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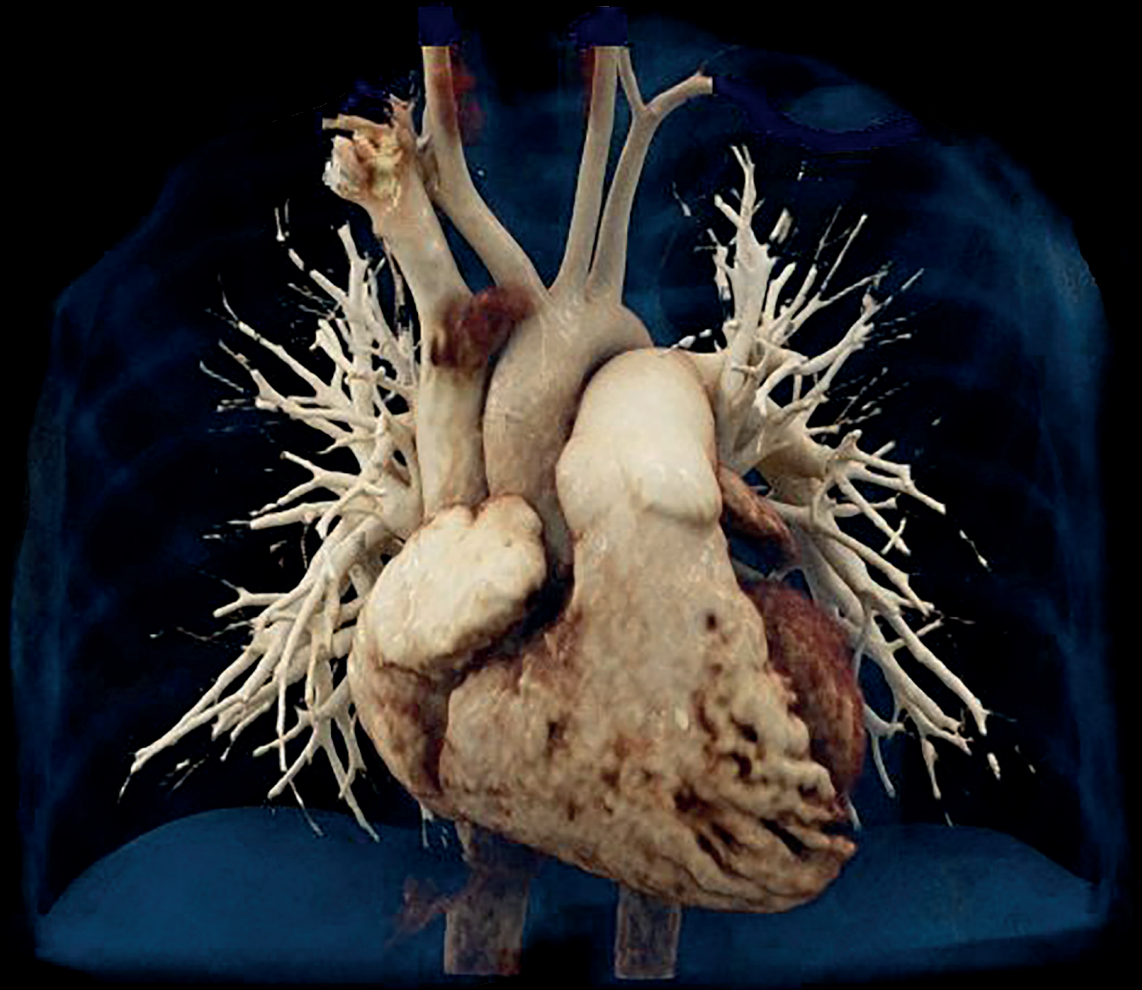
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# Advances in CT Pulmonary Angiography for Pulmonary Embolism



Ludovicus Franciscus Marie Beenen



# **Advances in CT Pulmonary Angiography for Pulmonary Embolism**

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# **Advances in CT Pulmonary Angiography for Pulmonary Embolism**

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor  
aan de Universiteit van Amsterdam  
op gezag van de Rector Magnificus  
prof. dr. ir. K.I.J. Maex

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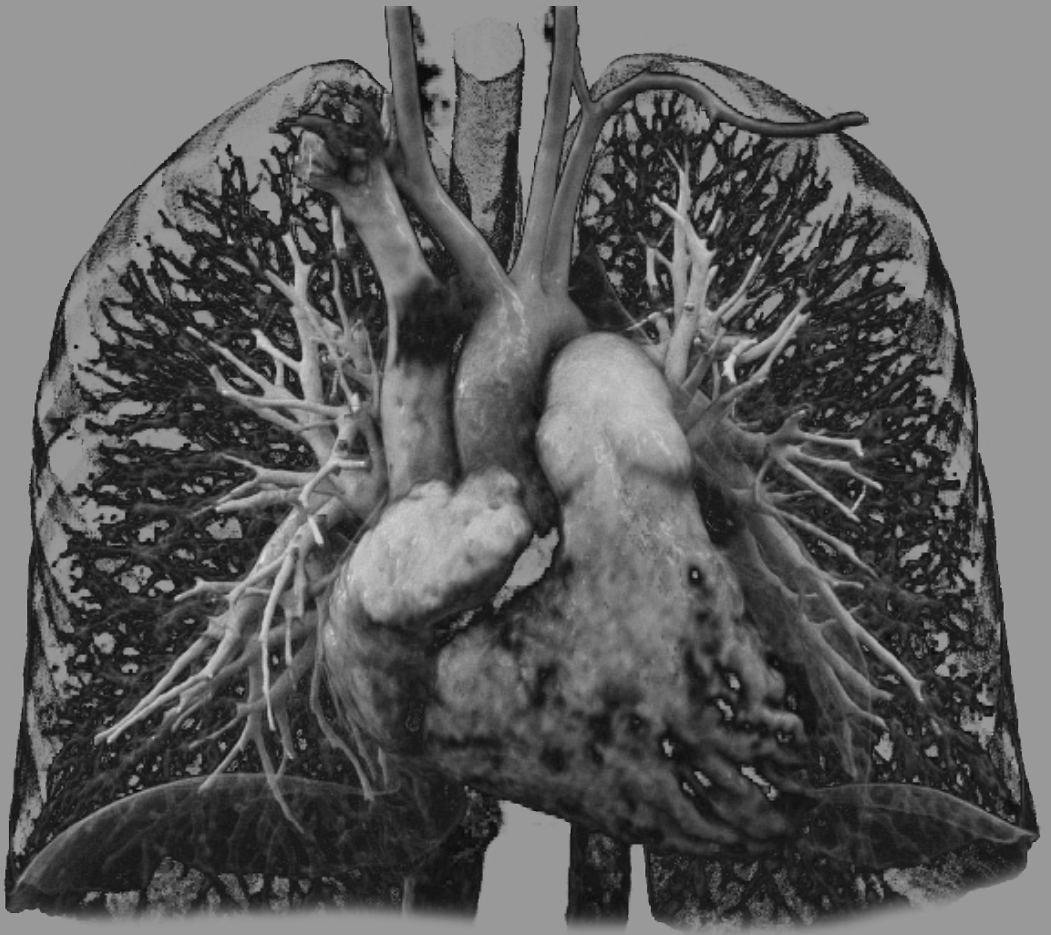
Medizinische Hochschule Hannover

Faculteit der Geneeskunde

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# **Chapter 1**

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**Introduction & General Outline**



## Introduction

Pulmonary embolism (PE) is the third most frequent acute cardiovascular disease, after acute myocardial infarction and stroke.<sup>1</sup> The annual incidence of pulmonary embolism is 1 per 1000 people and increases sharply with age,<sup>2</sup> with an pulmonary embolism related mortality of 7 deaths per 100 000 people per year.<sup>3</sup> After diagnosis of acute pulmonary embolism up to 9.1% and 19.6% of patients die within 1 and 6 months, respectively,<sup>4</sup> with some attributable to associated comorbidities rather than to pulmonary embolism.

A large strain on the right ventricle caused by obstructing blood clots in the pulmonary circulation is thought to be the main mechanism for the occurrence of heart failure and mortality in pulmonary embolism.<sup>5</sup> It is of great importance to have the diagnosis pulmonary embolism established rapidly in order to start treatment as early as possible: a delay in timing of anticoagulation in the ED results in higher 30-day mortality.<sup>6</sup>

Presenting symptoms of pulmonary embolism range between vague discomfort of the chest until collapse for which cardiopulmonary resuscitation is needed, and can mimic many other diseases. The fear of missing such an important and potentially life-threatening diagnosis harbours the risk that often, or even too often, pulmonary embolism is considered by the treating physician, which will consequently lead to more imaging.

Request for imaging can be based on a general clinical impression but this has a relatively low specificity and lacks standardization.<sup>7</sup> To achieve a higher diagnostic efficiency, clinical decision rules (CDRs) have been developed, consisting of a number of clinical and medical parameters. After assessing a low probability of pulmonary embolism the diagnosis can be safely ruled out and redundant exposure to ionizing radiation and contrast medium can be avoided. The most well-known clinical decision rule contains the Wells criteria in which seven items are attributed with a specific value.<sup>8</sup> For scores above a certain threshold probability of pulmonary embolism is high and further imaging needs to be performed. In case of a low score, as a second step the D-dimer level, a fibrin degradation product, is determined. If the D-dimer level is not increased, pulmonary embolism can be safely excluded and imaging is not needed. Generally speaking, a clinical decision rule combined with a CT pulmonary angiography (CTPA) is a safe and reliable strategy to exclude pulmonary embolism.

This thesis is divided into three parts. Part I describes improvements in the diagnostic work-up of patients with a clinical suspicion of pulmonary embolism. Part II focuses on the additional value of findings on CTPA with regard to prognosis and risk stratification. Part III explores venous thrombo-embolism (VTE) diagnostic modalities in patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) linked to COroNaVirus Disease (COVID-19) admitted to the hospital, and particularly differences between ward and ICU patients.

## **PART I - DIAGNOSIS**

Why don't physicians follow clinical guidelines? A clinical decision rule is less likely to be used when experienced as inconvenient or difficult to use.<sup>9</sup>

The *first part* of this thesis addresses the development, prospective validation and clinical impact of an improved diagnostic strategy for the evaluation of pulmonary embolism, called the YEARS algorithm. In daily clinical practice in busy emergency departments, during triage of patients suspected of pulmonary embolism d-dimer levels often are already measured even before assessment by the treating physician is performed. Hence, it would be logical to restructure this time-consuming two-step diagnostic strategy into one that integrates all assessments at presentation, and thus not only will prevent redundant CT-scanning for the patient, but also decreases the time spent in the emergency department.

## **PART II - PROGNOSIS**

The *second part* of this thesis addresses the added value of findings other than pulmonary embolism on CTPA. CTPA is considered the reference standard imaging technique for the evaluation of pulmonary emboli. CTPA has several advantages above other modalities: it is non-invasive, robust, globally widely available, has a high sensitivity and specificity, and shows directly the distribution and extent of thrombi.<sup>10,11</sup> Furthermore, CTPA can provide additional information, which cannot be delivered by other modalities. Alternative diagnoses can be observed in approximately 50-70% of patients, mostly pneumonia, pleural fluid, heart failure, but also less frequent pathologies like pericardial fluid or abdominal pathology.<sup>12</sup> How co-existence of these pathologies with pulmonary embolism influences outcome is not exactly known, and will be addressed in this part. Also, modern CT scanners nowadays have several possibilities for advanced imaging, like dual energy (DECT) scanning. Hereby the amount of iodine can be established, resulting in an overall iodine mapping image, quite similar to the well-known ventilation-perfusion

scintigraphy images. Wedge shaped zones with less iodine suggests presence of an obstructing thrombus that otherwise possibly could have been missed. The total volume of these defects reflects the amount of lung tissue that is involved, which is associated with the development of pulmonary hypertension and mortality.<sup>13</sup>

Initial hemodynamic instability is an important marker of prognosis and occurs in approximately 5% of cases, with short term mortality exceeding 15%. For the remaining 95% of patients with acute pulmonary embolism, several prognostic scores consisting of simple clinical criteria have been proposed to estimate intermediate or low risk of an adverse outcome. Of these, the Pulmonary Embolism Severity Index (PESI) and the simplified-PESI (sPESI) are incorporated in the European Society of Cardiology (ESC)-guidelines to guide treatment.<sup>5</sup> To further estimate the risk of adverse outcome of pulmonary embolism, assessment of right ventricular dysfunction (RVD) is recommended, using biomarkers like NT-proBNP and echocardiography. Besides providing the diagnosis CTPA potentially could harbour such prognostic features. Many radiological parameters have been studied and proposed, including several scores that evaluate location and magnitude of clot distribution.<sup>14</sup> However, there is no consensus on the parameters that should be used, as the underlying evidence comes from low-quality studies and from different populations. Which of several potentially interesting parameters works best is addressed in this part: right ventricle/left ventricle ratio (RV/LV), enlarged pulmonary trunk, septal bowing, contrast medium reflux?

### **PART III - COVID**

The *third part* of this thesis is dedicated to the interaction between COVID-19 and venous thromboembolism. In 2020 COVID-19 posed unprecedented health care problems, both on a global scale and for many individual patients. Acute respiratory failure is the most common reason for hospital admission. The mortality of these patients during the first wave of the pandemic was particularly high. Several hypotheses emerged on contributing factors, as e.g. imbalance of the bradykinin-kallikrein system with pulmonary oedema and inflammatory thrombotic microangiopathy. The differences between ICU and ward patients with regard to occurrence of pulmonary embolism and deep vein thrombosis, and consequences on pulmonary perfusion is explored in this part.

## General outline

In **chapter 1** I present an overview of pulmonary embolism and the role of CTPA and advanced imaging in the diagnostic work-up and risk estimation of prognosis.

## PART I - DIAGNOSIS

In *Part I* we explored improvements in diagnostic decision support and the appropriate use of CTPA for patients suspected of pulmonary embolism. First, in **chapter 2**, we evaluated the value of each of the items in the Wells criteria, in conjunction with a known elevated D-dimer. This resulted in the development of the YEARS decision rule, for which a multicentre clinical validation study is described in **chapter 3**.

## PART I - PROGNOSIS

*Part II* focuses on the value of findings on CTPA in risk assessment and prognosis of patients with confirmed pulmonary embolism. I performed post hoc analyses in patients with pulmonary embolism who have been included in the Hokusai-VTE randomized clinical trial on anticoagulant therapy. In **chapter 4** the association between radiological parameters on CTPA and associated right ventricular dysfunction with short and long-term clinical outcome is investigated. The association of these parameters with body mass index is determined in **chapter 5**. The impact of co-existence of pulmonary embolism with several common pulmonary and cardiac pathologies on CTPA is described in **chapter 6**.

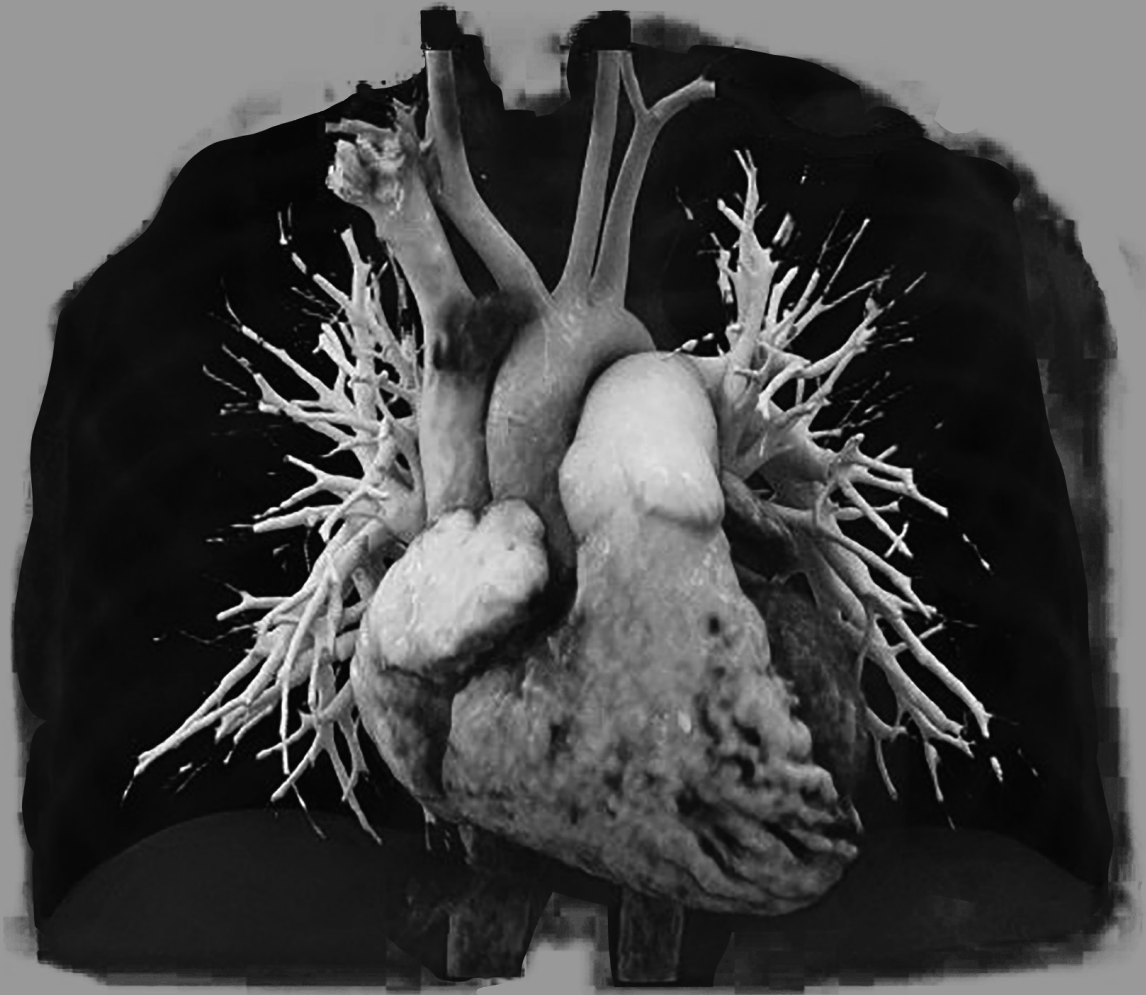
## PART III - COVID

*Part III* is dedicated to COVID-19 and VTE. The incidence of pulmonary embolism and DVT in hospitalized patients with COVID-19 is described in **chapter 7**. In **chapter 8**, we describe the occurrence and possible significance of perfusion defects on dual energy CTPA in a sample of these patients during the first wave of the COVID-19 pandemic.

## References

1. Di Nisio M, van Es N, Buller HR. Deep vein thrombosis and pulmonary embolism. *Lancet (London, England)* 2016; **388**(10063): 3060-73.
2. Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: update on management and controversies. *BMJ (Clinical research ed)* 2020; **370**: m2177.
3. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. *The Lancet Respiratory medicine* 2020; **8**(3): 277-87.
4. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* 2021; **143**(8): e254-e743.
5. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *European heart journal* 2020; **41**(4): 543-603.
6. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest* 2010; **137**(6): 1382-90.
7. Lucassen WA, Beenen LF, Buller HR, et al. Concerns in using multi-detector computed tomography for diagnosing pulmonary embolism in daily practice. A cross-sectional analysis using expert opinion as reference standard. *Thrombosis research* 2013; **131**(2): 145-9.
8. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. *Ann Intern Med* 2011; **154**(11): 709-18.
9. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Jama* 1999; **282**(15): 1458-65.
10. Zhang LJ, Lu GM, Meinel FG, McQuiston AD, Ravenel JG, Schoepf UJ. Computed tomography of acute pulmonary embolism: state-of-the-art. *European radiology* 2015; **25**(9): 2547-57.
11. Albrecht MH, Bickford MW, Nance JW, Jr., et al. State-of-the-Art Pulmonary CT Angiography for Acute Pulmonary Embolism. *AJR American journal of roentgenology* 2017; **208**(3): 495-504.
12. van Es J, Douma RA, Schreuder SM, et al. Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism. *Chest* 2013; **144**(6): 1893-9.
13. Ruggiero A, Screaton NJ. Imaging of acute and chronic thromboembolic disease: state of the art. *Clinical radiology* 2017; **72**(5): 375-88.
14. Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. *The European respiratory journal* 2014; **43**(6): 1678-90.

