which was however accompanied with higher predicted failure rates varying between 2-4% in the subgroups. Still, despite exceeding the failure rate margin of 2% recommended by Internal Society on Thrombosis and Hemostasis standards[7], we concluded that all studied strategies might be considered safe across all the predefined patient subgroups. This conclusion was drawn based on the arguments of the theorem of Bayes, stating that a higher failure rate is to be expected in groups with a higher PE prevalence[7], as well as the presence of differential verification bias, which may have led to an overestimation of predicted failure rates of strategies with adapted D-dimer thresholds.[8] As such, we could not identify an overall preferred diagnostic strategy, but

for obvious reasons of efficacy, this IPDMA supports the application of adapted D-dimer thresholds. What this study adds to the literature is that most previous studies were underpowered to perform reliable subgroup analyses. The very large sample size in this study enabled us to perform more robust subgroup analyses on frequently encountered subgroups than possible in these individual studies alone. This is of utmost relevance as it is recognized that non-invasive diagnostic strategies might me less safe and efficient in specific patient subgroups, hampering the use of these strategies in clinical practice.

Chapter 4 describes the results of a systematic review and meta-analysis of individual patient data focusing on the performance of non-invasive diagnostic strategies for ruling out PE in pregnant women. Since prospective diagnostic studies in pregnant women are very scarce we were able to use individual patient data from the two available studies: the CT-PE Pregnancy study[9] and the Artemis study[10]. Importantly, as most international guidelines have not been updated with the study results of these two studies yet, they still present contradictory recommendations regarding the utility of non-invasive diagnostic strategies in pregnancy. This IPDMA showed that both the Wells rule (with fixed and adapted D-dimer threshold) as the YEARS algorithm were able to safely rule out PE in pregnant women, with a failure rate varying between 0.37-1.4%. In our study, efficiency increased substantially when applying pre-test probability dependent D-dimer thresholds. Following these adapted strategies PE could be ruled out in up to 40% of the pregnant women. This is especially important as referral for imaging tests is complicated by concerns about radiation exposure to both mother and fetus. Our results are in line with the latest guideline recommendations (ESC 2019 [11]) and underline the applicability of pre-test probability assessment and D-dimer tests to rule out PE in pregnant women. This study with almost 900 patients is the largest study to date to evaluate non-invasive diagnostic strategies for suspected PE in pregnant patients using patient level data of prospective management studies. We believe that these results will support harmonization of international guidelines, in order to improve the diagnostic approach of pregnant women with suspected PE and reduce the need for chest imaging.

Chapter 5 shows the results of a post-hoc analysis of the YEARS study[12], in which we externally validated the newly derived 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS).[13] The 4PEPS strategy integrates different aspects from currently available diagnostic strategies, including the identification of very low risk patients in whom D-dimer testing can be withhold[14], and the use of an age-adjusted and CPTP dependent D-dimer threshold. In our study, efficiency of 4PEPS was a non-significantly 10% higher than that of the originally applied YEARS algorithm (58% vs. 48%), but at the cost of a 3-fold higher failure rate (1.3% vs. 0.42%). Up to now, a formal prospective management outcome study of the 4PEPS strategy is lacking. Our study provides external validation

of the score in an independent cohort of patients and confirms the efficiency of the 4PEPS strategy. Nevertheless, as the observed failure rate appeared to be higher than with YEARS, this study emphasizes the need for a formal prospective management study before the score can be used in clinical practice.

An overview of the diagnostic approach of patients with suspected PE is given in **Chapter 6**, addressing the different methods for assessing clinical pre-test probability, approaches to D-dimer testing and available imaging tests methods. Moreover, this chapter provides clinicians with practical diagnostic guidance when facing a patient within a special patient subgroup (elderly patients, patients with cancer, pregnant patients and patients with COVID-19). Also, current guideline recommendations are discussed.