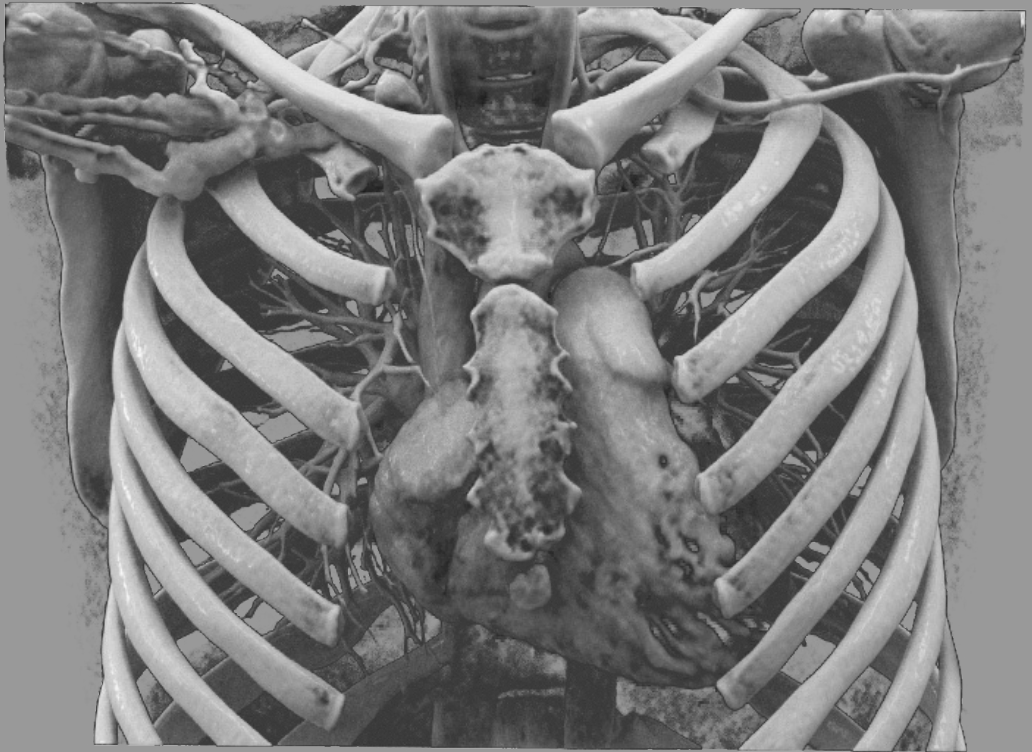




# **PART I**

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Optimising diagnosis  
of pulmonary embolism



# Chapter 2

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A simple decision rule including  
D-dimer to reduce the need for  
CT-scanning in patients with  
suspected pulmonary embolism

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J. van Es, L.F.M. Beenen, R.A. Douma, P.L. den Exter, I.C.M. Mos,  
K. Kaasjager, M.V. Huisman, P.W. Kamphuisen, S. Middeldorp, P.M.M. Bossuyt

## **Abstract**

### **Background**

An ‘unlikely’ clinical decision rule with a negative D-dimer result safely excludes pulmonary embolism (PE) in 30% of presenting patients. We aimed to simplify this diagnostic approach and to increase its efficiency.

### **Methods**

Data of 723 consecutive patients with suspected PE were analysed (22% PE prevalence). After constructing a logistic regression model with the D-dimer test result and items from Wells’ score, we identified the most prevalent combinations of influential items and selected new D-dimer positivity thresholds. The performance was separately validated in data from 2,785 consecutive patients with suspected PE.

### **Discussion**

Three Wells items significantly added incremental value to the D-dimer test: haemoptysis, signs of deep vein thrombosis and ‘PE most likely’. Based on the most frequent combinations of these three items, we identified two groups: (1) none of these three items positive (41%), (2) one or more of these items positive (59%). When applying a 1000 µg/L D-dimer threshold in group 1 and 500 µg/L in group 2, PE could be excluded without CT-scanning in 36%, at a false-negative rate of 1.2% (95% CI 0.04-3.3%). In the validation set, these proportions were 46% and 1.9% (95% CI 1.2-2.7%), respectively. Using the conventional Wells score with a normal D-dimer result, these rates were respectively 22% and 0.6% (95% CI 0.10-2.4%).

### **Conclusions**

Combining Wells items with the D-dimer test resulted in a simplified decision rule, which reduces the need for CT-scanning in patients with suspected PE. A prospective validation is required before it can be implemented in clinical practice.

## Introduction

The clinical presentation of patients with acute pulmonary embolism (PE) is non-specific and varies widely.<sup>1,2</sup> CT scanning has now become the first-line imaging modality in patients with suspected PE.<sup>3</sup> In the majority of these patients, computerized tomography pulmonary angiography (CTPA) does not show signs of PE.<sup>4,5</sup> As CTPA is also associated with an increased lifetime risk of malignancy from radiation exposure and the risk of contrast nephropathy,<sup>6</sup> clinicians are in need of a diagnostic strategy that safely reduces the number of required CTPAs.

In the past decade, standardized clinical decision rules have been derived and implemented in clinical practice. The most commonly used clinical decision rule in PE was developed by Wells *et al.*<sup>7</sup> It is based on calculating a score using six objective items from the clinical history and physical examination and one subjective item, inviting the physician to indicate whether or not an alternative diagnosis is more likely than the presence of acute PE.<sup>7</sup> The Wells score is used in combination with a highly sensitive D-dimer test.<sup>5</sup> The sensitivity of combining D-dimer at a 500  $\mu\text{g L}^{-1}$  cut-off with the Wells score was estimated at nearly 100%. Its specificity, however, is only 30 to 40%.<sup>8,9</sup>

The combination of the Wells score and D-dimer leads to CT scanning in all patients with a slightly elevated D-dimer, even in patients with a Wells score of zero, although the accuracy of D-dimer testing has been demonstrated to be substantially different in this subgroup.<sup>10</sup> In clinical practice, D-dimer testing is often performed at a low clinical threshold, regardless of the Wells score,<sup>8</sup> and even routinely in some cases, ordered before clinical evaluation.<sup>11</sup> This results in even more patients being referred for CTPA.

The aim of this study was to derive a new clinical decision rule, combining Wells items and D-dimer testing, with a sensitivity similar to that of the original clinical decision rule but with an enhanced specificity, in order to safely reduce the number of (negative) CTPAs.

## Methods

### *Development*

We analyzed data from 807 patients with clinically suspected PE included in a prospective multicenter cohort study, the design of which has been reported in detail elsewhere.<sup>12</sup> Briefly, the study population consisted of consecutive in- and outpatients in whom acute PE was clinically suspected. Patients were identified in seven academic and non-academic hospitals in the Netherlands. For each included patient, the dichotomized Wells score and a high-sensitivity quantitative D-dimer test were performed in all patients (VIDAS D-dimer assay, bioMérieux, Marcy-l'

Étoile, France; Tina-quant assay, Roche Diagnostics, Mannheim, Germany; STA Liatest D-Di, Diagnostica Stago, Asnières-sur-Seine, France; or Innovance D-dimer, Siemens, Marburg, Germany).<sup>12</sup> The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree (either [sub-] segmental, lobar or central). Patients were followed for 3 months and objective, imaging diagnostic tests were done if PE or DVT was suspected.<sup>12</sup> The ethical review boards of all participating hospitals approved the study protocol and informed consent was obtained from all included patients.

### ***Validation***

For the validation, data from a large prospective multicenter cohort study were used.<sup>5</sup> This study had evaluated the clinical effectiveness of an algorithm based on the dichotomized Wells score, D-dimer testing and CTPA scanning in patients with suspected PE. The study design and results are reported elsewhere.<sup>5</sup> In short, the study group consisted of 3306 patients, who all underwent a sequential diagnostic work-up, consisting of clinical probability calculation (Wells score), a D-dimer test and CTPA scanning. PE was excluded by either an ‘unlikely’ Wells score ( $\leq 4$ ) combined with a D-dimer test  $\leq 500 \mu\text{g L}^{-1}$  (either VIDAS or Tinaquant D-dimer test) or a negative CTPA scan in all other patients. Patients were followed for 3 months.<sup>5</sup>

### ***Statistical analysis***

We aimed for a simple decision rule, with a sensitivity comparable to that of the original Wells-D-dimer strategy, but with an enhanced specificity. To identify the relevant variables, we used multivariable logistic regression to build a model with the original Wells items and the D-dimer test result, using PE as the dependent variable. To arrive at a parsimonious model, we then eliminated all Wells items not significantly associated with PE at a significance level of  $P > 0.20$ . The accuracy of the final model was evaluated by calculating the area under the receiver operating characteristics curve (AUC).

We then calculated the frequency of the informative Wells variables, the ones retained in the final model. Based on the most frequent combinations of these influential Wells items, we identified patient subgroups. In each of the resulting subgroups we then identified a D-dimer threshold that would lead to a sensitivity rate comparable to that of the original decision rule. Combining the items to define the subgroups with the new D-dimer thresholds resulted in a new decision rule. Additionally, we performed a subgroup analysis in in- and outpatients, because D-dimer is less specific in inpatients.<sup>13</sup>

The sensitivity of this new clinical decision rule was estimated as the proportion of patients with PE, as confirmed by CTPA, classified as positive with the clinical decision rule. Specificity was estimated as the proportion of patients without PE classified as negative with the clinical decision rule. The positive predictive value

(PPV) was defined as the proportion of patients with a positive clinical decision rule who had PE confirmed by CTPA; the negative predictive value (NPV) was defined as the proportion of patients with a negative clinical decision rule in whom PE was excluded by CTPA. Additionally, we calculated the false-negative rate, defined as the proportion of patients classified as negative with the rule who had PE during follow-up. We also assessed the number of patients who experienced DVT during follow-up.

Clinical utility was assessed by calculating the overall proportion of negatives: patients in whom further diagnostic testing could be safely withheld in principle, based on the new rule. The NPV and sensitivity, as well as the clinical utility of the new clinical decision rule, were compared with those of the original rule at a Wells score cut-off  $\leq 4$  in combination with a normal D-dimer result ( $\leq 500 \mu\text{g L}^{-1}$ ). The 95% confidence interval (CI) for the 3-month incidence rate of PE with both decision rules was calculated. The new clinical decision rule, combined with a D-dimer test result, was considered acceptable if the confidence interval around the observed diagnostic failure rate did not exceed 3%.<sup>14</sup>

All p-values were two-tailed and statistical significance was defined as  $P < 0.05$ , except where indicated otherwise. All analyses were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill, USA).

## Results

In 84 patients with clinically suspected PE in the derivation set no D-dimer test was available, and these patients were excluded. Of the remaining 723 patients, 156 (22%) had PE. The clinical characteristics of the two study groups are summarized in Table 1. When using the regular Wells score combined with the conventional D-dimer threshold, the number of patients in whom PE could be excluded was 160 (22%; 95% CI, 19%–25%). The corresponding PPV and NPV were 0.28 (95% CI, 0.24–0.31) and 0.99 (95% CI, 0.99–1.00), respectively.

### *Influential Items*

Table 2 shows the multivariable logistic regression model, fitted to the data of the derivation set, using all the original Wells items. This table also shows the coefficients for a second model, one that additionally includes the D-dimer test result. When including the D-dimer test result, only three of the seven Wells items were significantly associated with PE (at  $P < 0.2$ ): two clinical items (hemoptysis and clinical signs of DVT) and the subjective item (PE most likely). The other items (history of DVT or PE, malignancy and immobilization, and tachycardia) provided no or limited incremental value, conditional on the D-dimer test result. Figure 1 shows the receiver operating characteristic (ROC) curve for the corresponding model, with the three variables and the D-dimer test result, which had an AUC of 0.83 (95% CI, 0.80–0.87).



**Table 1: Clinical characteristics.**

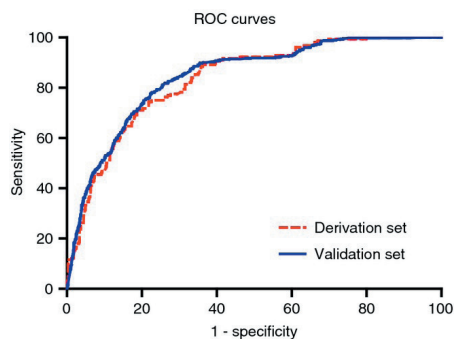
	Derivation set, <i>n</i> = 723	Validation set, <i>n</i> = 2785
Mean age in years (SD)	52 (17)	52 (18)
Median D-dimer level in $\mu\text{g L}^{-1}$ (IQR)	1000 (500–2200)	700 (300–1830)
In patients with PE	2695 (148–50000)	2647 (1470–50000)
In patients without PE	730 (400–1500)	520 (290–1255)
Female	441 (61%)	1580 (57%)
Active malignancy	90 (12%)	357 (13%)
COPD	67 (9%)	277 (10%)
Heart failure	38 (5%)	212 (7%)
Use of medication containing oestrogens	92 (13%)	375 (14%)
Outpatients	591 (82%)	2303 (83%)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation.

**Table 2: Multivariable logistic regression models.**

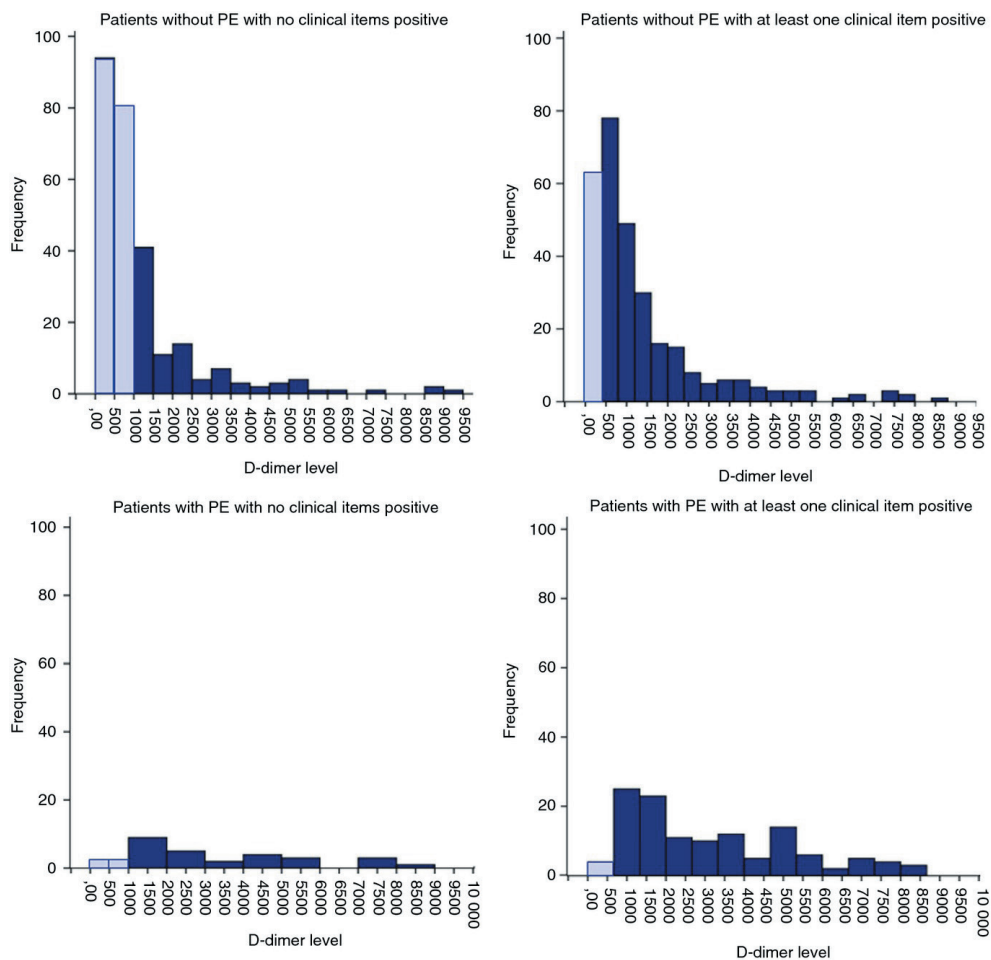
Wells items	Points	<i>N</i>	Wells items	Wells items and D-dimer test result
			OR (95% CI)	OR (95% CI)
Clinically suspected DVT	3	39 (5%)	3.94 (1.93–8.03)	2.99 (1.41–6.33)
Active malignant condition	1	90 (12%)	1.08 (0.91–1.90)	0.94 (0.51–1.74)
Previous DVT or PE	1.5	35 (5%)	3.30 (1.56–6.99)	2.25 (0.96–5.28)
Alternative diagnosis less likely than PE	3	399 (55%)	2.65 (1.76–3.98)	2.43 (1.56–3.77)
Heart rate $\geq$ 100 beats per minute	1.5	152 (21%)	1.59 (1.03–2.55)	1.29 (0.80–2.07)
Immobilization/surgery in past 4 weeks	1.5	145 (20%)	1.92 (1.23–3.00)	1.27 (0.77–2.09)
Haemoptysis	1	37 (5%)	2.86 (1.36–6.03)	2.84 (1.29–6.24)
D-dimer test result			–	1.58 (1.42–1.75)

Both models fitted to the data of 723 patients in the derivation set. DVT, deep venous thrombosis; PE, pulmonary embolism.

**Figure 1:**

Receiver operating characteristic curves illustrating the diagnostic performance of a logistic regression model with the two clinical items (hemoptysis and clinical signs of deep venous thrombosis) and the subjective item (pulmonary embolism most likely), and the D-dimer test result in the derivation and validation sets. The areas under the curve were 0.83 (95% confidence interval (CI), 0.80–87) and 0.84 (95% CI, 0.83–0.86), respectively.

Four combinations of the three remaining Wells items could be identified: (i) none of the three items positive ( $n = 298$ , 41%), (ii) only the subjective item positive, neither of the other two items positive ( $n = 354$ , 49%), (iii) one or two clinical items positive ( $n = 26$ , 3.6%), and (iv) the subjective item and one or more clinical items positive ( $n = 45$ , 6.2%). Based on these frequencies, we defined two groups: group 1, with none of the three items positive (41%), and group 2, with one or more items positive (59%).

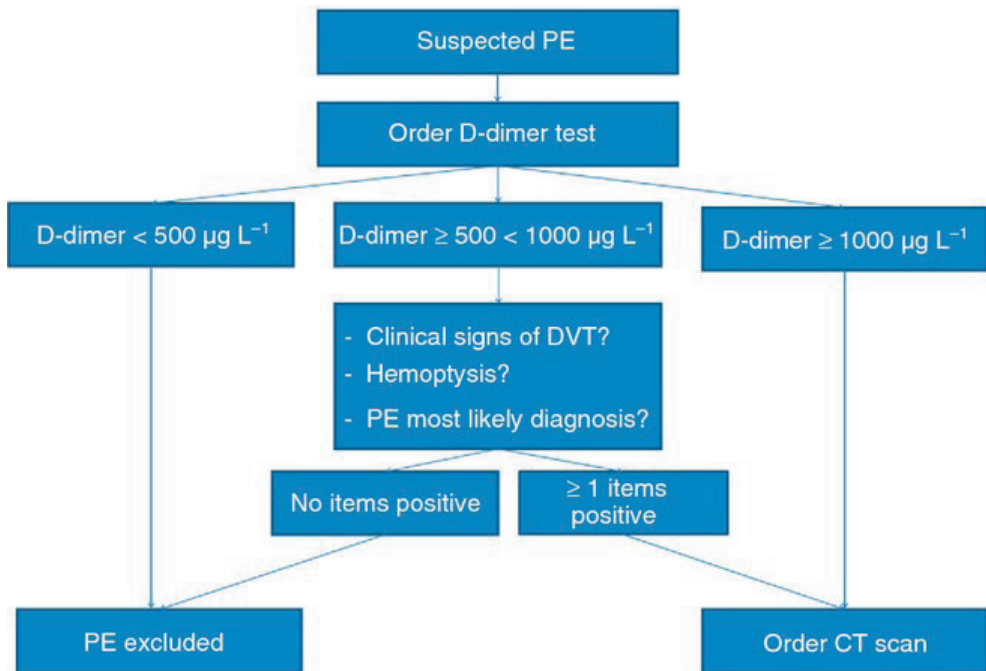


**Figure 2:** The number of D-dimer levels in patients without PE and no clinical items positive, patients without PE and at least one \*item positive, patients with PE with no clinical items positive and patients with PE with at least one\* item positive. \* 'PE is the most likely diagnosis', clinical signs of DVT or hemoptysis.

For patients with none of the three items present, the median D-dimer level was  $725 \mu\text{g L}^{-1}$  (interquartile range [IQR], 400–1512). Patients in this group without PE had a median D-dimer level of 653 (IQR, 374–1237); in the patients with PE this median level was  $2826 \mu\text{g L}^{-1}$  (IQR, 1648–4950). For patients with at least one of the items present, the overall median D-dimer level was  $1170 \mu\text{g L}^{-1}$  (IQR 584–2587). These median levels were  $821 \mu\text{g L}^{-1}$  (IQR 442–1704  $\mu\text{g L}^{-1}$ ) and  $2690 \mu\text{g L}^{-1}$  (IQR 1445–5000  $\mu\text{g L}^{-1}$ ) for patients without and with PE, respectively. (See Figure 2 for the distribution of the D-dimer level in the different subgroups.)

We then calculated two D-dimer cut-off levels, one for group 1 and one for group 2, in steps of  $100 \mu\text{g L}^{-1}$  and compared the clinical utility and safety. Considering the advantage of simple cut-off levels, we selected  $1000 \mu\text{g L}^{-1}$  for group 1 and  $500 \mu\text{g L}^{-1}$  for group 2. Using these cut-off levels we found the D-dimer result to be negative in 83 (12%) patients in group 1 (no items positive) and 176 (24%) patients in group 2.

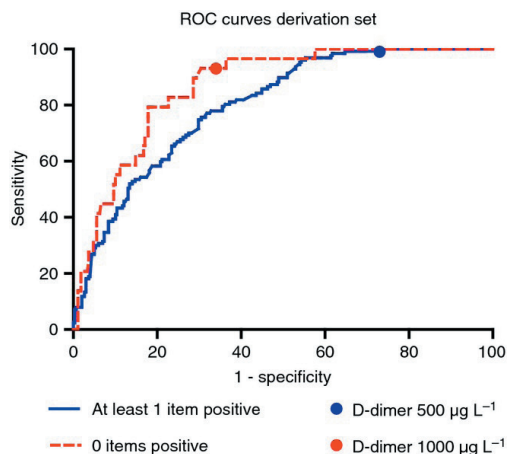
The two different D-dimer cut-off levels, in patients with and without positive Wells items, translates into a new decision rule for patients with suspected PE (Figure 3).