In **Chapter 7**, the performance of the generic National Early Warning Score (NEWS)[15] was compared to the (simplified) Pulmonary Embolism Severity Index ((s)PESI)[16,17] in predicting early ICU admission and mortality in patients with a recent diagnosis of acute PE. This study was a post-hoc analysis of the YEARS study[12] and included hemodynamically stable patients with confirmed PE. This study demonstrated that NEWS had a comparable performance to (s)PESI in predicting 30-day mortality in acute PE patients, and possibly even better performance in predicting 7-day ICU admission. These results suggest that NEWS could form an alternative risk stratification score in patients with acute PE. That could be beneficial, as the NEWS is a generic tool for identifying patient deterioration in acute settings and the application of a single scoring system in acute care may simplify decision-making and improve adherence to prognostic scores.

Part 2: Venous thrombotic complications in COVID-19 patients

The outbreak of COVID-19 has led to accumulating studies reporting high incidences of thrombotic complications in hospitalized COVID-19 patients, especially in patients admitted to the Intensive Care Unit (ICU).[18-21] Contrarywise, the incidence of clinically relevant thrombosis in patients with other viral respiratory infections was hitherto underreported as only small case series have been published.[22,23] Consequently, it was unknown how this high incidence of thrombotic complications in COVID-19 patients compares to those observed in hospitalized patients with other viral pneumonias such as influenza. Results of our study focusing on this research question are presented in **Chapter 8**. For this retrospective cohort study, we used data from Statistics Netherlands on thrombotic complications in hospitalized patients with influenza. In parallel, we gathered data on hospitalized COVID-19 patients by scrutinizing patients charts in three hospitals in the Netherlands. Compared to hospitalized patients with influenza, patients admitted with COVID-19 had a distinctly increased risk for thrombotic complications (30-day cumulative incidence 25% in COVID-19 vs. 11% in influenza). This risk was foremost

driven by a difference in venous thrombotic complications (23% in COVID-19 vs. 3.6% in influenza) and was particularly observed in patients admitted to the ICU. Remarkably, patients with influenza were more often diagnosed with arterial thrombotic complications (4.4% in COVID-19 vs. 7.5% in influenza). To our knowledge, this study was the first to evaluate the incidence of thrombotic complications in hospitalized COVID-19 patients as opposed to that observed in hospitalized patients with influenza.

Since COVID-19 is associated with a high risk for VTE, clinicians frequently face the challenge of correctly diagnosing PE in a patient with COVID-19. Diagnosing PE in the absence of COVID-19 is already notoriously difficult and COVID-19 challenges this diagnostic process even more. Diagnosing PE in the setting of COVID-19 is particularly challenging because of the wide overlap between signs and symptoms of both conditions, moreover, D-dimer levels are often elevated in the absence of thrombosis[24,25] and imaging tests may not always be feasible in critically ill patients or patients with severe renal insufficiency. Unfortunately, guidance on the best diagnostic approach for clinically suspected PE in COVID-19 patients is lacking. These difficulties and available literature and guidelines on this topic are discussed in **Chapter 9**. In this narrative review, we specifically focused on identifying symptoms with a high suspicion for PE and on the performance of diagnostic strategies for suspected PE in COVID-19. In the absence of prospective diagnostic management studies, this review proposed to adhere to current diagnostic strategies applying pre-test probability assessment and D-dimer testing as available evidence suggests that these might be considered safe, an advice which is being supported by current international consensus documents and guidelines. Still, efficiency could be diminished in the setting of COVID-19.

Chapter 10 discusses the results of a prospective multicenter study evaluating the performance of validated diagnostic strategies for ruling out PE in patients with (suspected) COVID-19. 707 patients were included, of whom 36% were managed by the YEARS algorithm, 4.2% by the Wells rule and 52% directly proceeded to CTPA; 7.4% of the patients were not tested because of hemodynamic or respiratory instability. With YEARS, PE could be ruled out in 29% of the patients, of which one patient developed a nonfatal PE during follow-up (failure rate 1.4% 95% CI 0.04-7.8). These results underline the applicability of YEARS in (suspected) COVID-19 patients with clinically suspected PE. Another important observation in our study was that the failure rate after a negative CTPA, used as a sole test (3.6%) or within YEARS (8.8%), was high. This reflects the high thrombotic risk in these patients, stressing the importance of remaining alert for incident (new) VTE during follow-up and warranting ordering new diagnostic tests if the clinical situation deteriorates.