**Figure 3:**

Diagnostic work-up for suspected pulmonary embolism (PE), a combination of two cut-off levels of the D-dimer and three clinical items. DVT, deep venous thrombosis; PE, pulmonary embolism.

If the D-dimer result is  $\geq 1000 \mu\text{g L}^{-1}$ , refer for CT scan. If the D-dimer result is  $< 500 \mu\text{g L}^{-1}$ , exclude PE. If the D-dimer result is  $\geq 500$  and  $< 1000 \mu\text{g L}^{-1}$ , order a CT scan only if PE is the most likely diagnosis, or if the patient has signs of DVT or hemoptysis. If none of these three items is present with a D-dimer result between 500 and  $1000 \mu\text{g L}^{-1}$ , the diagnosis may be excluded. Consequently, in the case of a D-dimer lower than  $500 \mu\text{g L}^{-1}$ , none of the Wells items seemed to be of importance, including clinical gestalt. The corresponding rule had an AUC of 0.87 (95% CI, 0.81–0.92) and 0.78 (95% CI, 0.76–84), respectively (Figure 4).



**Figure 4:**

The performance of D-dimer in patients with and without positive items. Items considered: two clinical items (hemoptysis and clinical signs of deep venous thrombosis) and the subjective item (pulmonary embolism most likely).

Table 3 shows additional information on the characteristics of patients who could be excluded by the new strategy and the original Wells score/D-dimer test combination.

With this new rule, PE could be excluded in 259 patients (36%; 95% CI, 32–39); CTPA would be needed in the remaining 64%. Compared with the conventional Wells rule with a  $500 \mu\text{g mL}^{-1}$  D-dimer positivity threshold, the number of patients in whom PE could be excluded with the new rule increased from 160 to 259 (absolute increase 14%, relative increase of 62% [99/160]). The false-negative rate increased from 0.6% (1/160; 95% CI, 0.10–3.4%) to 1.2% (3/259; 95% CI, 0.04–3.3).

**Table 3: Additional patients in whom PE could be ruled out by the new decision rule.**

Cohort	PE additionally ruled out by new decision rule		
	Wells score $>4.5$ points	D-dimer $> 500 \mu\text{g L}^{-1}$	Total
Derivation	65	75	99
Validation	98	260	306

Numbers indicate patients qualifying for CT scanning based on the conventional Wells/D-dimer strategy but in whom PE could be ruled out with the new strategy.

One patient with a malignancy experienced DVT during follow-up; this patient had none of the items positive and a D-dimer test result of 980  $\mu\text{g mL}^{-1}$ . Table 4 lists the characteristics of the rules in terms of sensitivity, specificity, PPV and NPV. An additional analyses on the in- and outpatients did not show significant differences (data not shown).

**Table 4: Test characteristics of the new diagnostic strategy combined with D-dimer cut-off values 1000/500  $\mu\text{g L}^{-1}$  and the conventional Wells score with the D-dimer test (cut-off 500  $\mu\text{g L}^{-1}$ ).**

	New CDR including D-dimer cut-off levels 1000/500 $\mu\text{g L}^{-1}$	Wells score ‘unlikely’ ( $\leq 4$ ) and D-dimer < 500 $\mu\text{g L}^{-1}$
Derivation set, $n = 723$		
Number (%) of patients in whom PE can be excluded	259 (36)	160 (22)
Sensitivity (95% CI)	0.981 (0.946–0.994)	0.994 (0.965–0.999)
Specificity (95% CI)	0.452 (0.411–0.493)	0.280 (0.245–0.319)
PPV (95% CI)	0.330 (0.289–0.374)	0.275 (0.240–0.314)
NPV (95% CI)	0.988 (0.967–0.997)	0.994 (0.966–0.999)
Validation set, $n = 2785$		
Number (%) of patients in whom PE can be excluded	1295 (46)	989 (36)
Sensitivity (95% CI)	0.951 (0.929–0.967)	0.990 (0.977–0.996)
Specificity (95% CI)	0.555 (0.535–0.575)	0.430 (0.409–0.450)
PPV (95% CI)	0.315 (0.292–0.339)	0.272 (0.252–0.294)
NPV (95% CI)	0.982 (0.973–0.986)	0.995 (0.988–0.998)

CDR, clinical decision rule; NPV, negative prospective value; PPV, positive prospective value; PE, pulmonary embolism.

### **Validation set**

In 515 patients in the validation set with an ‘unlikely’ outcome of the Wells decision rule, D-dimer test results were recorded only qualitatively; these were excluded from this analysis. In another six patients, one of the Wells items was missing; these patients were also excluded. Of the remaining 2785 patients, 491 patients were diagnosed with PE (17.6%). The clinical characteristics were similar to those of the patients in the derivation set (Table 1).

For patients with none of the three Wells items positive, the overall median D-dimer level was 500  $\mu\text{g L}^{-1}$  (IQR, 260–1241). Patients in this group without PE had a D-dimer median level of 430 (IQR, 240–1053) and in the patients with PE this median level was 2593  $\mu\text{g L}^{-1}$  (IQR, 1330–4799). For patients with at least one of the items present, the overall median D-dimer level was 900  $\mu\text{g L}^{-1}$  (IQR, 400–2303). These median levels were 633  $\mu\text{g L}^{-1}$  (IQR, 300–1499  $\mu\text{g L}^{-1}$ ) and 2660  $\mu\text{g L}^{-1}$  (IQR, 1497–5049  $\mu\text{g L}^{-1}$ ) for patients without and with PE, respectively. When using the original Wells score combined with a normal D-dimer test result, the number of patients in whom PE could be excluded was 989 (35%; 95% CI, 34 to 37%). The PPV of this new rule was 0.27 (95% CI, 0.25–0.29); the NPV was 0.99 (95% CI, 0.99–1.00) (Table 4).

The logistic regression model with the three influential Wells items and the D-dimer test result had an AUC of 0.84 (95% CI, 0.83–0.86) (Fig. 1). For 1135 (41%) patients in the validation set, none of the three informative Wells items was positive, whereas in the other 1649 patients (59%) one or more items were positive.

Applying the new rule, PE could be excluded in 1295 patients (46%; 95% CI, 45–48%), with a false-negative rate of 1.9% (24/1295; 95% CI, 1.2–2.7%). Compared with the conventional decision rule, the number of patients in whom PE could be excluded increased from 989 to 1295 (absolute increase 11%, relative increase of 31%). The false-negative rate increased from 0.5% (5/989; 95% CI, 0.2–1.2%) to 1.9% (24/1295; 95% CI, 1.2–2.7%) (Table 4). Subgroup analyses for in- and outpatients did not show significant differences (data not shown).

## Discussion

We derived a simple clinical decision rule in which the D-dimer test and three Wells items were incorporated. Conditional on the D-dimer result, only three of the original Wells items proved to be informative. The new rule was based on these three informative items and on the D-dimer test result, with a different D-dimer threshold for those with no items positive, vs. those with one or more items positive. Combining the D-dimer test result with items of the Wells score resulted in a simple clinical decision rule with a high sensitivity and a significantly higher specificity, compared with the currently used diagnostic algorithm, consisting of the Wells score-D-dimer combination.

Based on two large prospective cohort studies of patients with suspected PE, with this new clinical decision rule, approximately 36% and 46% of patients with suspected PE can be withheld from further diagnostic imaging, a proportion substantially higher than that obtained with the original decision rule (22% and 36%). It is widely accepted that the confidence intervals of the diagnostic failure rate of a diagnostic strategy for PE should not exceed 3%.<sup>14</sup> This safety limit was not exceeded in the new strategy in the derivation set or the validation set. However, compared with the conventional strategy, the point estimate of the false-negative rate increased with this new rule, although it was still below 2%.<sup>15,16</sup>

In primary care, physicians already make use of a validated clinical decision rule for DVT, including seven clinical items and D-dimer testing.<sup>17,18</sup> A positive D-dimer result contributes six of the total 13 points. Using this rule, the proportion of patients with suspected DVT referred for imaging could be reduced from 100% to 77%, at the expense of not referring 0.7% of all DVT cases. However, it has only recently been demonstrated that for patients with suspected PE in primary care, the traditional Wells rule followed by a D-dimer test can safely exclude PE.<sup>19</sup> Several studies using a higher cut-off level of the D-dimer reported higher specificity

without a relevant fall in sensitivity.<sup>20</sup> Kline *et al.* recently doubled the threshold of the D-dimer, in a prospective study with 678 patients with suspected PE and an unlikely pretest probability.<sup>21</sup> They found the threshold of 1000  $\mu\text{g L}^{-1}$  to be safe for excluding PE in patients with a Wells score of 4 points or less. Similarly, it has been shown that in 860 patients with a first episode of suspected DVT, with a low clinical probability, a D-dimer cut-off of 1000  $\mu\text{g L}^{-1}$  is as safe as the conventional cut-off point of 500  $\mu\text{g L}^{-1}$ .<sup>22</sup> Other studies also demonstrated that a D-dimer cut-off value that is adapted to the clinical probability category of the patient has greater utility for exclusion of PE compared with the use of a single D-dimer cut-off value, regardless of the clinical probability.<sup>21,23</sup> The proposed cut-off value was kept at 500  $\mu\text{g L}^{-1}$  for patients with an intermediate clinical suspicion of PE, but was doubled in patients with a low clinical suspicion, and halved in patients with a high clinical suspicion of PE. In a study by Kabrhel *et al.*,<sup>23</sup> the conventional cut-off of 500  $\mu\text{g L}^{-1}$  had an overall sensitivity of 94% and a specificity of 58%. These rates were 88% and 75%, respectively, when probability-dependent cut-offs were used.

Some may wonder why some of the Wells items are no longer incorporated in the decision rule proposed here, despite the fact that additional evaluations have confirmed their association with PE. Apparently, when the D-dimer test result is already known, the additional value from items such as malignancy, immobilization, history of DVT or PE and tachycardia is less than that in the absence of D-dimer testing. The first three are risk factors, and their diagnostic value is more limited in the presence of objective laboratory testing, as is the case with D-dimer. It is known from other fields that risk factor information, known to be associated with the condition of interest, may have limited value in those presenting with signs and symptoms suggestive of that same condition.<sup>24,25</sup>

What then should take precedence: history taking and physical examination or objective testing? With the original rule, D-dimer testing was only needed in those with a 'PE unlikely' classification based on the Wells rule.<sup>3</sup> In current clinical practice, D-dimer testing is regularly ordered in all patients with suspected PE, often even before pretest probability is estimated.<sup>11,26</sup> Yet D-dimer should definitely not be used in isolation, as a standalone test; its accuracy is far from perfect and it may yield false-negative and false-positive results.<sup>8</sup>

With this new strategy, D-dimer takes a more prominent place in the diagnostic strategy and is necessary in all patients with suspected pulmonary embolism. Compared with the old strategy, this may come with extra costs and waiting time in clinical practice. On the other hand, our strategy predicts that fewer CT scans will be needed to exclude the diagnosis of PE in the patient population. Furthermore, PE can now be ruled out by only a low D-dimer ( $< 500 \mu\text{g L}^{-1}$ ). We are aware that previous reports showed that D-dimer can lead to false-negatives in the case of a high clinical suspicion.<sup>8,27</sup> We believe that the value of our findings lies in two observations: first,

the specificity of the clinical decision rule, based on the Wells score, is increased, substantially reducing the need for CTPA with its associated potential for harm and over-diagnosis.<sup>28</sup> Second, our proposed strategy could be considerably easier to apply in a busy clinical practice, because fewer items need to be evaluated, counted and summed.

The conclusions of this study are strengthened by its large sample of patients and its multicenter design, which enhance the extrapolation of our findings to other clinics. Limitations include that a D-dimer test was not performed in some of the patients in the derivation set, and that other patients in the validation set had to be excluded because no qualitative D-dimer test was available.

Although our analysis was based on prospectively collected data and separately validated in an independent cohort, it was retrospective in design. We believe that the safety and efficiency of this new strategy have to be further validated in future studies before it can be implemented in clinical practice.

### ***Addendum***

J. van Es performed the analyses, wrote the manuscript and participated in designing the study. P. M. M. Bossuyt supervised and participated in the analyses, and writing and designing the study. R. A. Douma, S. Middeldorp, P. L. den Exter and L. F. M. Beenen helped in designing and writing the study. H. A. H. Kaasjager, I. C. M. Mos, P. W. Kamphuisen and M. V. Huisman participated in gathering the data. All authors reviewed the manuscript carefully.

### ***Disclosure of Conflict of Interests***

The authors state that they have no conflict of interest.



## References

1. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Archives of internal medicine* 1998; **158**(6): 585-93.
2. Lapner ST, Kearon C. Diagnosis and management of pulmonary embolism. *BMJ (Clinical research ed)* 2013; **346**: f757.
3. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. *Lancet (London, England)* 2002; **360**(9349): 1914-20.
4. Le Gal G, Righini M, Roy PM, et al. Differential value of risk factors and clinical signs for diagnosing pulmonary embolism according to age. *Journal of thrombosis and haemostasis : JTH* 2005; **3**(11): 2457-64.
5. van Belle A, Büller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *Jama* 2006; **295**(2): 172-9.
6. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *Jama* 2007; **298**(3): 317-23.
7. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thrombosis and haemostasis* 2000; **83**(3): 416-20.
8. Gibson NS, Sohne M, Gerdes VEA, Nijkeuter M, Buller HR. The importance of clinical probability assessment in interpreting a normal d-dimer in patients with suspected pulmonary embolism. *Chest* 2008; **134**(4): 789-93.
9. Douma RA, van Sluis GL, Kamphuisen PW, et al. Clinical decision rule and D-dimer have lower clinical utility to exclude pulmonary embolism in cancer patients. Explanations and potential ameliorations. *Thrombosis and haemostasis* 2010; **104**(4): 831-6.
10. van Es J, Beenen LF, Gerdes VE, Middeldorp S, Douma RA, Bossuyt PM. The accuracy of D-dimer testing in suspected pulmonary embolism varies with the Wells score. *Journal of thrombosis and haemostasis : JTH* 2012; **10**(12): 2630-2.
11. Jones P, Elangbam B, Williams NR. Inappropriate use and interpretation of D-dimer testing in the emergency department: an unexpected adverse effect of meeting the "4-h target". *Emergency medicine journal : EMJ* 2010; **27**(1): 43-7.
12. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. *Annals of internal medicine* 2011; **154**(11): 709-18.
13. Söhne M, Kamphuisen PW, van Mierlo PJ, Büller HR. Diagnostic strategy using a modified clinical decision rule and D-dimer test to rule out pulmonary embolism in elderly in- and outpatients. *Thrombosis and haemostasis* 2005; **94**(1): 206-10.
14. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Büller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. *Annals of internal medicine*

- 2003; **138**(12): 941-51.
15. Lucassen W, Geersing GJ, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Annals of internal medicine* 2011; **155**(7): 448-60.
  16. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism--a critical review. *Clinical radiology* 2001; **56**(10): 838-42.
  17. Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thrombosis and haemostasis* 2005; **94**(1): 200-5.
  18. Toll DB, Oudega R, Bulten RJ, Hoes AW, Moons KG. Excluding deep vein thrombosis safely in primary care. *J Fam Pract* 2006; **55**(7): 613-8.
  19. Geersing GJ, Erkens PM, Lucassen WA, et al. Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study. *BMJ (Clinical research ed)* 2012; **345**: e6564.
  20. Douma RA, le Gal G, Söhne M, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. *BMJ (Clinical research ed)* 2010; **340**: c1475.
  21. Kline JA, Hogg MM, Courtney DM, Miller CD, Jones AE, Smithline HA. D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. *Journal of thrombosis and haemostasis : JTH* 2012; **10**(4): 572-81.
  22. Linkins LA, Bates SM, Lang E, et al. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. *Annals of internal medicine* 2013; **158**(2): 93-100.
  23. Kabrhel C, Mark Courtney D, Camargo CA, Jr., et al. Potential impact of adjusting the threshold of the quantitative D-dimer based on pretest probability of acute pulmonary embolism. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2009; **16**(4): 325-32.
  24. Han JH, Lindsell CJ, Storrow AB, et al. The role of cardiac risk factor burden in diagnosing acute coronary syndromes in the emergency department setting. *Annals of emergency medicine* 2007; **49**(2): 145-52, 52.e1.
  25. Ferencik M, Schlett CL, Bamberg F, et al. Comparison of traditional cardiovascular risk models and coronary atherosclerotic plaque as detected by computed tomography for prediction of acute coronary syndrome in patients with acute chest pain. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2012; **19**(8): 934-42.
  26. Newnham M, Stone H, Summerfield R, Mustafa N. Performance of algorithms and pre-test probability scores is often overlooked in the diagnosis of pulmonary embolism. *BMJ (Clinical research ed)* 2013; **346**: f1557.
  27. Risch L, Monn A, Lüthy R, Honegger H, Huber AR. The predictive characteristics of D-dimer testing in outpatients with suspected venous thromboembolism: a Bayesian approach. *Clinica chimica acta; international journal of clinical chemistry* 2004; **345**(1-2): 79-87.
  28. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ (Clinical research ed)* 2013; **347**: f3368.



# Chapter 3

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Simplified diagnostic management  
of suspected pulmonary embolism  
(the YEARS study):  
a prospective, multicentre, cohort study

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## Abstract

### Background

Validated diagnostic algorithms in patients with suspected pulmonary embolism are often not used correctly or only benefit subgroups of patients, leading to overuse of computed tomography pulmonary angiography (CTPA). The YEARS clinical decision rule that incorporates differential D-dimer cut-off values at presentation, has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. We aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

### Methods

We did a prospective, multicentre, cohort study in 12 hospitals in the Netherlands, including consecutive patients with suspected pulmonary embolism between Oct 5, 2013, to July 9, 2015. Patients were managed by simultaneous assessment of the YEARS clinical decision rule, consisting of three items (clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis), and D-dimer concentrations. In patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL, pulmonary embolism was considered excluded. All other patients had CTPA. The primary outcome was the number of independently adjudicated events of venous thromboembolism during 3 months of follow-up after pulmonary embolism was excluded, and the secondary outcome was the number of required CTPA compared with the Wells' diagnostic algorithm. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. This trial is registered with the Netherlands Trial Registry, number NTR4193.

### Results

3616 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 151 (4%) were excluded. The remaining 3465 patients were assessed of whom 456 (13%) were diagnosed with pulmonary embolism at baseline. Of the 2946 patients (85%) in whom pulmonary embolism was ruled out at baseline and remained untreated, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up (0.61%, 95% CI 0.36–0.96) of whom six had fatal pulmonary embolism (0.20%, 0.07–0.44). CTPA was not indicated in 1651 (48%) patients with the YEARS algorithm compared with 1174 (34%) patients, if Wells' rule and fixed D-dimer threshold of less than 500 ng/mL would have been applied, a difference of 14% (95% CI 12–16).

### Conclusions

In our study pulmonary embolism was safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients is the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

## Introduction

The clinical diagnosis of pulmonary embolism is non-specific and should therefore be followed by objective testing. Because of its diagnostic accuracy and wide availability, multidetector row computed tomography pulmonary angiography (CTPA) is the imaging test of choice to confirm acute pulmonary embolism in most patients. Increasing use of CTPA with diminishing prevalence of pulmonary embolism—to even less than 10%<sup>1</sup>—has led to overdiagnosis of mostly subsegmental pulmonary embolism and unnecessary risks of radiation exposure and contrast medium induced nephropathy.<sup>2-6</sup> To avoid these problems, validated diagnostic algorithms for suspected acute pulmonary embolism, using sequential testing, have been introduced.<sup>7</sup> In these algorithms, a normal D-dimer test result in patients with low probability safely excludes pulmonary embolism.<sup>8</sup> Correct application of these algorithms obviates the need for CTPA in 20–30% of patients, with an overall 3-month diagnostic failure rate of less than 1.5% after initial negative ruling of the algorithm.<sup>7-9</sup> An age-adjusted D-dimer threshold (age × 10 ng/mL for patients aged >50 years) has been validated prospectively, reporting an absolute reduction of 11.6% (95% CI 10.5–12.9) in the need for CTPA.<sup>10</sup> Importantly, only patients aged 50 years or older, and foremost those older than 75 years benefit from this strategy whereas when considering the life-time attributable cancer risk, the exposure to unnecessary radiation is considered more relevant to younger individuals, particularly women.<sup>3</sup>

Despite firm evidence of its safety and efficiency, adherence to recommended diagnostic strategies in clinical practice is variable. This variation might be partly due to complexity of these strategies, and insufficient time at busy emergency departments, which hampers the use of sequential tests.<sup>11-14</sup> In daily practice, D-dimer testing is frequently ordered and known at a low clinical threshold or even before the clinical assessment.<sup>15,16</sup> Improved adherence to the algorithm, for instance by implementation of a clinical decision support system, has been shown to significantly decrease the mean number of diagnostic tests used along with—and more importantly—the number of diagnostic failures.<sup>17,18</sup>

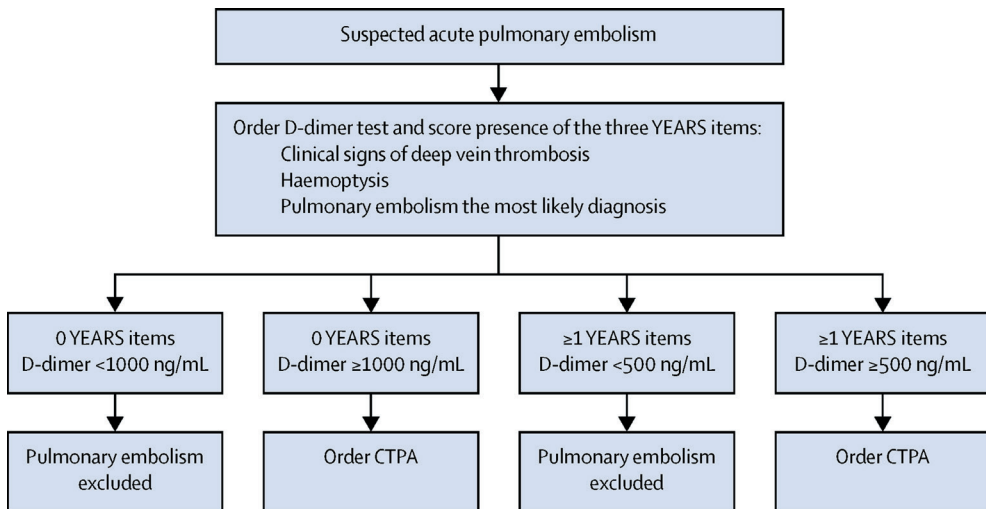
On the basis of a post-hoc derivation and validation study,<sup>19</sup> three items of the original Wells' clinical decision rule—i.e., clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis—were the most predictive for pulmonary embolism. They allowed the use of a differential D-dimer threshold based on the presence of one of these items, without losing sensitivity. Hence, this algorithm—which we call YEARS—involves the simultaneous assessment of only the three abovementioned items and a D-dimer test threshold of 500 ng/mL in presence, and 1000 ng/mL in absence of one of the YEARS items. The YEARS algorithm was designed to be more easily applied in a busy clinical practice than currently used diagnostic strategies, and to further

decrease the number of necessary CTPA examinations in patients of all ages. In this study, we aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

## Materials and Methods

### *Study design and patients*

We did a prospective, multicentre, cohort outcome study evaluating the safety and efficiency of the YEARS algorithm in patients with suspected acute pulmonary embolism between Oct 5, 2013, and July 9, 2015 (Figure 1).<sup>19</sup> The algorithm was implemented as standard diagnostic strategy in 12 participating hospitals in the Netherlands.



**Figure 1: YEARS algorithm.**

CTPA=computed tomography pulmonary angiography.

### *Patients*

Consecutive outpatients and inpatients with clinically suspected acute (first or recurrent) pulmonary embolism were eligible for inclusion if they were aged 18 years or older. Exclusion criteria were treatment with therapeutic doses of anticoagulants initiated 24 hours or more before eligibility assessment, life expectancy less than 3 months or geographic inaccessibility precluding follow-up, pregnancy, or allergy to intravenous contrast agent. The protocol was centrally approved by the institutional review board of the Leiden University Medical Center, Leiden, Netherlands, which waived the need for informed consent; this decision was endorsed by the local institutional review board of each participating centre.

### ***YEARS diagnostic algorithm***

An attending physician who suspected acute pulmonary embolism assessed the patients, and then evaluated the YEARS score by assessing the presence or absence of each of the YEARS items—ie, symptomatic deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis—(scored as yes or no) with the pretest probability dependent threshold of the D-dimer test (Figure 1). D-dimer concentrations were measured upon presentation of the patient, according to local practice, with automated well validated high-sensitive quantitative D-dimer assays (Vidas D-dimer Exclusion, Biomerieux, Marcy-L'Étoile, France; Tinaquant, Roche Diagnostica, Mannheim, Germany; STA-LIA, DiagnosticaStago, Asnieres, France; and Innovance, Siemens, Marburg, Germany). Our study reflected daily clinical practice in which D-dimer concentrations are often determined at presentation to the emergency ward. Physicians were not blinded for the D-dimer test result when they assigned the YEARS items.

In patients with no YEARS items and a D-dimer concentration less than 1000 ng/mL, pulmonary embolism was considered excluded and further testing was withheld. In patients with one or more YEARS items and a D-dimer concentration less than 500 ng/mL, pulmonary embolism was also considered excluded and further testing was withheld. All other patients—ie, either with no YEARS item and a D-dimer concentration of 1000 ng/mL or more, or with one or more items and a concentration of 500 ng/mL or more—were referred for CTPA to show or exclude the diagnosis of pulmonary embolism. Patients in whom pulmonary embolism was ruled out were left untreated and followed up for 3 months. They were instructed to return to the hospital in the event of symptoms of venous thromboembolism, after which objective diagnostic tests were done to confirm or refute the disease. Follow-up consisted of a scheduled outpatient visit or telephone interview after 3 months. At this visit, information about complaints suggestive of venous thromboembolism was obtained. Patients in whom acute pulmonary embolism was confirmed at baseline were treated with anticoagulants according to international guidelines.

### ***Outcomes***

The primary outcome was the 3-month incidence of symptomatic venous thromboembolism in the overall population and in patients managed with and without CTPA separately. The diagnosis of pulmonary embolism or deep vein thrombosis was based on predefined criteria. In case of clinically suspected pulmonary embolism or deep vein thrombosis, objective diagnostic tests were required, including CTPA for suspected pulmonary embolism and compression ultrasonography for suspected deep vein thromboembolism. In case of death, information was obtained from the hospital records. Deaths were classified as caused by pulmonary embolism if it was confirmed by autopsy, was shown by objective testing before death, or could not be confidently



excluded as a cause of death. An independent adjudication committee assessed and adjudicated all suspected venous thromboembolism and deaths during follow-up.

The secondary outcome was the proportion of required CTPA examinations to complete the YEARS algorithm at baseline, as compared post hoc with the theoretical proportion of CTPA examinations that would have been required if the algorithm, using the two-level Wells' rule outcome and fixed D-dimer threshold of less than 500 ng/mL, would have been applied in the study population and to historical data.<sup>20</sup> Finally, we compared the efficiency to the scenario in which the age-adjusted D-dimer concentration would have been applied (calculated by  $\text{age} \times 10 \mu\text{g/L}$  in patients  $>50$  years). This comparison was done post hoc because the final evidence supporting this approach was not available at the moment of drafting of the protocol.<sup>10</sup> The Wells' rule was calculated by an independent researcher (TvdH) based on the YEARS criteria entered in the case record form and information from the medical charts.

### *Statistical analysis*

On the basis of derivation cohort of the YEARS algorithm, we expected a failure rate of 1.2% in patients managed without CTPA.<sup>19</sup> The sample size was based on this assumption, with the aim to keep the upper limit of the 95% CI of this point estimate below 2.7%.<sup>21</sup> This number reflects the 3-month incidence of venous thromboembolism after normal conventional pulmonary angiography. Any venous thromboembolism incidence with a complete confidence interval below this safety threshold was considered to be safe. We calculated that we needed to include 1333 patients managed without CTPA, with a two-sided  $\alpha$  of 5% and a  $\beta$  of 80%. Because 44% of patients in the combined YEARS derivation and validation cohort could have been managed without CTPA and accounting for up to 7.5% loss to follow-up, a total of 3260 patients with suspected pulmonary embolism would be required.<sup>19</sup> For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. The difference between approaches was how to report the number of CTPA that were done but not indicated by the strategy. By using this approach, pulmonary embolism diagnosed at presentation on a CTPA that was not indicated was considered as failures of the diagnostic strategy.

For the secondary outcome analysis, we determined the absolute difference in the number of required CTPA examinations between the different clinical scenarios. Finally, we reported outcomes of not predefined post-hoc analyses for relevant subgroups: patients with malignancy, patients 50 years or older, patients with a history of venous thromboembolism, and inpatients and patients with complaints for more than 7 days. All descriptive parameters and exact 95% CIs around the observed incidences were calculated. All analyses were done with SPSS (version 23). This study is registered with the Netherlands Trial Register, number NTR4193.

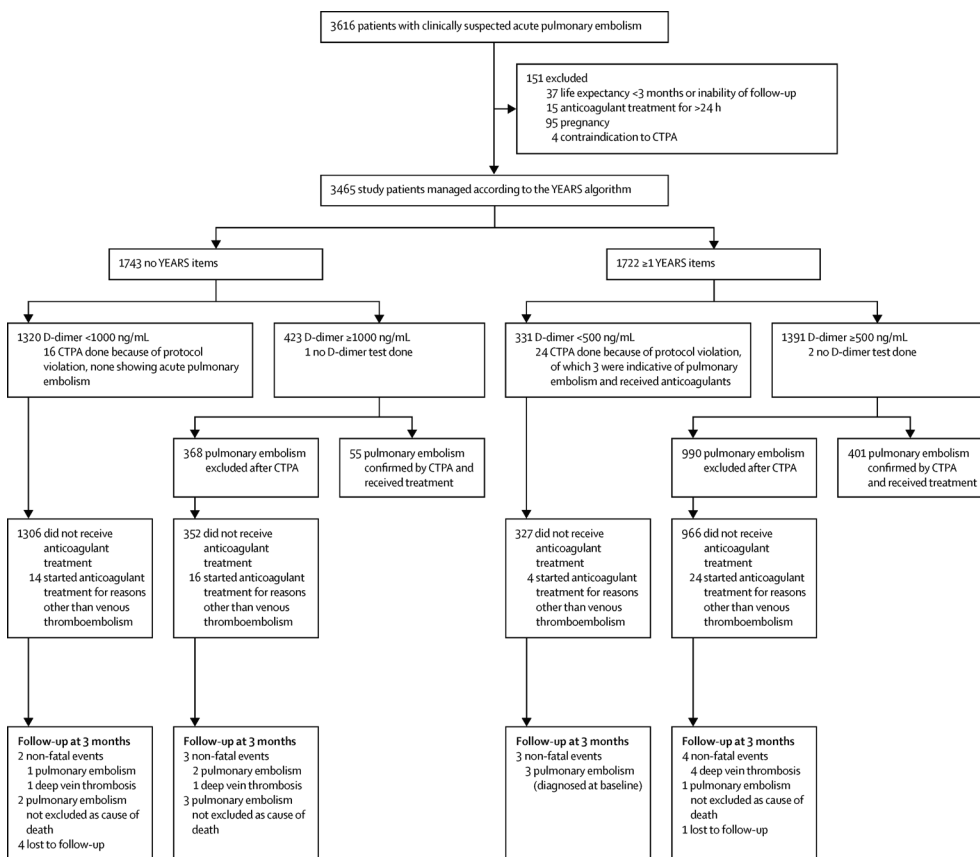
## Role of the funding source

This study was an academically sponsored trial. The steering committee, consisting of the authors, had final responsibility for the study design, oversight, and data verification and analyses. The sponsor was not involved in the study. All members of the steering committee contributed to the interpretation of the results, approved the final version of the manuscript, and vouch for the accuracy and completeness of the data reported. The final decision to submit the manuscript was made by the corresponding author on behalf of all coauthors.

## Results

### Study Patients

From Oct 5, 2013, to July 9, 2015, 3616 consecutive patients with clinically suspected pulmonary embolism were screened in the 12 participating hospitals, of whom 151 (4.2%) were excluded (Figure 2).



**Figure 2: Flowchart of study patients.**  
CTPA=computed tomography pulmonary angiography.

Table 1 summarises the baseline characteristics. Overall, pulmonary embolism was detected in 456 (13%) of 3465 patients: in 55 (3.2%) of 1743 patients with none of the YEARS items and 401 (23%) of 1722 patients with one or more YEARS items.

**Table 1: Baseline characteristics of patients with suspected pulmonary embolism.**

	Patients (n=3465)
Mean age (years)	53 (18)
Women	2154 (62%)
Median duration of complaints (days)	3 (1–8)
COPD with treatment	423 (12%)
Heart failure with treatment	137 (4%)
Oestrogen use (% of women)	337 (16%)
Immobilisation or surgery in the past 4 weeks	407 (12%)
Outpatient	2996 (86%)
Heart rate greater than 100 beats per min	683 (20%)
History of pulmonary embolism or deep vein thrombosis	359 (10%)
Malignancy	336 (9.7%)

Data are mean (SD), n (%), or median (IQR). COPD=chronic obstructive pulmonary disease.

### ***Safety of the overall YEARS algorithm***

According to the intention-to-diagnose approach, of the 2946 (85%) patients in whom pulmonary embolism was ruled out at baseline, who remained untreated, and completed the follow-up period, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up, with an incidence of 0.61% (95% CI 0.36–0.96). The incidence of fatal pulmonary embolism was 0.20% (six patients, 95% CI 0.07–0.44; Table 2). In a worst case scenario, accounting the five patients who were lost to follow-up (four patients had pulmonary embolism excluded without CTPA and one patient had a negative CTPA) as recurrent venous thromboembolism, the 3-month incidence would have been 0.78% (23 of 2951 patients, 95% CI 0.49–1.2). For the per-protocol approach, the failure rate of the diagnostic algorithm was 0.51% (15 of 2943 patients, 95% CI 0.31–0.84) with a 0.20% 3-month risk of fatal pulmonary embolism (six of 2943, 0.08–0.46).

**Table 2: Primary outcomes of venous thromboembolism events during 3-month follow-up.**

	Patients (n)	Total venous thromboembolism (n [%], 95% CI)	Fatal pulmonary embolism* (n [%], 95% CI)
Completed algorithm	2946	18 (0.61%, 0.36–0.96)	6 (0.20%, 0.07–0.44)
Patients managed without CTPA	1629	7 (0.43%, 0.17–0.88)	2 (0.12%, 0.01–0.44)
Patients managed with CTPA	1317	11 (0.84%, 0.47–1.5)	4 (0.30%, 0.12–0.78)

Patients in whom pulmonary embolism was excluded by either a low YEARS score or CT scanning were left untreated. CTPA=computed tomography pulmonary angiography. \* Patients who remained untreated and were not lost to follow-up.

### ***Efficiency of the overall YEARS algorithm***

In the intention-to-diagnose approach, CTPA was not done in 1611 (46%) patients and it was not indicated in 1651 (48%) patients following the per-protocol approach. If the standard diagnostic algorithm using Wells' rule and D-dimer with fixed threshold of <500 ng/mL would have been applied, 1174 (34%) patients could have been managed without CTPA at baseline, for an absolute difference of 13% (difference in intention-to-diagnose approach 437 CTPA examinations, 95% CI 10–15%) and 14% (difference in per-protocol approach 477 CTPA examinations, 12–16%) in favour of the YEARS algorithm.

If Wells' rule and the age-adjusted D-dimer threshold would have been applied, 1348 (39%) patients could have been managed without CTPA at baseline, an absolute difference of 8.7% (difference in per-protocol approach CTPA examinations 303, 95% CI 6.4–11%) and of 7.6% (difference in intention-to-diagnose approach CTPA examinations 263, 95% CI 5.3–9.9%).

In the subgroups of patients younger than 50 years and 50 years and older, a 14% absolute reduction in the number of required CTPA examinations was observed when the YEARS algorithm was applied compared with the standard diagnostic algorithm, with failure rates of 0.11% (one of 894, 95% CI 0.02–0.63) and 0.81% (six of 740, 0.37–1.8), respectively. Table 3 summarises the results for the other subgroups.

**Table 3: Primary outcome and efficiency in subgroups of the total study population.**

	Patients	PE at baseline	Risk of VTE during 3-month follow-up			Efficiency compared with Wells' rule in combination with a D-dimer threshold of <500 ng/mL						
			Managed without CTPA	Incidence in patients managed without CTPA	Incidence in patients managed with CTPA	Overall incidence after pulmonary embolism was excluded at baseline	Managed without CTPA (n)	Difference with YEARS algorithm	n/N	% (95% CI)		
			Events / patients	% (95% CI)	Events/ patients	% (95% CI)	Events/ patients	% (95% CI)				
Malignancy	336	57 (17%)	2/61	3.2 (0.90-11)	5/211	2.4 (1.0-5.4)	7/272	2.6 (1.3-5.2)	37	25/336	7.4 (5.0-11)	
No malignancy	3129	399 (13%)	5/1573	0.32 (0.14-0.74)	6/1106	0.54 (0.25-1.2)	11/79	0.41 (0.23-0.73)	1137	453/3129	1.5 (1.3-1.6)	
Aged <50 years	1448	126 (8.7%)	1/894	0.11 (0.02-0.63)	1/415	0.24 (0.04-1.4)	2/1309	0.15 (0.04-0.56)	704	196/1448	1.4 (1.2-1.5)	
Aged ≥50 years	2017	330 (16%)	6/740	0.81 (0.37-1.8)	10/902	1.1 (0.6-2.0)	16/1642	0.98 (0.6-1.6)	470	282/2017	1.4 (1.3-1.6)	
History of VTE	359	107 (30%)	1/117	0.85 (0.15-4.7)	1/124	0.81 (0.14-4.6)	2/241	0.83 (0.23-3.0)	54	69/359	1.9 (1.5-2.4)	
No history of VTE	3106	349 (11%)	6/1517	0.40 (0.18-0.86)	10/1193	0.84 (0.46-1.5)	16/2710	0.59 (0.36-0.96)	1120	409/3106	1.3 (1.2-1.4)	
Inpatient	469	66 (14%)	1/195	0.51 (0.09-2.9)	3/198	1.5 (0.52-4.4)	4/393	1.0 (0.40-2.6)	135	65/469	1.4 (1.1-1.7)	
Outpatient	2996	390 (13%)	6/1439	0.42 (0.19-0.91)	8/1119	0.71 (0.36-1.4)	14/2558	0.55 (0.33-0.92)	1039	413/2996	1.4 (1.3-1.5)	
Complaints ≤7 days	2599	362 (14%)	7/1253	0.56 (0.27-1.2)	9/942	0.96 (0.50-1.8)	16/2195	0.73 (0.45-1.2)	901	365/2599	1.4 (1.3-1.5)	
Complaints >7 days	866	94 (11%)	0/381	0 (0-1.0)	2/375	0.53 (0.15-1.9)	2/756	0.26 (0.07-0.96)	273	113/866	1.3 (1.1-1.5)	

Data are n or n (%), unless otherwise specified. PE=pulmonary embolism. CTPA=computed tomography pulmonary angiography. VTE=venous thromboembolism.

**Table 4: Diagnostic failures in patients who were managed without CTPA at baseline.**

Patient	Sex	Age (years)	YEARS score	Wells' score*	D-dimer (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 1	F	59	0	0	609	54	Death	Patient developed cardiac arrest during admission for acute severe pancreatitis, and was known to have myotonic dystrophy type 1 with severe cardiomyopathy and arrhythmias; implantable cardioverter-defibrillator was deactivated after regular unjustified defibrillations; resuscitation was unsuccessful	Pulmonary embolism not excluded as cause of death
Patient 2	M	78	0	1	898	11	Death	Patient was diagnosed with end-stage metastasised oropharyngeal carcinoma; found deceased in nursing home	Pulmonary embolism not excluded as cause of death
Patient 3	F	89	0	1.5	610	18	Pulmonary embolism	Patient diagnosed on CTPA with subsegmental pulmonary embolism during admission for pneumonia and acute heart failure related to severe aortic valve stenosis and mitral valve insufficiency. Patient died 7 days after treatment, which was voluntarily withheld	Non-fatal pulmonary embolism
Patient 4	M	52	0	1	560	49	Deep vein thrombosis	Patient had deep vein thrombosis 14 days after surgery for glioblastoma multiforme	Deep vein thrombosis
Patient 5	F	21	2	5.5	380	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism
Patient 6	M	58	1	3	420	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism
Patient 7	F	71	1	6	410	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism

CTPA=computed tomography pulmonary angiography. \* Calculated post hoc. Patients managed without CTPA.

Table 5: Diagnostic failures in patients who were managed with CTPA at baseline.

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 1	M	50	0	1.5	1070	34	Deep vein thrombosis	Patient had vena cava superior syndrome caused by thrombosis at the site of the pacemaker leads	Thrombosis of the vena cava superior
Patient 2	F	73	0	3	1480	69	Death	Patient died in hospital under the clinical diagnosis of a pneumonia and acute heart failure	Pulmonary embolism not excluded as cause of death
Patient 3	F	79	0	3	2400	26	Pulmonary embolism	Initiation of anticoagulation because of suspected pulmonary embolism without CTPA confirmation after hospital admission because of heart failure and COPD exacerbation	Non-fatal pulmonary embolism
Patient 4	F	82	0	0	2550	?	Death	Patient died in nursing home after hospital admission because of acute heart failure and exacerbation of COPD	Pulmonary embolism not excluded as cause of death
Patient 5	F	57	0	1	4170	12	Pulmonary embolism	Patient was known to have recurrent sarcoma of the uterus; subsegmental pulmonary embolism diagnosed postoperatively; patient died 33 days after diagnosis of pulmonary embolism during palliative care in a hospice	Non-fatal pulmonary embolism
Patient 6	F	70	0	1	2400	17	Death	Patient died after sudden collapse followed by unsuccessful resuscitation 1 day after surgery for gastric carcinoma	Pulmonary embolism not excluded as cause of death

**Table 5: Diagnostic failures in patients who were managed with CTPA at baseline.**

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 7	F	73	1	5.5	2500	6	Deep vein thrombosis	Patient was known to have leukaemia; developed thrombosis of the brachial vein after superficial thrombophlebitis related to an intravenous catheter	Deep vein thrombosis
Patient 8	M	84	1	4	5000	32	Deep vein thrombosis	Patient was known to have metastasised prostate cancer; developed deep vein thrombosis after immobilisation during admission at the hospital	Deep vein thrombosis
Patient 9	F	66	1	7	1325	43	Death	Patient had curative treatment for lung cancer and a stent placed for post-radiation stenosis of the trachea; patient died at home after sudden haemoptysis	Pulmonary embolism not excluded as cause of death
Patient 10	M	70	1	3	5000	68	Deep vein thrombosis	Patient had subclavian vein thrombus associated with intravenous catheter	Deep vein thrombosis
Patient 11	F	48	1	3	747	78	Deep vein thrombosis	Patient developed deep vein thrombosis and was diagnosed with antiphospholipid syndrome	Deep vein thrombosis

Diagnostic failures in patients who were managed with CTPA at baselineCTPA=computed tomography pulmonary angiography. COPD=chronic obstructive pulmonary disease.  
\* Calculated post hoc.