Future perspectives

Over the last decades, many important improvements have been made in the diagnostic management of suspected acute PE. With the recent introduction and validation of D-dimer thresholds dependent on age or clinical pre-test probability, the proportion of patients requiring imaging has decreased from about 70% to 40-50%. While these diagnostic strategies have proven to be safe and efficient in the general population, their diagnostic performance in specific subgroups, such as patient with cancer, elderly patients, and pregnant patients, who have often been excluded from participating in trials, is unknown. Not surprisingly, diagnosis of PE is frequently considered in patients from these categories, as they represent specific high-risk groups for VTE. Despite our large systematic review and individual patient data meta-analysis in which we evaluated the most commonly used diagnostic strategies across different relevant patient subgroups (presented in Chapter 3), uncertainty about the appropriate diagnostic management in these patients remains. In the future, randomized controlled trials comparing the application of different diagnostic strategies in these patient subgroups are necessary to prove that these strategies are definitely safe and efficient in the particular subgroups. These trials should evaluate how the failure rate of a certain diagnostic strategy relates to the failure rate of a 'negative' CTPA. Until now, strategies are often deemed unsafe in high-risk patients based on higher observed failure rates in available studies presenting subgroup analyses. However, some VTE failures are not necessarily a failure of the diagnostic strategy at baseline, but instead, are new thrombotic events unrelated to the index presentation. As such, these failures would also be observed in the randomization arm of patients that are immediately referred for imaging. As an example, the ongoing Hydra study evaluates the safety and efficiency of the YEARS algorithm versus CTPA only in patients with cancer and suspected PE.

Until now, most of the available diagnostic strategies have focused on simplicity, since the decision rules needed to be calculated at the bedside to rapidly identify patients who should be referred for imaging. It is known that the benefit of diagnostic strategies is foremost dependent on their correct application and more complex scores could lead to inadequate use at busy emergency departments. However, the current evolution of digitalized storage of healthcare data and the increasing use of smartphone applications and websites for the calculation of risk scores creates important opportunities. For further research it is therefore less important to focus on simplicity. Instead of scores that operate at a population-level and discriminate patients between requiring imaging yes or no, future research may also focus on developing strategies that provide an absolute and individual probability estimate of PE. Models that provide individualized estimates can better discriminate between patients with and without PE at an individual level. Also, safety thresholds can be tailored to specific healthcare settings or

comorbidity and risk estimates can be explicitly communicated to patients and used in the process of shared decision making. Together with E-health facilities, these developments increase patient-self management and individualized management decisions. Still, a binary decision should be made between referring patients for imaging or not. How to interpret these individualized estimates is the greatest challenge, especially for physicians less experienced in the field of venous thromboembolism. Importantly, before implementation in clinical practice, clinical utility of such an model should be evaluated in a prospective management outcome study in which imaging is withheld based on the estimated PE probability.

Although PE-related clinical research is evolving at a rapid pace, important clinical questions for the future remain. Such as whether it's safe to use D-dimer testing for the exclusion of VTE in already anticoagulated patients, a situation that physicians often encounter in clinical practice. Evidence for the use of D-dimer in these patients is very scarce. Moreover, it is known that anticoagulants can lower D-dimer levels leading to false negative test results and missed diagnoses.[26] To answer the ongoing debate on the applicability of D-dimer testing for the exclusion of PE in anticoagulated patients, a randomized controlled trial making a direct comparison should be initiated. This trial should include patients on therapeutic dose anticoagulants and suspected PE and randomize patients between management with a diagnostic strategy (including D-dimer; e.g. YEARS) versus CTPA alone. The trial should be designed as a non-inferiority trial for the main safety outcome (3-month VTE rate). If non-inferiority has been demonstrated, at secondary stage superiority for the efficiency outcome (number of CTPAs avoided) should be evaluated. Secondary outcomes should include PE related mortality, the timing, location and severity of recurrent VTE, patient-reported outcomes (including quality of life indicators and VTE-related utilization of healthcare resources), contrast material induced reactions and bleeding complications in both study arms. Unfortunately, such a trial shall probably require a very large sample size, as the occurrence of PE while already on therapeutic anticoagulant therapy is low.

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