Figure 2 shows the management of all 3465 included patients. Of the 1651 patients who should have been managed without CTPA, the protocol was violated in 40 patients. CTPA showed pulmonary embolism in three patients who were treated with anticoagulants. These observations were considered diagnostic failures and are included in the primary outcome. Furthermore, 18 (1.1%) of 1651 patients were treated with oral anticoagulants for other reasons (i.e., eight atrial fibrillation, one superficial thrombophlebitis, and nine other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and four (0.24%) of 1651 patients were lost to follow-up. Four of the remaining 1589 patients returned with symptomatic events of venous thromboembolism (Table 4). The 3-month incidence of venous thromboembolism in patients who did not have CTPA according to the YEARS algorithm was 0.43% (seven of 1629, 95% CI 0.17–0.88) and of fatal pulmonary embolism was 0.12% (two of 1629, 0.01–0.44; Table 2). Seven other patients (0.43%) died of non-venous-thromboembolism-related causes.

#### ***Patients managed with CTPA***

Of the 1358 patients in whom CTPA ruled out pulmonary embolism, 40 patients (2.95%) were treated with anticoagulants for other reasons (i.e., 20 atrial fibrillation, three superficial thrombophlebitis, one splanchnic vein thrombosis, one thrombus in the left ventricle, one high-dose thrombosis prophylaxis, one suspected but later ruled out pulmonary vein thrombosis, one vena cava superior syndrome due to mediastinal mass, and 12 other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and one patient (0.07%) was lost to follow-up. Of the 1317 remaining patients, 11 patients returned with symptomatic events of venous thromboembolism (Table 5). The 3-month incidence of venous thromboembolism was 0.84% (11 of 1317, 95% CI 0.47–1.5) and incidence of fatal pulmonary embolism was 0.30% (four of 1317, 0.12–0.78; Table 2). 85 other patients (6.5%) died of non-venous-thromboembolism-related causes.

## Discussion

Our study showed that the YEARS algorithm safely excluded acute pulmonary embolism. An absolute 14% decrease in the need for CTPA was achieved, compared with the standard algorithm. The 3-month incidence of venous thromboembolism in patients who did not undergo CTPA was in line with that observed in studies using algorithms with sequential diagnostic testing and traditional two-level Wells' score, and a fixed cutoff concentration of D-dimer of 500 ng/mL: 0.43% (95% CI 0.17–0.88) in our study versus 0.34% (0.036–0.96) reported by a meta-analysis.<sup>20</sup> Moreover, the risk of recurrent venous thromboembolism in patients with a normal CTPA was comparable to the risk observed in previous studies using standard algorithms: 0.84% (95% CI 0.47–1.5) versus 1.2% (0.8–1.8).<sup>22</sup> Additionally, fatal pulmonary embolism occurred in 0.30% (95% CI 0.12–0.78) of patients in our study compared with 0.6% (0.4–1.1) in another study using standard algorithms.<sup>22</sup>

The advantage of the YEARS algorithm over existing algorithms is the large reduction in the need for CTPA, which reduces radiation exposure and overdiagnosis,<sup>1–4,23</sup> and is achieved by using variable D-dimer thresholds depending on the clinical probability. This study is the first prospective outcome study that validated a D-dimer threshold of 1000 ng/mL in patients with a low clinical probability.

While our study was ongoing, another strategy to reduce the number of CTPA has been validated in a prospective outcome study: the age-adjusted D-dimer threshold.<sup>10</sup> If this strategy would have been applied to our study population, the YEARS algorithm would have led to an absolute reduction of 8.7% (95% CI 6.4–11) of CTPA. The main reason for this difference is the applicability of the YEARS algorithm to patients with suspected acute pulmonary embolism in all ages, and not only in patients older than 50 years. In patients younger than 50 years, the YEARS algorithm leads to a 14% absolute reduction of CTPA. Of note, reducing the number of CTPA is very relevant for young patients, particularly women, in whom concerns have been raised about long-term effects of radiation on the risk of breast cancer.

Methodological strengths of the study include the large number of consecutive patients, the near complete follow-up, and the independent adjudication of endpoints. Furthermore, by studying a real-world cohort of patients in daily practice, we expect that the YEARS algorithm can be easily implemented outside the participating study sites, and that our data for safety and efficiency are representative for non-trial conditions. Additionally, our results are in line with the numbers reported in the initial derivation and retrospective validation study of our algorithm.<sup>19</sup> Of note, although haemodynamic instability was not a formal exclusion criterion of this study, we have described a cohort of only haemodynamically stable patients.

Limitations of our the study are the absence of a control group because we

did not do a randomised study and could therefore not directly compare the risk of venous thromboembolism with a control group that would have been managed with traditional algorithms. However, the low observed 3-month risk of venous thromboembolism and near complete follow-up strongly support the chosen study design. Moreover, although an independent committee evaluated and adjudicated all endpoints, autopsy was hardly scarcely done. As a consequence, it was difficult to exclude pulmonary embolism as a possible cause of death in six patients during follow-up. These patients already had or developed extensive comorbidity, or went into the final stage of a terminal illness during the follow-up period, with most of them dying in an outpatient setting. Even so, although pulmonary embolism was conservatively adjudicated as the cause of death in these patients, the recurrence rate observed in our study remained well below the safety threshold, reinforcing the validity of our findings. Furthermore, the prevalence of pulmonary embolism was higher than observed in large cohorts in North America, but lower than observed in previous studies in Europe. The study patients were relatively young, but identical to those in an earlier large diagnostic management study by our group.<sup>7</sup> The results of the subgroup analyses, however, confirm the validity of applying the YEARS algorithm in a patient cohort with higher pulmonary embolism prevalence of up to 30% and provide evidence of the generalisability of our findings. Lastly, there were 43 violations of the study protocol, with a D-dimer test not done in three patients and a non-indicated CTPA done in 40 patients, of which three confirmed the presence of acute pulmonary embolism. This number is comparable to that in the Christopher study, in which two of 25 unjustified CTPA examinations revealed pulmonary embolism.<sup>7</sup> Finally, because of the small number of patients with cancer included in our study, the safety of this algorithm for patients with suspected pulmonary embolism in the presence of cancer remains to be determined.

In conclusion, the YEARS diagnostic algorithm safely ruled out acute pulmonary embolism in patients presenting with clinically suspected pulmonary embolism, with a low risk for venous thromboembolism during a 3-month follow-up. The main advantage of the YEARS algorithm is the absolute 14% decrease in the number of CTPA examinations that is applicable to all ages and was shown consistently across subgroups.

### **Contributors**

TvdH, FAK, JvE, SM, and MVH designed the study. TvdH, FAK, and MVH managed the study with support and input from all other authors. TvdH, FAK, and MVH analysed the data, which were interpreted by all other authors. TvdH, FAK, and MVH wrote the first draft of the manuscript, which was reviewed, modified, and approved by all other authors. All authors vouch for the accuracy and completeness of the data reported and for keeping the study to the protocol.

### **Declaration of interests**

We declare no competing interests.

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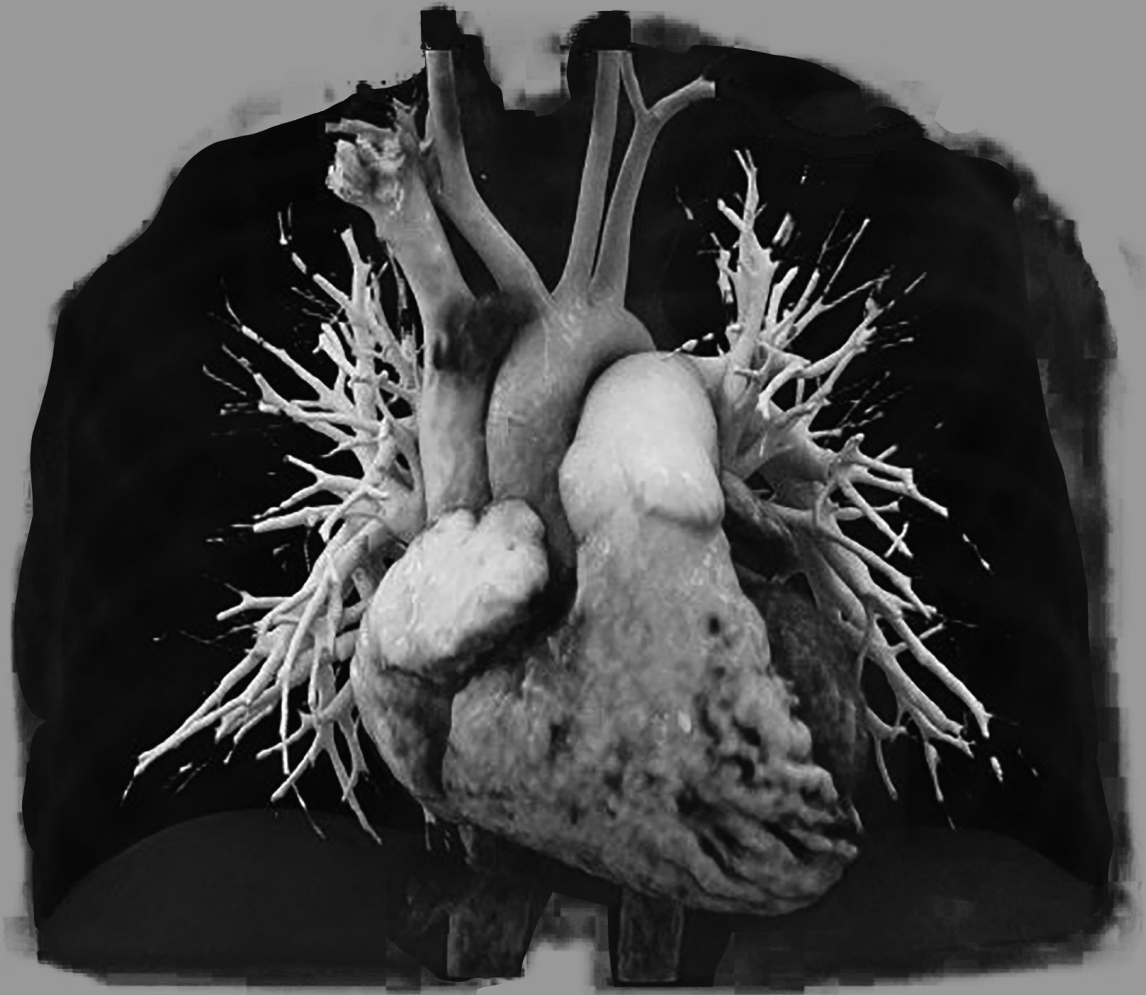
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## References

1. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Archives of internal medicine* 2011; **171**(9): 831-7.
2. Sarma A, Heilbrun ME, Conner KE, Stevens SM, Woller SC, Elliott CG. Radiation and chest CT scan examinations: what do we know? *Chest* 2012; **142**(3): 750-60.
3. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *The New England journal of medicine* 2007; **357**(22): 2277-84.
4. O'Neill J, Murchison JT, Wright L, Williams J. Effect of the introduction of helical CT on radiation dose in the investigation of pulmonary embolism. *The British journal of radiology* 2005; **78**(925): 46-50.
5. Kooiman J, Klok FA, Mos IC, et al. Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism. *Journal of thrombosis and haemostasis : JTH* 2010; **8**(2): 409-11.
6. Schuur JD, Carney DP, Lyn ET, et al. A top-five list for emergency medicine: a pilot project to improve the value of emergency care. *JAMA internal medicine* 2014; **174**(4): 509-15.
7. van Belle A, Büller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *Jama* 2006; **295**(2): 172-9.
8. van Es N, van der Hulle T, van Es J, et al. Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. *Annals of internal medicine* 2016; **165**(4): 253-61.
9. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. *Annals of internal medicine* 2011; **154**(11): 709-18.
10. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *Jama* 2014; **311**(11): 1117-24.
11. Roy PM, Meyer G, Vielle B, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Annals of internal medicine* 2006; **144**(3): 157-64.
12. Newnham M, Stone H, Summerfield R, Mustafa N. Performance of algorithms and pre-test probability scores is often overlooked in the diagnosis of pulmonary embolism. *BMJ (Clinical research ed)* 2013; **346**: f1557.
13. Teismann NA, Cheung PT, Frazee B. Is the ordering of imaging for suspected venous thromboembolism consistent with D-dimer result? *Annals of emergency medicine* 2009; **54**(3): 442-6.
14. Adams DM, Stevens SM, Woller SC, et al. Adherence to PIOPED II investigators' recommendations for computed tomography pulmonary angiography. *The American journal of medicine* 2013; **126**(1): 36-42.

15. Jones P, Elangbam B, Williams NR. Inappropriate use and interpretation of D-dimer testing in the emergency department: an unexpected adverse effect of meeting the “4-h target”. *Emergency medicine journal : EMJ* 2010; **27**(1): 43-7.
16. Gibson NS, Sohne M, Gerdes VEA, Nijkeuter M, Buller HR. The importance of clinical probability assessment in interpreting a normal d-dimer in patients with suspected pulmonary embolism. *Chest* 2008; **134**(4): 789-93.
17. Roy PM, Durieux P, Gillaizeau F, et al. A computerized handheld decision-support system to improve pulmonary embolism diagnosis: a randomized trial. *Annals of internal medicine* 2009; **151**(10): 677-86.
18. Jiménez D, Resano S, Otero R, et al. Computerised clinical decision support for suspected PE. *Thorax* 2015; **70**(9): 909-11.
19. van Es J, Beenen LF, Douma RA, et al. A simple decision rule including D-dimer to reduce the need for computed tomography scanning in patients with suspected pulmonary embolism. *Journal of thrombosis and haemostasis : JTH* 2015; **13**(8): 1428-35.
20. Pasha SM, Klok FA, Snoep JD, et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. *Thrombosis research* 2010; **125**(4): e123-7.
21. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism--a critical review. *Clinical radiology* 2001; **56**(10): 838-42.
22. Mos IC, Klok FA, Kroft LJ, A DER, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. *Journal of thrombosis and haemostasis : JTH* 2009; **7**(9): 1491-8.
23. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ (Clinical research ed)* 2013; **347**: f3368.

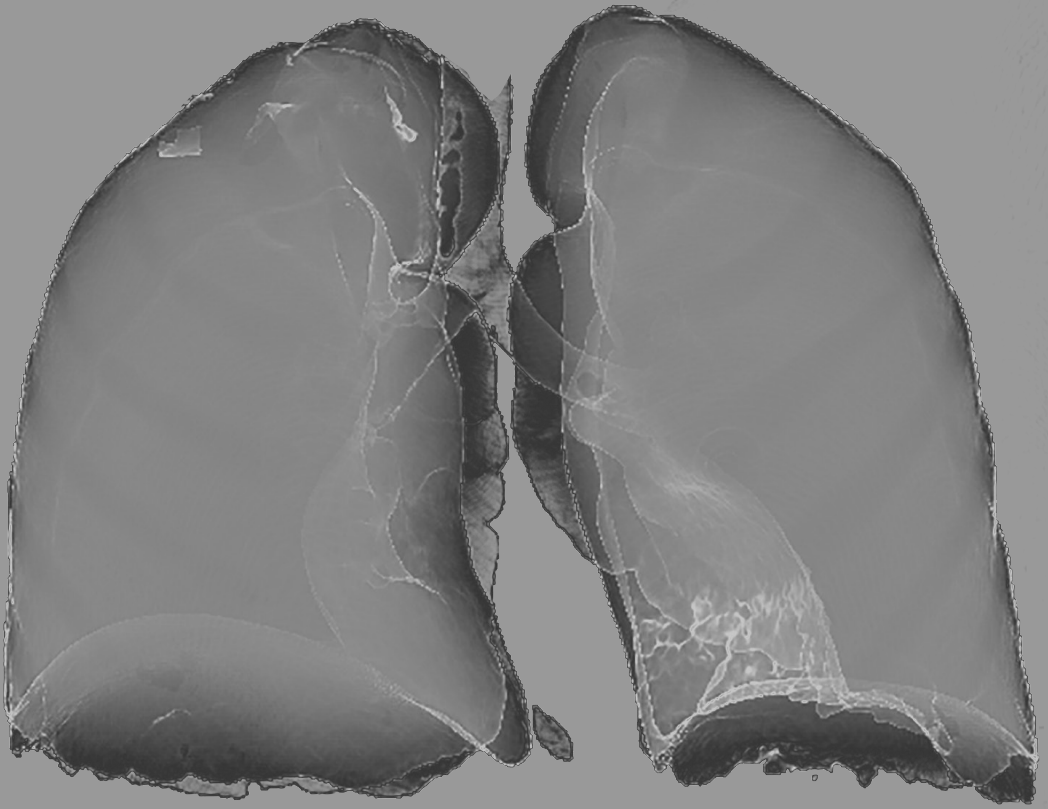


# **PART II**

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**Radiology and prognosis  
of pulmonary embolism**





# Chapter 4

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Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism

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## **Abstract**

### **Background**

The value of various computed tomography parameters for prognosis and risk stratification in acute pulmonary embolism is controversial. Our objective was to evaluate the impact of specific cardiovascular computed tomography pulmonary angiography parameters on short-and long-term clinical outcomes.

### **Methods**

We analysed radiological and clinical data of 1950 patients with acute pulmonary embolism who participated in an international randomised clinical trial on anticoagulants. Parameters included right/left ventricular ratio, septal bowing, cardiothoracic ratio, diameters of pulmonary trunk and aorta, and intrahepatic/azygos vein contrast medium backflow. Associations with mortality, recurrent venous thrombo-embolism (VTE), hospitalisation, bleeding and adverse events were assessed over the short term (1 week and 1 month) and long term (12 months).

### **Results**

Pulmonary trunk enlargement was the only parameter significantly associated with mortality over both the short and long term (odds ratio 4.18 (95%CI 1.04–16.8) at 1 week to OR 2.3 (95%CI 1.36–3.97) after 1 year, as well as with recurrent VTE and hospitalisation.

### **Conclusions**

Most of the evaluated radiological parameters do not have strong effects on the short- or long-term outcome in patients with acute pulmonary embolism. Only an enlarged pulmonary trunk diameter carries an increased risk of mortality and recurrent VTE up to 12 months, and can be used for risk stratification.

## Introduction

Pulmonary embolism (PE) is the third cardiovascular disease worldwide with mortality ranging up to 25%.<sup>1</sup> Calculating the risks of adverse outcome for a patient can guide therapeutic decision (home therapy, hospitalization, or thrombolysis).<sup>2-4</sup> This risk can be based on clinical, biochemical and imaging parameters.<sup>5-7</sup> The detrimental consequences from PE are thought to be mainly associated with the development of right ventricular dysfunction (RVD), which could cause increase of cardiac biomarkers such as NT-proBNP.<sup>8</sup> The burden to the heart would lead to overall heart failure and subsequent death.

ESC guidelines categorize the risk of adverse outcome as high, intermediate or low. Risk calculations are based on sPESI, and are suggested to guide treatment accordingly.<sup>2</sup> For the large intermediate risk group, fine tuning can be done on the presence of RVD, categorizing patients to intermediate-high or intermediate-low risk as assessed by biomarkers or imaging.<sup>9</sup> In daily practice however, additional tests such as ultrasound or NT-proBNP are frequently not performed.<sup>10</sup> It would be ideal, if CT Pulmonary angiography (CTPA), the reference standard for the diagnosis of PE, could also be used to assess the prognosis.<sup>11</sup> So far, heterogeneity in study groups, definitions, and outcomes prohibits consensus on the prognostic performance of CTPA.<sup>12</sup> Two multicentre prospective studies have suggested that the right-to-left ventricular ratio can be used as a predictor for mortality. As these studies did not investigate other potential predictive parameters, the unique position of the right-to-left ventricular ratio can be questioned.<sup>13,14</sup> Other reported radiological findings such as cardiovascular diameters, backflow or clot burden have been evaluated but findings on their value are inconsistent.<sup>15-20</sup> Consequently, it is unclear if one or more CTPA parameters can contribute to risk stratification in patients with acute PE.

To add strong evidence to the debate on the value of CTPA parameters in risk stratification we analysed imaging, clinical and follow-up data collected in a prospective multicentre trial in patients with acute PE.<sup>21</sup> Our focus was on the evaluation of the predictive effects of baseline CTPA parameters on short and long term clinical outcome.

## Materials and Methods

### *Patients and study design*

Patient data and images were collected in the context of a large international randomized clinical trial comparing two anticoagulant regimens in patients with venous thrombo-embolism (VTE). The results, design and methods of the Hokusai-VTE study have been described in detail previously (ClinicalTrials.gov identifier: NCT00986154).<sup>21</sup> In short, eligible patients were patients aged 18 years or older

with acute, symptomatic venous thromboembolism (deep vein thrombosis and/or PE). Patients were excluded in case of contraindications to heparin or warfarin, severely impaired renal function or pregnancy. The institutional review board at each participating centre approved the general study protocol, and all patients provided written informed consent.

Patients were enrolled between January 2010 and October 2012 at 439 centres in 37 countries. All data for the present analysis had been collected and assessed prospectively before the trial data lock. Follow-up was 12 months, covering both the in-hospital period as well as regular outpatient clinic controls, and patients on and off anticoagulant treatment. Adverse events were noted on separate forms, as well as whether this was PE related. An independent committee adjudicated all predefined outcomes.

For this additional study all patients with PE, either with or without DVT, were selected. Excluded were patients with DVT only, patients not evaluated by CTPA, or when images were not available in DICOM format or inaccessible for reading in the used image viewer (e.g. hard copy, corrupted discs).

### ***Data collection***

All clinical and radiological data were anonymized, and centrally registered with double data entry by an independent trial data management agency. Clinical data were retrieved from the original CRFs. In all patients NT-proBNP levels were measured at baseline.

CT-data were acquired from the local participating centres, using local settings and protocols. This means that a wide variety of CT-scanners were used, from basic until high-end CT. For quality evaluation a 5-point Likert scale was used, anchored at 1 (unacceptable), 2 (poor), 3 (satisfactory), 4 (good) and 5 (excellent quality). The enhancement of the pulmonary trunk was assessed by measuring a 1 cm region of interest (ROI) and expressed in Hounsfield Units (HU).

Anonymized patient images from the central database were evaluated by a radiologist (LB) with 12 years of experience in chest imaging supported by a dedicated research assistant. Both were unaware of patient details and clinical information. For image reading a commercially available image viewer was used (eFilm Workstation for Windows Version 3.4.0, Build 10, Merge Technologies Inc., Milwaukee, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting (MPR). Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation if deemed necessary. Data were registered on a specially designed CRF.

A random sample of 50 patients was used to evaluate the intra-observer variability for the main study parameters, as assessed by Cohen's k-statistic. Intra-

observer agreement was graded according to Landis and Koch, with 0-20 indicating poor correlation, 20-40 moderate, 40-60 fair, 60-80 good, and 80-100 excellent correlation. No additional readers were engaged as intra-observer agreement for the selected parameters is reportedly high.<sup>22-24</sup>

All continuous variables were noted in millimetres where applicable. The following parameters were assessed: transverse diameter of right ventricle, left ventricle (both on axial and reformatted short axis view), pulmonary trunk, ascending aorta, inferior and superior caval vein, azygos vein, right atrium, and heart and intrathoracic diameters. For the ventricular diameters, the largest cross-sectional distance between ventricular surfaces was taken. The right atrium was measured at its largest transverse diameter. Pulmonary trunk was measured at its largest transverse diameter, the ascending aorta at the level of the carina, the caval veins were measured 2 cm from their entrance into the right atrium, and the azygos vein at its most cranial part. For the heart volume and the intrathoracic distance, the largest transverse diameters from pericardial contours and costal margins were taken.

The right-to-left ventricular (RV/LV), right-to-left ventricular short axis (RV/LVsa), and pulmonary trunk-to-aorta (TP/Ao) ratios were calculated by dividing the values of respective transverse diameters. All obtained values were then dichotomized at earlier reported thresholds (RV/LV > 1.0; RV/LVsa > 0.9; TP/Ao > 1.0, TP > 29 mm; cardiothoracic ratio > 0.50).

Ordinal measures were: bowing of the interventricular septum (negative, neutral, positive); reflux of contrast medium in the inferior caval vein (no, only into the IVC, intrahepatic < 3 cm, and intrahepatic veins > 3 cm) and in the azygos vein (yes or no). Interventricular septum bowing was considered present when the septum was curved to the left ventricle, or flattened if the septum was straightened or bowed. Backflow was considered positive if reflux was into the intrahepatic veins; only into the inferior caval vein was considered negative. Azygos vein reflux was considered present if it reached the crossing with the right main stem bronchus.

Events were analysed focusing on 4 time points: early (1 week and 1 month) and late (on treatment, mostly 3-6 months, and 12 month) period. For right ventricular dysfunction the reference standard was an increased value of NT-proBNP  $\geq$  600 pg/ml at baseline.<sup>2</sup>

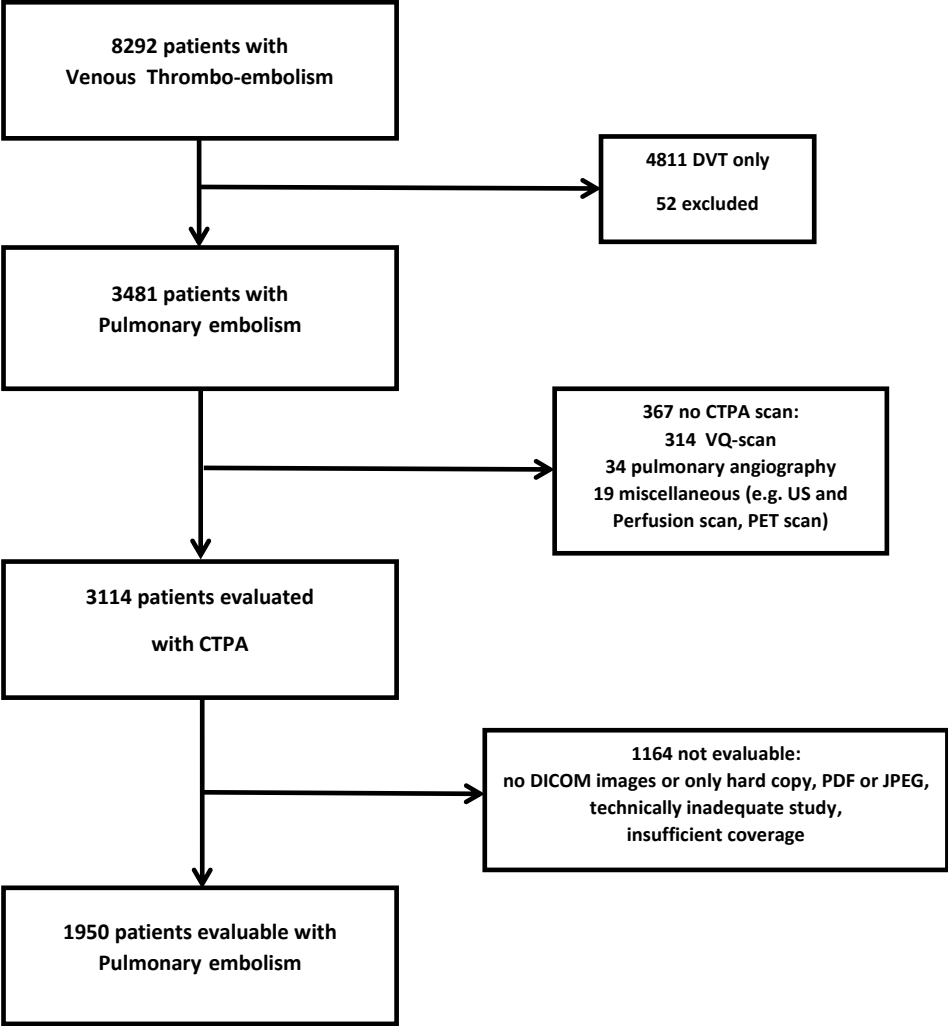
### ***Statistical analysis***

Primary outcome for the study was mortality, secondary outcomes were recurrent VTE, hospitalization, bleeding and all adverse events. We calculated odds ratios with 95% confidence intervals (CI) to express the strength of the association between cardiovascular CTPA parameters and mortality, as well as other clinical outcomes. We also calculated estimates of sensitivity and specificity, PPV and NPV for mortality. Missing data were excluded from the analysis. No correction for multiple testing

was performed. Significance of differences were evaluated with two-sided p-values; a p-value < 0.05 was considered to imply statistical significance. All statistics were performed in SPSS version 23 (SPSS Inc, Chicago Ill).

**Results**

In the RCT, 3,481 patients had PE, of which 3114 had been diagnosed using CTPA. After screening, 1164 of these were excluded because images were presented on hard copies, jpeg or pdf only, no DICOM images were available, or because of a technically inadequate study as e.g. insufficient coverage of heart and chest (Figure 1).



**Figure 1: Inclusion flowchart.**  
CTPA: computed tomography pulmonary angiography; V/Q: ventilation/perfusion; PET: positron emission tomography.

To address possible selection bias, we compared baseline characteristics of included and excluded patients and found no relevant differences. One year outcomes also were not different, as mortality and recurrent VTE was 3.0 and 2.6% for the included and 3.1% and 2.7% for the excluded group, respectively. Hence, data of 1950 patients were included in this evaluation. Of these, 1049 (54%) were male. Mean age was 57 years. A summary of their characteristics is shown in Table 1. PE was provoked in 1288 patients, 456 patients had PE with concomitant DVT. In 565 patients the NT-proBNP level was > 600 pg/ml.

**Table 1: Baseline characteristics.**

	Included		Excluded	
	n	% (or SD)	n	% (or SD)
	1950	100	1531	100
<b>Clinical</b>				
Age (mean, SD)	57.0	16.6	57.5	16.5
Age > 65Y	714	36.6	560	36.6
Male	1049	53.8	793	51.8
Female	901	46.2	738	48.2
Weight (mean, SD)	84.5	20.1	79.8	19.9
Concomitant DVT	456	23.4	363	23.7
Smoking	854	43.8	635	41.5
Alcohol	754	38.7	446	29.1
US Right ventricular dimension *	37.2	28.2	31.8	22
Systolic Blood Pressure mmHg (mean, SD)	128	16.5	127	16.4
Diastolic Blood Pressure mmHg (mean, SD)	76	11	76	10.9
Heart Rate (mean, SD)	80	14	80	13.9
Respiratory Rate (mean, SD)	16	2.6	19.2	2
sPESI High Risk**	1051	53.9	990	64.8
<b>Risk Factors</b>				
Provoked PE	1288	66.1	959	62.6
Recent surgery, trauma, or immobilization	372	19.1	282	18.4
Sitting > 4 hours	185	9.5	121	7.9
Estrogen containing drugs use (Females)	196	21.8	103	6.7
Active cancer	56	2.9	34	2.2
Previous episodes of DVT/PE	415	21.3	305	19.9
Thrombophilic condition	94	4.8	59	3.9
<b>Concomitant Disease History</b>				
Hypertension	810	41.5	645	42.2
Diabetes	199	10.2	155	10.1
Cardiovascular Disease	314	16.1	274	17.9
CHF	35	1.8	62	4.1
Cerebrovascular Disease	73	3.7	65	4.3
Stroke	35	1.8	38	2.5
Renal Disease	129	6.6	132	8.6
Hepatic Disease	212	10.9	195	12.8
Pulmonary Disease	401	20.6	446	29.2
COPD	103	5.3	116	7.6
Interstitial Lung Disease	11	0.6	3	0.2
Pulmonary hypertension	43	2.2	56	3.7
Cancer	228	11.7	148	9.7

Data are number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DVT –Deep Vein Thrombosis; PE – Pulmonary Embolus; sPESI – simplified pulmonary embolism severity index; US – Ultrasound. . \* - 523/1950 included and 496/1531 excluded patients (mm: mean , SD); \*\* sPESI- item on O2 considered positive if patient needed oxygen administration.



### Quality

Overall quality of the scans was good (3.7/5; SD=0.8). Mean Hounsfield Units in the pulmonary trunk was 325 (SD=118). Intra-observer agreement on a random sample from the complete database scored twice was excellent ( $\kappa=0.9$ ).

**Table 2: CT Pulmonary Angiography diameters.**

	n	missing	mean	SD	Min	Max	IQR
RV axial plane	1950	0	38.3	7.8	17	67	33 - 43
LV axial plane	1950	0	41.5	7.1	18	69	37 - 48
RV short axis	1906	44	39.7	7.7	20	71	34 - 45
LV short axis	1906	44	42.6	6.7	22	73	38 - 47
Aorta	1949	1	32.3	4.9	18	52	29 - 35
Pulmonary Trunk	1949	1	27.7	4.6	15	52	25 - 31
Azygos	1947	3	8.3	2.3	2	20	7 - 10
SVC	1949	1	18.9	4.1	8	33	16 - 22
RV Wall Thickness	1950	0	1.5	0.8	1	8	1 - 2
RA	1950	0	49.0	9.1	24	88	43 - 55
IVC	1942	8	22.7	4.3	8	41	20 - 25
Heart	1950	0	128.6	14.9	85	228	119 - 138
Chest	1950	0	259.1	24.2	126	344	242 - 276
RV/LV Axial	1950	0	0.95	0.27	0.39	2.61	0.78 - 1.00
RV/LV short axis	1950	0	0.96	0.26	0.47	2.11	0.80 - 1.02
PT/Ao	1950	0	0.87	0.15	0.42	2.08	0.77 - 0.96
CTR	1950	0	0.50	0.06	0.34	0.97	0.46 - 0.54

### Frequencies

The median right-to-left-ventricle ratio on CTPA was 0.89 (SD=0.27); 621 patients (32%) had a ratio >1 (Tables 2 and 3). Compared to those without RVD on CT, in patients with RV/LV>1 NT-proBNP more often was raised. The median short axis right-to-left-ventricle ratio was 0.88, of which 890 (47%) were > 0.90.

In 538 (28%) patients the septum was flattened, septal bowing occurred in 153 patients (7.9%). The pulmonary trunk was enlarged in 634 patients (33%). A pulmonary trunk/aorta ratio > 1 was present in 408 patients (20.9%). Backflow of contrast medium into the hepatic veins occurred in 261 (15%), and into the azygos vein in 445 (23%) patients.

**Table 3: Frequency of abnormal cardiovascular radiological parameters.**

	n	missing	normal	%	abnormal	%
RV/LV > 1	1950	0	1329	68.2	621	31.8
RV/LVsa > 0.9	1914	36	1024	53.5	890	46.5
Septal Bowing	1949	1	1796	92.1	153	7.9
Septal Flattening	1949	1	1411	72.4	538	27.6
Aorta > 40 mm	1840	110	1800	97.8	40	2.2
Pulmonary Trunk > 29 mm	1949	1	1315	67.5	634	32.5
PT/Aorta > 1.0	1950	0	1542	79.1	408	20.9
Cardiothoracic ratio > 0,50	1833	117	897	48.9	936	51.1
Backflow IVC	1754	196	1105	63	649	37
Intrahepatic Contrast Reflux	1754	196	1493	85.1	261	14.9
Backflow azygos vein	1947	3	1502	77.1	445	22.9

**Short term outcomes**

A summary of the investigated cardiovascular radiological parameters and their correlation with short and long term adverse events are displayed in Tables 4 and 5 (mortality) and Table 6 (recurrent VTE, hospitalization, major bleeding and all adverse events).

**Table 4: Short and long term mortality: Odds ratios.**

<b>1 Week</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	6	66.7	3	33.3	1.07	0.27 - 4.29
RV/LVsa > 0,9	1914	4	44.4	5	55.6	1.44	0.39 - 5.38
Septal Bowing	1949	8	100.0	0	0.0		
Septal flattening	1949	5	62.5	3	37.5	1.58	0.38 - 6.62
Aorta > 40 mm	1840	9	100.0	0	0.0		
Pulmonary Trunk > 29 mm	1949	3	33.3	6	66.7	4.18	1.04 - 16.76
PT/Aorta > 1.0	1950	6	66.7	3	33.3	1.90	0.47 - 7.62
Cardiothoracic ratio > 0,50	1833	2	22.2	7	77.8	3.37	0.70 - 16.28
Backflow IVC	1754	5	62.5	3	37.5	1.02	0.24 - 4.29
Intrahepatic Reflux	1754	6	75.0	2	25.0	1.91	0.38 - 9.53
Backflow azygos vein	1947	7	77.8	2	22.2	0.96	0.20 - 4.66

<b>1 Month</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	15	71.4	6	28.6	0.86	0.33 - 2.21
RV/LVsa > 0,9	1914	8	38.1	13	61.9	1.88	0.78 - 4.56
Septal Bowing	1949	20	100.0	0	0.0		
Septal flattening	1949	13	65.0	7	35.0	1.42	0.56 - 3.57
Aorta > 40 mm	1840	20	100.0	0	0.0		
Pulmonary Trunk > 29 mm	1949	10	47.6	11	52.4	2.30	0.97 - 5.45
PT/Aorta > 1.0	1950	14	66.7	7	33.3	1.91	0.76 - 4.75
Cardiothoracic ratio > 0,50	1833	7	33.3	14	66.7	1.93	0.78 - 4.81
Backflow IVC	1754	12	60.0	8	40.0	1.14	0.46 - 2.80
Intrahepatic Reflux	1754	15	75.0	5	25.0	1.92	0.69 - 5.34
Backflow azygos vein	1947	18	85.7	3	14.3	0.56	0.16 - 1.91

<b>Complete On Treatment period</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	20	66.7	10	33.3	1.07	0.50 - 2.30
RV/LVsa > 0,9	1914	12	40.0	18	60.0	1.74	0.83 - 3.63
Septal Bowing	1949	29	100.0	0	0.0		
Septal flattening	1949	20	69.0	9	31.0	1.18	0.54 - 2.62
Aorta > 40 mm	1840	29	100.0	0	0.0	0.98	0.98 - 0.99
Pulmonary Trunk > 29 mm	1949	13	43.3	17	56.7	2.76	1.33 - 5.72
PT/Aorta > 1.0	1950	17	56.7	13	43.3	2.95	1.42 - 6.13
Cardiothoracic ratio > 0,50	1833	10	33.3	20	66.6	1.94	0.90 - 4.16
Backflow IVC	1754	17	60.7	11	39.3	1.10	0.51 - 2.37
Intrahepatic Reflux	1754	21	75.0	7	25.0	1.93	0.81 - 4.59
Backflow azygos vein	1947	26	86.7	4	13.3	0.52	0.18 - 1.48

<b>1 Year Study period</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	42	72.4	16	27.6	0.81	0.45 - 1.45
RV/LVsa > 0,9	1914	28	48.3	30	51.7	1.24	0.74 - 2.09
Septal Bowing	1949	55	96.5	2	3.5	0.42	0.10 - 1.74
Septal flattening	1949	43	75.4	14	24.6	0.85	0.46 - 1.57
Aorta > 40 mm	1840	52	94.5	3	5.5	2.73	0.81 - 9.13
Pulmonary Trunk > 29 mm	1949	23	39.7	35	60.3	2.33	1.36 - 3.97
PT/Aorta > 1.0	1950	40	69.0	18	31.0	1.73	0.98 - 3.06
Cardiothoracic ratio > 0,50	1833	23	40.4	34	59.6	1.43	0.94 - 2.45
Backflow IVC	1754	28	54.9	23	45.1	1.41	0.81 - 2.48
Intrahepatic Reflux	1754	40	78.4	11	21.6	1.60	0.81 - 3.16
Backflow azygos vein	1947	51	87.9	7	12.1	0.46	0.21 - 1.01

**Table 5: Short- and long-term mortality: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).**

<b>1 Week</b>	<b>Sens</b>		<b>CI</b>		<b>Sens</b>		<b>CI</b>		<b>PPV</b>	<b>CI</b>		<b>NPV</b>	<b>CI</b>
RV/LV > 1	0.33	0.03	0.64	0.68	0.66	0.70	0.00	0.00	0.01	1.00	0.99 - 1.00		
RV/LVsa > 0,9	0.56	0.23	0.88	0.54	0.51	0.56	0.01	0.00	0.01	1.00	0.99 - 1.00		
Septal Bowing	0.00	0.00	0.00	0.92	0.91	0.93	0.00	0.00	0.00	1.00	0.99 - 1.00		
Septal flattening	0.38	0.04	0.71	0.72	0.70	0.74	0.01	0.00	0.01	1.00	0.99 - 1.00		
Aorta > 40 mm	0.00	0.00	0.00	0.98	0.97	0.98	0.00	0.00	0.00	1.00	0.99 - 1.00		
Pulm. Trunk > 29 mm	0.67	0.36	0.97	0.68	0.66	0.70	0.01	0.00	0.02	1.00	1.00 - 1.00		
PT/Aorta > 1.0	0.33	0.03	0.64	0.79	0.77	0.81	0.01	0.00	0.02	1.00	0.99 - 1.00		
Cardiothor. ratio > 0,50	0.78	0.51	1.05	0.49	0.47	0.51	0.01	0.00	0.01	1.00	0.99 - 1.00		
Backflow IVC	0.38	0.04	0.71	0.63	0.61	0.65	0.00	0.00	0.01	1.00	0.99 - 1.00		
Intrahepatic Reflux	0.25	0.00	0.55	0.85	0.83	0.87	0.01	0.00	0.02	1.00	0.99 - 1.00		
Backflow azygos vein	0.22	0.00	0.49	0.77	0.75	0.79	0.00	0.00	0.01	1.00	0.99 - 1.00		

<b>1 Month</b>	<b>Sens</b>		<b>CI</b>		<b>Sens</b>		<b>CI</b>		<b>PPV</b>	<b>CI</b>		<b>NPV</b>	<b>CI</b>
RV/LV > 1	0.29	0.09	0.48	0.68	0.66	0.70	0.01	0.00	0.02	0.99	0.98 - 0.99		
RV/LVsa > 0,9	0.62	0.41	0.83	0.54	0.51	0.56	0.01	0.01	0.02	0.99	0.99 - 1.00		
Septal Bowing	0.00	0.00	0.00	0.92	0.91	0.93	0.00	0.00	0.00	0.99	0.98 - 0.99		
Septal flattening	0.35	0.14	0.56	0.72	0.70	0.74	0.01	0.00	0.02	0.99	0.99 - 1.00		
Aorta > 40 mm	0.00	0.00	0.00	0.98	0.97	0.98	0.00	0.00	0.00	0.99	0.98 - 0.99		
Pulm. Trunk > 29 mm	0.52	0.31	0.74	0.68	0.66	0.70	0.02	0.01	0.03	0.99	0.99 - 1.00		
PT/Aorta > 1.0	0.33	0.13	0.53	0.79	0.77	0.81	0.02	0.00	0.03	0.99	0.99 - 1.00		
Cardiothor. ratio > 0,50	0.67	0.47	0.87	0.49	0.47	0.51	0.01	0.01	0.02	0.99	0.99 - 1.00		
Backflow IVC	0.40	0.19	0.61	0.63	0.61	0.65	0.01	0.00	0.02	0.99	0.98 - 1.00		
Intrahepatic Reflux	0.25	0.06	0.44	0.85	0.84	0.87	0.02	0.00	0.04	0.99	0.98 - 1.00		
Backflow azygos vein	0.14	0.00	0.29	0.77	0.75	0.79	0.01	0.00	0.01	0.99	0.98 - 0.99		

<b>On Treatment period</b>	<b>Sens</b>		<b>CI</b>		<b>Sens</b>		<b>CI</b>		<b>PPV</b>	<b>CI</b>		<b>NPV</b>	<b>CI</b>
RV/LV > 1	0.33	0.16	0.50	0.68	0.66	0.70	0.02	0.01	0.03	0.98	0.98 - 0.99		
RV/LVsa > 0,9	0.60	0.42	0.78	0.54	0.51	0.56	0.02	0.01	0.03	0.99	0.98 - 0.99		
Septal Bowing	0.00	0.00	0.00	0.92	0.91	0.93	0.00	0.00	0.00	0.98	0.98 - 0.99		
Septal flattening	0.31	0.14	0.48	0.72	0.70	0.74	0.02	0.01	0.03	0.99	0.98 - 0.99		
Aorta > 40 mm	0.00	0.00	0.00	0.98	0.97	0.98	0.00	0.00	0.00	0.98	0.98 - 0.99		
Pulmonary Trunk > 29 mm	0.57	0.39	0.74	0.68	0.66	0.70	0.03	0.01	0.04	0.99	0.98 - 1.00		
PT/Aorta > 1.0	0.43	0.26	0.61	0.79	0.78	0.81	0.03	0.01	0.05	0.99	0.98 - 0.99		
Cardiothoracic ratio > 0,50	0.67	0.50	0.84	0.49	0.47	0.52	0.02	0.01	0.03	0.99	0.98 - 1.00		
Backflow IVC	0.39	0.21	0.57	0.63	0.61	0.65	0.02	0.01	0.03	0.98	0.98 - 0.99		
Intrahepatic Reflux	0.25	0.09	0.41	0.85	0.84	0.87	0.03	0.01	0.05	0.99	0.98 - 0.99		
Backflow azygos vein	0.14	0.01	0.26	0.77	0.75	0.79	0.01	0.00	0.02	0.98	0.98 - 0.99		

<b>1 Year</b>	<b>Sens</b>		<b>CI</b>		<b>Sens</b>		<b>CI</b>		<b>PPV</b>	<b>CI</b>		<b>NPV</b>	<b>CI</b>
RV/LV > 1	0.28	0.16	0.39	0.68	0.66	0.70	0.03	0.01	0.04	0.97	0.96 - 0.98		
RV/LVsa > 0,9	0.52	0.39	0.65	0.54	0.51	0.56	0.03	0.02	0.05	0.97	0.96 - 0.98		
Septal Bowing	0.04	0.00	0.08	0.92	0.91	0.93	0.01	0.00	0.03	0.97	0.96 - 0.98		
Septal flattening	0.25	0.13	0.36	0.72	0.70	0.74	0.03	0.01	0.04	0.97	0.96 - 0.98		
Aorta > 40 mm	0.05	0.00	0.11	0.98	0.97	0.99	0.08	0.01	0.16	0.97	0.96 - 0.98		
Pulm. Trunk > 29 mm	0.52	0.39	0.65	0.68	0.66	0.70	0.05	0.03	0.06	0.98	0.97 - 0.99		
PT/Aorta > 1.0	0.31	0.19	0.43	0.79	0.78	0.81	0.04	0.02	0.06	0.97	0.97 - 0.98		
Cardiothor. ratio > 0,50	0.60	0.47	0.72	0.49	0.47	0.52	0.04	0.02	0.05	0.97	0.96 - 0.98		
Backflow IVC	0.45	0.31	0.59	0.63	0.61	0.66	0.04	0.02	0.05	0.97	0.97 - 0.98		
Intrahepatic Reflux	0.22	0.10	0.33	0.85	0.84	0.87	0.04	0.02	0.07	0.97	0.97 - 0.98		
Backflow azygos vein	0.12	0.04	0.20	0.78	0.76	0.80	0.02	0.00	0.03	0.97	0.96 - 0.98		

**Table 6: 1 Month and 1 year recurrent VTE, hospitalization, major bleeding and adverse events.****Recurrent VTE**

<b>1 Month</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	7	53.8	6	46.2	1.84	0.62 - 5.51
RV/LVsa > 0,9	1914	5	38.5	8	61.5	1.85	0.60 - 5.67
Septal Bowing	1949	11	91.7	1	8.3	1.07	0.14 - 8.32
Septal flattening	1949	6	50.0	6	50.0	2.64	0.85 - 8.23
Aorta > 40 mm	1840	11	91.7	1	8.3	4.17	0.53 - 33.10
Pulmonary Trunk > 29 mm	1949	7	53.8	6	32.4	1.79	0.60 - 5.33
PT/Aorta > 1.0	1950	8	61.5	5	38.5	2.38	0.77 - 7.31
Cardiothoracic ratio > 0,50	1833	6	50.0	6	50.0	0.96	0.31 - 2.98
Backflow IVC	1754	7	63.6	4	36.4	0.97	0.28 - 3.34
Intrahepatic Reflux	1754	9	81.8	2	18.2	1.27	0.27 - 5.93
Backflow azygos vein	1947	12	92.3	1	7.7	0.28	0.04 - 2.16

<b>1 Year</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	33	66.0	17	34.0	1.11	0.61 - 2.00
RV/LVsa > 0,9	1914	24	48.0	56	52.0	1.25	0.72 - 2.20
Septal Bowing	1949	45	91.8	4	8.2	1.05	0.37 - 2.94
Septal flattening	1949	35	71.4	14	28.6	1.05	0.56 - 1.97
Aorta > 40 mm	1840	45	95.7	2	4.3	2.05	0.48 - 8.77
Pulmonary Trunk > 29 mm	1949	35	70.0	15	30.0	0.89	0.48 - 1.64
PT/Aorta > 1.0	1950	41	82.0	9	18.0	0.83	0.40 - 1.71
Cardiothoracic ratio > 0,50	1833	25	51.0	24	49.0	0.92	0.52 - 1.62
Backflow IVC	1754	28	65.1	15	34.9	0.91	0.48 - 1.72
Intrahepatic Reflux	1754	34	79.1	9	20.9	1.53	0.73 - 3.23
Backflow azygos vein	1947	42	84.0	8	16.0	0.64	0.30 - 1.37

**Hospitalisation**

<b>1 Month</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	62	68.9	28	31.1	0.97	0.61 - 1.52
RV/LVsa > 0,9	1914	47	52.2	43	47.8	1.06	0.69 - 1.61
Septal Bowing	1949	81	91.0	8	9.0	1.17	0.55 - 2.46
Septal flattening	1949	65	73.0	24	27.0	0.97	0.60 - 1.56
Aorta > 40 mm	1840	82	96.5	3	3.5	1.70	0.51 - 5.63
Pulmonary Trunk > 29 mm	1949	54	60.0	36	40.0	1.41	0.91 - 2.17
PT/Aorta > 1.0	1950	67	74.4	23	25.6	1.32	0.81 - 2.14
Cardiothoracic ratio > 0,50	1833	41	46.1	48	53.9	1.13	0.74 - 1.73
Backflow IVC	1754	48	61.5	30	38.5	1.07	0.67 - 1.70
Intrahepatic Reflux	1754	66	84.6	12	15.4	1.04	0.56 - 1.96
Backflow azygos vein	1947	76	84.4	14	15.6	0.61	0.34 - 1.09

<b>1 Year</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	62	68.9	28	31.1	0.97	0.61 - 1.52
RV/LVsa > 0,9	1914	47	52.2	43	47.8	1.06	0.69 - 1.61
Septal Bowing	1949	81	91.0	8	9.0	1.17	0.55 - 2.46
Septal flattening	1949	65	73.0	24	27.0	0.97	0.60 - 1.56
Aorta > 40 mm	1840	82	96.5	3	3.5	1.70	0.51 - 5.63
Pulmonary Trunk > 29 mm	1949	54	60.0	36	40.0	1.41	0.91 - 2.17
PT/Aorta > 1.0	1950	67	74.4	23	25.6	1.32	0.81 - 2.14
Cardiothoracic ratio > 0,50	1833	41	46.1	48	53.9	1.13	0.74 - 1.73
Backflow IVC	1754	48	61.5	30	38.5	1.07	0.67 - 1.70
Intrahepatic Reflux	1754	66	84.6	12	15.4	1.04	0.56 - 1.96
Backflow azygos vein	1947	76	84.4	14	15.9	0.61	0.34 - 1.09

**Table 6: Continued.****Major bleeding**

<b>1 Month</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	7	53.8	6	46.2	1.84	0.62 - 5.51
RV/LVsa > 0,9	1914	7	53.8	6	46.2	0.99	0.33 - 2.95
Septal Bowing	1949	12	92.3	1	7.7	0.98	0.13 - 7.57
Septal flattening	1949	9	69.2	4	30.8	1.17	0.36 - 3.81
Aorta > 40 mm	1840	13	100.0	0	0.0	0.99	0.99 - 1.00
Pulmonary Trunk > 29 mm	1949	6	46.2	7	53.8	2.44	0.82 - 7.28
PT/Aorta > 1.0	1950	7	53.8	6	46.2	3.27	1.09 - 9.79
Cardiothoracic ratio > 0,50	1833	3	23.1	10	76.9	3.22	0.88 - 11.73
Backflow IVC	1754	7	53.8	6	46.2	1.46	0.49 - 4.37
Intrahepatic Reflux	1754	9	69.2	4	30.8	2.57	0.78 - 8.40
Backflow azygos vein	1947	9	69.2	4	30.8	1.51	0.46 - 4.91

<b>1 Year</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	18	60.0	12	40.0	1.43	0.69 - 3.00
RV/LVsa > 0,9	1914	15	51.7	14	48.3	1.08	0.52 - 2.24
Septal Bowing	1949	25	83.3	5	16.7	2.39	0.90 - 6.34
Septal flattening	1949	21	70.0	9	30.0	1.13	0.51 - 2.47
Aorta > 40 mm	1840	27	96.4	1	3.6	1.68	0.22 - 12.71
Pulmonary Trunk > 29 mm	1949	11	36.7	19	63.3	3.66	1.73 - 7.74
PT/Aorta > 1.0	1950	18	60.0	12	40.0	2.57	1.23 - 5.37
Cardiothoracic ratio > 0,50	1833	10	34.5	19	65.5	1.84	0.85 - 3.97
Backflow IVC	1754	16	57.1	12	42.9	1.28	0.60 - 2.73
Intrahepatic Reflux	1754	23	82.1	5	17.9	1.25	0.47 - 3.31
Backflow azygos vein	1947	24	80.0	6	20.0	0.84	0.34 - 2.07

**All Adverse Events**

<b>1 Month</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	92	69.7	40	30.3	0.93	0.63 - 1.36
RV/LVsa > 0,9	1914	66	50.4	65	49.6	1.14	0.80 - 1.63
Septal Bowing	1949	121	92.4	10	7.6	0.97	0.50 - 1.89
Septal flattening	1949	96	73.3	35	26.7	0.95	0.64 - 1.42
Aorta > 40 mm	1840	120	96.8	4	3.2	1.56	0.55 - 4.44
Pulmonary Trunk > 29 mm	1949	75	56.8	57	43.2	1.63	1.14 - 2.34
PT/Aorta > 1.0	1950	96	72.7	36	27.3	1.46	0.98 - 2.17
Cardiothoracic ratio > 0,50	1833	58	45.0	71	55.0	1.19	0.83 - 1.70
Backflow IVC	1754	71	61.2	45	38.8	1.09	0.74 - 1.60
Intrahepatic Reflux	1754	94	81.0	22	19.0	1.37	0.84 - 2.22
Backflow azygos vein	1947	110	83.3	22	16.7	0.66	0.41 - 1.05

<b>1 Year</b>	<b>n</b>	<b>no</b>	<b>%</b>	<b>present</b>	<b>%</b>	<b>OR</b>	<b>CI</b>
RV/LV > 1	1950	92	69.7	40	30.3	0.93	0.63 - 1.36
RV/LVsa > 0,9	1914	66	50.4	65	19.6	1.14	0.80 - 1.63
Septal Bowing	1949	121	92.4	10	7.6	0.97	0.50 - 1.89
Septal flattening	1949	96	73.3	35	26.7	0.95	0.64 - 1.42
Aorta > 40 mm	1840	120	96.8	4	3.2	1.56	0.55 - 4.44
Pulmonary Trunk > 29 mm	1949	75	56.8	57	43.2	1.63	1.14 - 2.34
PT/Aorta > 1.0	1950	96	72.7	36	27.3	1.46	0.98 - 2.17
Cardiothoracic ratio > 0,50	1833	58	45.0	71	55.0	1.19	0.83 - 1.70
Backflow IVC	1754	71	61.2	45	38.8	1.09	0.74 - 1.60
Intrahepatic Reflux	1754	94	81.0	22	19.0	1.37	0.84 - 2.22
Backflow azygos vein	1947	110	83.3	22	16.7	0.66	0.41 - 1.05

During the first month 29 adverse events occurred, including 18 deaths, 12 recurrent VTEs, 13 bleedings. There were 26 hospitalisations.

During the first month 29 adverse events occurred, including 18 deaths, 12 recurrent VTEs, 13 bleedings. There were 26 hospitalisations.

Of all the radiological parameters evaluated, only pulmonary trunk diameter  $> 29$  mm was significantly associated with mortality at 1 week (OR 4.18, CI=1.04-16.8;  $p=0.028$ , Table 2 and 3). The odds ratio at 1 month was lower and not statistically significant (OR 2.30, CI=0.97-5.45;  $p=0.051$ ). All other parameters (RV/LV ratio, RV/LV short axis, septal bowing, pulmonary trunk/aorta ratio, cardiothoracic ratio and backflow to hepatic veins or azygos vein) were not significantly associated with mortality. Of the 9 patients that died within the first week, 6 (66.7%) had an enlarged pulmonary trunk. In total 18 patients died within one month, an enlarged pulmonary trunk was present in half of these 18 patients. In patients who survived one week or subsequently one month an enlarged pulmonary trunk was present in 628 and 625 patients (32.4%,  $p = 0.028$  respectively 32.4%,  $p=0.11$ ).

An enlarged pulmonary trunk diameter was also associated with recurrent VTE (OR 5.22, CI=1.01-26.7;  $p=0.028$ ) at 1 week. Here also the odds ratio was lower and not significant at 1 month (1.8, CI=0.6-5.3;  $p=0.051$ ). None of the evaluated radiological parameters, apart from enlarged pulmonary trunk diameter was associated with hospitalization. Sensitivities were low for all the researched parameters, as were the specificities and positive predictive values; however, all parameters showed a high negative predictive value.

### ***Long term outcomes***

The median on treatment time was 215 days (IQR 178-358 days). During the complete 1 year period, 143 adverse events were registered in 131 patients. In total 58 patients died, 49 had recurrent VTE, 30 had a major bleeding and 90 were hospitalized.

An enlarged pulmonary trunk diameter was significantly associated with mortality during the on-treatment time as well as for the complete 12 months ( $p=0.004$  resp. 0.001). A TP/Aorta ratio  $> 1.0$  was also significantly associated with mortality during treatment ( $p=0.002$ ; Table 4) but not for the complete period ( $p=0.055$ ). Of the 11 patients with interstitial lung disease, 2 patients that had an enlarged pulmonary trunk died. In 43 patients with a history of pulmonary hypertension, 21 had an enlarged pulmonary trunk of which 2 died. All other evaluated cardiovascular parameters were not significantly associated with mortality or other adverse events.

### **Discussion**

Our study showed that most of the investigated cardiovascular radiological parameters -including RV/LV ratio, septal bowing, cardiothoracic ratio and contrast medium backflow - have no prognostic value for short or long term mortality. The

exception was an enlarged pulmonary trunk diameter, which on both short and long term was associated with increased mortality and the risk of recurrent VTE and hospitalization.

A strength of our study is that data were prospectively collected in a large international trial, and both imaging data and clinical outcomes were assessed blinded for treatment and outcome.

Our study also has limitations. Although in literature many parameters have been evaluated, we only analysed the most frequently used radiological parameters and cut off values as these would be most easily implementable, had we found any of these to be of value. As reconstructed views yield comparative values but are more time-consuming, plain axial transverse images generally are preferred given the simplicity of analysis.<sup>25</sup> We evaluated observer agreement only for the main continuous variables, and not for the ordinal measurements. We also did not perform separate assessments for treatment allocation to edoxaban or enoxaparin followed by warfarin, as this subgroup analysis was done in the original dataset.<sup>21</sup> We did not perform a multivariable analysis, as we first aimed to assess the prognostic value of each parameter separately. Also, echocardiography can be a useful tool for short term mortality risk stratification.<sup>12</sup> As only 523 (26.8%) of the evaluated patients received this test, this was not analysed in the present study. We are aware that patients included in a randomized controlled trial do not necessarily reflect all those presenting in regular practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients, patients with a limited life expectancy and pregnant women.

How do our findings fit into the current assessment of prognosis in patients with acute PE? We need better tools to identify high risk patients with a favourable risk-benefit ratio from thrombolysis, or, alternatively, to identify those who would benefit from close clinical monitoring in order to provide them with rescue thrombolysis. As the beneficial effect of thrombolysis primarily reflects the first days, an easily applicable modifier like an enlarged pulmonary trunk would probably facilitate such processes. In recent ESC guidelines primary categorization into low, intermediate or high risk is based on sPESI. In second instance either biomarkers, RV/LV ratio or echocardiography can be used for further stratification on RVD. However, no consensus exists on its usefulness, as well as on the threshold, as RVD values reported in the literatures are ranging from 0.9 until 1.8.<sup>26</sup>

Several studies have reported that RVD on CTPA is an indicator of the risk of adverse events.<sup>13,27</sup> Many studies however had a single centre, retrospective design, with short follow up and surrogate outcomes. As such, they have intrinsic methodological limitations that weaken their validity and generalizability. The larger series have shown conflicting results, either confirming or denying that right-to-left ventricular ratio is associated with an increased mortality.<sup>14,28,29,30</sup>

A recent systematic review stated that although RVD assessed by CT showed an association with an increased risk of mortality in patients with hemodynamically stable PE, it resulted in only small increases in the ability to classify risk.<sup>31</sup> Although additional publications confirmed this finding,<sup>31,32</sup> apparently, RV enlargement alone is not sufficient to indicate a poor short-term prognosis, and other factors should also be taken into consideration.<sup>33</sup> For the long-term persistent RV dysfunction seems common, reflecting on diminished exercise capacity and reduced quality of life.<sup>34</sup> One of the differences with the published cohorts is the fact that our study contains a population that was included in a randomized clinical trial rather than a prospective cohort study of consecutive patients, and thus could reflect different study populations. Our finding that right-to-left ventricular ratio is not associated with an increased mortality could thus be an incentive to reconsider the risk stratification algorithm.

Reports on the other investigated outcomes –recurrent VTE, hospitalization, bleeding and adverse effects- are scarce, as most often they are used as a composite outcome, or focus on differences between treatment regimens.<sup>35</sup>

Although an enlarged pulmonary trunk diameter is an established feature in the work up of chronic PE, for acute PE findings are contradictory, as an association with increased risk was not always observed in previous studies.<sup>36-40</sup> However, most of these studies were retrospective with limited number of patients. The assessment however is rather easy and not as time consuming as e.g. clot obstruction scores, and thus could be used easily in daily practice. Sensitivity for enlarged pulmonary trunk diameter may be low, but as specificity was high, we may be able to better identify specific risk groups. Its high negative predictive value indicates that it may be useful for identification of those patients that have a low risk for adverse events who will not need for aggressive therapy, and can be discharged home early. However, for prognostication towards high risk measures like admission to ICU or thrombolysis a multifactorial risk-benefit analysis would be necessary.

One intriguing point is the apparent discrepancy between the relative high number of RVD observed in the earlier published studies, and the fortunately relatively low mortality percentages. In other words: although many patients are categorized as high risk, be it from radiological, biochemical, or combined, this does not translate in the same manner in mortality and adverse events. From this point it should be logical to better investigate the role of radiological cardiovascular parameters in risk stratification, both separately, as well as in combination with other biomarkers. At present, in patients with an intermediate risk profile the ESC guidelines recommend to use an increased RV/LV-ratio either in CT or echocardiographic evaluation, after patients have been stratified by clinical parameters sPESI.<sup>2</sup> No statement has been made on the use of enlarged pulmonary trunk diameters. Our results on the PA diameter should be considered explorative findings, done in a trial population. The



findings are promising with regard to predict poor prognosis/mortality but should be confirmed in consecutive cohorts. Measurement of PA is quicker to perform than a RV/LV ratio assessment, and hence easier to integrate/accept/adopt in daily practice. Incorporation of enlarged pulmonary trunk diameters is an attractive radiological marker to be further investigated in clinical management studies.

In conclusion, we found that several of the widely suggested radiological cardiovascular parameters did not show an association with short or long term adverse events like mortality, recurrent VTE, bleeding, hospitalization. Only an enlarged pulmonary trunk diameter was associated with an increased risk of mortality, recurrent VTE both on short as well as long term.

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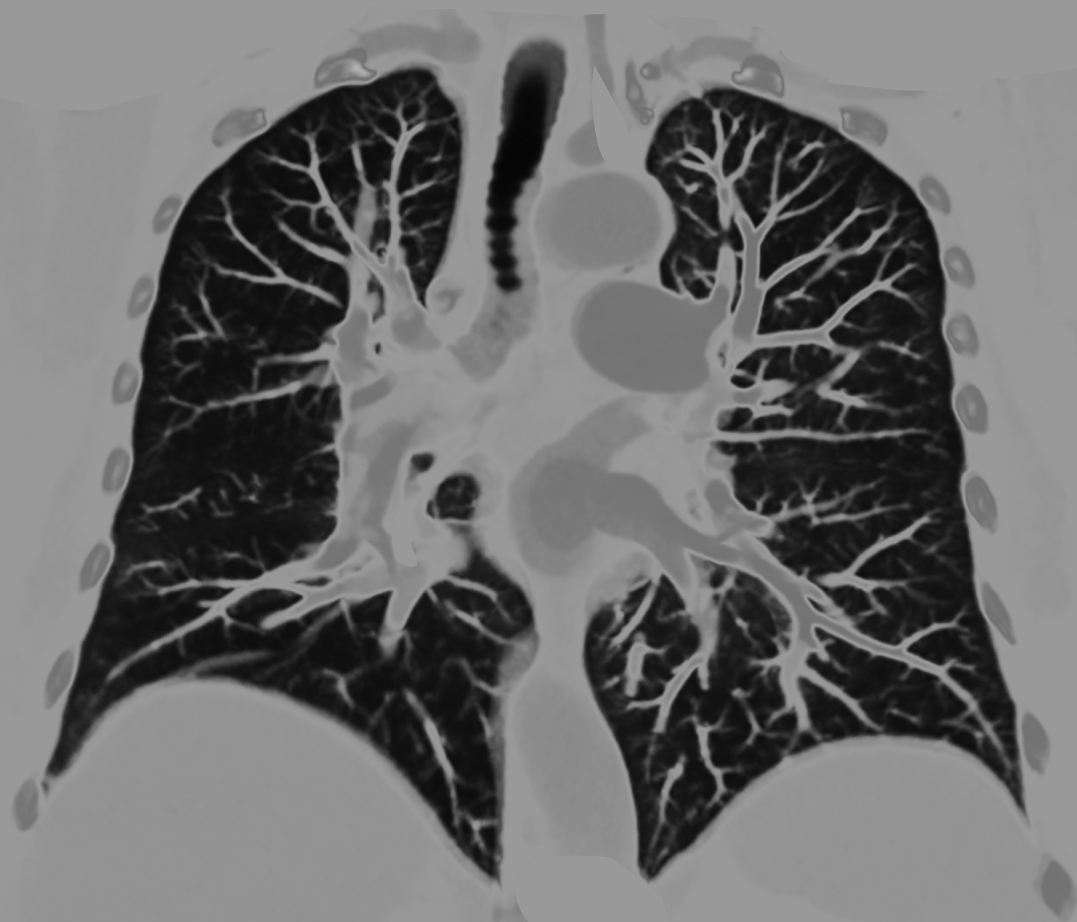
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## References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**(10): e146-e603.
2. Konstantinides S, Torbicki A. Management of venous thrombo-embolism: an update. *European heart journal* 2014; **35**(41): 2855-63.
3. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011; **123**(16): 1788-830.
4. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *The New England journal of medicine* 2014; **370**(15): 1402-11.
5. Agrawal N, Ramegowda RT, Patra S, et al. Predictors of inhospital prognosis in acute pulmonary embolism: keeping it simple and effective! *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* 2014; **25**(5): 492-500.
6. Henzler T, Roeger S, Meyer M, et al. Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. *The European respiratory journal* 2012; **39**(4): 919-26.
7. Meyer M, Fink C, Roeger S, et al. Benefit of combining quantitative cardiac CT parameters with troponin I for predicting right ventricular dysfunction and adverse clinical events in patients with acute pulmonary embolism. *European journal of radiology* 2012; **81**(11): 3294-9.
8. Castillo C, Tapon VF. Right ventricular responses to massive and submassive pulmonary embolism. *Cardiology clinics* 2012; **30**(2): 233-41.
9. Paiva L, Barra S, Providencia R. Pulmonary embolism risk stratification: the intermediate-risk group. *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* 2013; **24**(8): 896-8.
10. Spirk D, Willenberg T, Aujesky D, et al. Use of biomarkers or echocardiography in pulmonary embolism: the Swiss Venous Thromboembolism Registry. *QJM : monthly journal of the Association of Physicians* 2012; **105**(12): 1163-9.
11. Ghaye B, Ghuysen A, Bruyere PJ, D'Orio V, Dondelinger RF. Can CT pulmonary angiography allow assessment of severity and prognosis in patients presenting with pulmonary embolism? What the radiologist needs to know. *Radiographics : a review publication of the Radiological Society of North America, Inc* 2006; **26**(1): 23-39; discussion -40.
12. Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *European heart journal* 2008; **29**(12): 1569-77.
13. van der Meer RW, Pattynama PM, van Strijen MJ, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. *Radiology* 2005; **235**(3): 798-803.
14. Becattini C, Agnelli G, Vedovati MC, et al. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. *European heart journal* 2011; **32**(13): 1657-63.

15. Apfaltrer P, Walter T, Gruettner J, et al. Prediction of adverse clinical outcome in patients with acute pulmonary embolism: evaluation of high-sensitivity troponin I and quantitative CT parameters. *European journal of radiology* 2013; **82**(3): 563-7.
16. Choi KJ, Cha SI, Shin KM, et al. Prognostic implications of computed tomographic right ventricular dilation in patients with acute pulmonary embolism. *Thrombosis research* 2014; **133**(2): 182-6.
17. Etesamifard N, Shirani S, Jenab Y, Lotfi-Tokaldany M, Pourjafari M, Jalali A. Role of clinical and pulmonary computed tomography angiographic parameters in the prediction of short- and long-term mortality in patients with pulmonary embolism. *Internal and emergency medicine* 2016; **11**(3): 405-13.
18. Furlan A, Aghayev A, Chang CC, et al. Short-term mortality in acute pulmonary embolism: clot burden and signs of right heart dysfunction at CT pulmonary angiography. *Radiology* 2012; **265**(1): 283-93.
19. Heyer CM, Lemburg SP, Knoop H, Holland-Letz T, Nicolas V, Roggenland D. Multidetector-CT angiography in pulmonary embolism-can image parameters predict clinical outcome? *European radiology* 2011; **21**(9): 1928-37.
20. Jia D, Zhou XM, Hou G. Estimation of right ventricular dysfunction by computed tomography pulmonary angiography: a valuable adjunct for evaluating the severity of acute pulmonary embolism. *Journal of thrombosis and thrombolysis* 2017; **43**(2): 271-8.
21. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *The New England journal of medicine* 2013; **369**(15): 1406-15.
22. Jimenez D, Lobo JL, Monreal M, Otero R, Yusen RD. Prognostic significance of multidetector computed tomography in normotensive patients with pulmonary embolism: rationale, methodology and reproducibility for the PROTECT study. *Journal of thrombosis and thrombolysis* 2012; **34**(2): 187-92.
23. Kang DK, Ramos-Duran L, Schoepf UJ, et al. Reproducibility of CT signs of right ventricular dysfunction in acute pulmonary embolism. *AJR American journal of roentgenology* 2010; **194**(6): 1500-6.
24. Kumamaru KK, Hunsaker AR, Wake N, et al. The variability in prognostic values of right ventricular-to-left ventricular diameter ratios derived from different measurement methods on computed tomography pulmonary angiography: a patient outcome study. *Journal of thoracic imaging* 2012; **27**(5): 331-6.
25. Kamel EM, Schmidt S, Doenz F, Adler-Etehami G, Schnyder P, Qanadli SD. Computed tomographic angiography in acute pulmonary embolism: do we need multiplanar reconstructions to evaluate the right ventricular dysfunction? *Journal of computer assisted tomography* 2008; **32**(3): 438-43.
26. Plasencia-Martinez JM, Carmona-Bayonas A, Calvo-Temprano D, Jimenez-Fonseca P. Prognostic value of computed tomography in acute pulmonary thromboembolism. *Radiologia* 2016; **58**(5): 391-403.

27. Singanayagam A, Chalmers JD, Scally C, et al. Right ventricular dilation on CT pulmonary angiogram independently predicts mortality in pulmonary embolism. *Respiratory medicine* 2010; **104**(7): 1057-62.
28. Jimenez D, Lobo JL, Monreal M, et al. Prognostic significance of multidetector CT in normotensive patients with pulmonary embolism: results of the protect study. *Thorax* 2014; **69**(2): 109-15.
29. Meinel FG, Nance JW, Jr., Schoepf UJ, et al. Predictive Value of Computed Tomography in Acute Pulmonary Embolism: Systematic Review and Meta-analysis. *The American journal of medicine* 2015; **128**(7): 747-59 e2.
30. Araoz PA, Gotway MB, Trowbridge RL, et al. Helical CT pulmonary angiography predictors of in-hospital morbidity and mortality in patients with acute pulmonary embolism. *Journal of thoracic imaging* 2003; **18**(4): 207-16.
31. Trujillo-Santos J, den Exter PL, Gomez V, et al. Computed tomography-assessed right ventricular dysfunction and risk stratification of patients with acute non-massive pulmonary embolism: systematic review and meta-analysis. *Journal of thrombosis and haemostasis : JTH* 2013; **11**(10): 1823-32.
32. Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. *The European respiratory journal* 2014; **43**(6): 1678-90.
33. Stein PD, Beemath A, Matta F, et al. Enlarged right ventricle without shock in acute pulmonary embolism: prognosis. *The American journal of medicine* 2008; **121**(1): 34-42.
34. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. *Vascular medicine (London, England)* 2017; **22**(1): 37-43.
35. Brekelmans MP, Ageno W, Beenen LF, et al. Recurrent venous thromboembolism in patients with pulmonary embolism and right ventricular dysfunction: a post-hoc analysis of the Hokusai-VTE study. *The Lancet Haematology* 2016; **3**(9): e437-45.
36. Aviram G, Rogowski O, Gotler Y, et al. Real-time risk stratification of patients with acute pulmonary embolism by grading the reflux of contrast into the inferior vena cava on computerized tomographic pulmonary angiography. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(9): 1488-93.
37. Zhao DJ, Ma DQ, He W, Wang JJ, Xu Y, Guan CS. Cardiovascular parameters to assess the severity of acute pulmonary embolism with computed tomography. *Acta radiologica (Stockholm, Sweden : 1987)* 2010; **51**(4): 413-9.
38. Seon HJ, Kim KH, Lee WS, et al. Usefulness of computed tomographic pulmonary angiography in the risk stratification of acute pulmonary thromboembolism. Comparison with cardiac biomarkers. *Circulation journal : official journal of the Japanese Circulation Society* 2011; **75**(2): 428-36.
39. Atasoy MM, Sariman N, Levent E, et al. Nonsevere acute pulmonary embolism: prognostic CT pulmonary angiography findings. *Journal of computer assisted tomography* 2015; **39**(2): 166-70.
40. Bach AG, Nansalmaa B, Kranz J, et al. CT pulmonary angiography findings that predict 30-day mortality in patients with acute pulmonary embolism. *European journal of radiology* 2015; **84**(2): 332-7.



# Chapter 5

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Prognostic characteristics and body mass index in patients with pulmonary embolism: does size matter?

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## **Abstract**

### **Background**

The aim of this study was to explore the impact of body mass index (BMI) on prognostic indicators and clinical outcomes in patients with pulmonary embolism.

### **Methods**

Patients with pulmonary embolism from the Hokusai venous thromboembolism (VTE) randomised clinical trial that compared two anticoagulant regimens were followed up for 1 year (n=1911). Patients were analysed with regard to World Health Organisation (WHO) BMI categories at baseline (underweight (<18.5), normal (18.5 to < 25), overweight (25 to <30), obese I (30 to <35), obese II (35 to <40), and obese III ( $\geq$ 40). Clinical and radiological prognostic characteristics for right ventricular dysfunction and adverse events were assessed with normal weight as reference. Clinical outcomes were mortality, recurrent VTE, hospitalisation, bleeding and overall adverse events.

### **Results**

The relationship between BMI categories and both prognostic parameters and clinical outcomes showed U-shaped curves. Adjusted odds ratios (aOR) were highest in patients who were grade III obese for both clinical parameters (N-terminal pro-brain natriuretic peptide (NT-proBNP) >600 and simplified pulmonary embolism severity index (sPESI)  $\geq$ 1; 2.9 and 1.6), and radiological parameters (pulmonary trunk >29 mm, right-to-left ventricular ratio >1.0, and central emboli; aOR = 4.3, 2.1 and 2.3). Bleeding was observed more frequently in the higher categories of obesity. In patients who were underweight, for NT-proBNP >600 and sPESI  $\geq$ 1 the aOR were 2.6 and 2.5, respectively; however, no major bleeding occurred in this category.

### **Conclusions**

Several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism are not evenly distributed among BMI categories. This is reflected in a trend toward worse outcomes in patients who are overweight and underweight.

## Introduction

Patients with pulmonary embolism at extremes of body weight pose specific clinical considerations with regard to diagnosis, treatment and prognosis. Obese patients are at increased risk for both deep vein thrombosis (DVT) and pulmonary embolism (PE) compared to patients with a normal Body Mass Index (BMI - weight in kilograms divided by height in meters squared).<sup>1-3</sup> This risk increases with increasing body mass index.<sup>4,5</sup> Potential causal mechanisms for increased risk of venous thrombosis by obesity are venous stasis, chronic inflammation, adipokines, increased coagulation activity, decreased fibrinolytic activity, and procoagulant microparticles.<sup>6</sup>

Regarding treatment, it is debated whether the extremes in body weight should receive modified treatment regimens.<sup>7</sup> Because of limited clinical data available for obese patients, the International Society on Thrombosis and Haemostasis (ISTH) guidance document advises against use of direct oral anticoagulants in patients with a body weight higher than 120 kg or a BMI higher than 40.<sup>8</sup> Although currently unfractionated heparin with aPTT monitoring for patients with severe obesity is recommended,<sup>9</sup> an expert panel recently expressed the urgent need for data on heparin regimens in all obese patients.<sup>7</sup> This becomes even more prominent with the alarming increase in overweight people worldwide.<sup>10</sup>

Remarkably, with regard to diagnosis and prognosis, knowledge of the impact of BMI on clinical presentation and clot characteristics and burden is even more limited. Unfortunately, even in large randomized trials on efficacy of anticoagulation in patients with venous thrombo-embolism (VTE) no subgroup analysis on body weight or BMI has been performed to provide methodologically robust data on this subject. Therefore, how this could reflect on work up and prognosis is not exactly known. Should BMI be a modifier for individual patient tailored care? Does body size matter?

Our hypothesis was that in patients with pulmonary embolism clot characteristics and prognosis are different at the extremes of BMI. The aim of this study was to explore the impact of body size on presentation, prognostic characteristics and outcome of patients with pulmonary embolism in CT pulmonary angiography. Therefore, we studied in a large cohort of patients with pulmonary embolism established clinical and radiological parameters associated with right ventricular dysfunction and mortality, and stratified them according to BMI categories.

## Materials and Methods

### *Patients and study design*

This present study is a post hoc analysis of the Hokusai-VTE study, a large international randomized clinical trial in which two anticoagulant regimens were



compared in patients with venous thrombo-embolism (ClinicalTrials.gov identifier: NCT00986154).<sup>11,12</sup> In short, eligible patients were aged 18 years or older and had acute symptomatic deep vein thrombosis and/or pulmonary embolism. Patients were excluded in case of contraindications to heparin or warfarin, severely impaired renal function or pregnancy. The Hokusai VTE trial did not exclude patients based on body weight. The institutional review board at each participating centre approved the general study protocol, and all patients provided written informed consent. Follow-up was 12 months, covering the in-hospital period as well as regular outpatient clinic controls, and patients on and off anticoagulant treatment. Adverse events were noted on separate forms, as well as whether this was PE related. An independent committee adjudicated all predefined outcomes. In the trial, in the two treatment arms there was no difference in hazard ratio between patients with a body weight of 100 kg or less, and those over 100 kg; no further detailed analyses were performed for high body weight groups.<sup>11</sup> For the current analysis all patients with PE, either with or without DVT, were included. Excluded were patients not evaluated by CT pulmonary angiography (CTPA), or when images were not available in DICOM format or inaccessible for reading in the image viewer.<sup>12</sup>

### ***Data collection***

All clinical and radiological data were anonymized, and centrally registered with double data entry by an independent trial data management agency. Clinical data were retrieved from the original CRFs. In all patients NT-proBNP levels were measured at baseline. All data for the present analysis had been collected and assessed prospectively before the trial data lock.

CT-data were acquired from the local participating centres, using local settings and protocols, with a wide variety of CT-scanners, from basic until high-end CT. Anonymized patient images from the central database were evaluated by a radiologist (LB) with 12 years of experience in cardiovascular imaging supported by a dedicated research assistant, both blinded for patient details and clinical information. For image reading a commercially available image viewer was used (eFilm Workstation for Windows Version 3.4.0, Build 10, Merge Technologies Inc., Milwaukee, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting (MPR). Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation if deemed necessary. Data were registered on a specially designed CRF.

We investigated body size according to the body mass index categories as classified by the World Health Organization (WHO): underweight (<18.5), normal (18.5 to <25), overweight (25 to <30), obese I (30 to <35), obese II (35 to <40), and obese III ( $\geq 40$ ).

### ***Study outcomes: prognostic characteristics and clinical outcomes***

Both clinical and radiological prognostic characteristics for right ventricular dysfunction and adverse events were assessed. For baseline NT-proBNP a value of  $\geq 600$  pg/ml at baseline was considered abnormal;<sup>9</sup> for sPESI calculation the arterial oxyhaemoglobin saturation  $<90\%$  was not registered; this item was considered positive if patient required oxygen administration. The following radiological parameters for right ventricular dysfunction (RVD) were assessed: transverse diameter of right and left ventricle (axial view) and pulmonary trunk; bowing of the interventricular septum (negative, D-shaped/neutral, positive) and reflux of contrast medium in the intrahepatic veins). For the ventricular diameters, the largest cross-sectional distance between ventricular surfaces was taken. Pulmonary trunk was measured at its largest transverse diameter. All continuous variables were noted in millimetres where applicable. The right-to-left ventricular (RV/LV) ratios were calculated by dividing the values of respective transverse diameters. The obtained values were then dichotomized at regular used thresholds (RV/LV  $> 1.0$ ; pulmonary trunk (PT)  $> 29$  mm). Interventricular septum bowing was considered present when the septum was curved to the left ventricle, or flattened if the septum was straightened or bowed. Backflow was considered positive if contrast medium reflux was into the intrahepatic veins; only into the inferior caval vein was considered negative.

Clinical outcomes for the study were mortality, recurrent VTE, hospitalisation, bleeding and overall adverse events. Outcome events were analysed after a follow up of one year.

### ***Statistical analysis***

Descriptive statistics are displayed as mean  $\pm$  standard deviation (SD) for normally distributed variables and median  $\pm$  interquartile ranges (IQR, 25<sup>th</sup> to 75<sup>th</sup> percentile) for not normally distributed variables. For comparison on binary outcomes the Chi-square test for dichotomous variables were used. Between the groups categorical variables were compared using the Chi-square test for trend; for continuous data by Students T test or Mann-Whitney U test if non-normally distributed. A p-value  $< 0.05$  was considered statistical significant. We used logistic regression models to estimate odds ratios (OR) with 95% confidence intervals (CI) to investigate the association between the outcome variables and the BMI categories. In addition, where appropriate, we adjusted these analyses for age and sex. All statistical analyses were performed in SPSS version 23 (SPSS Inc, Chicago Ill), figures were designed in GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA.

## Results

Baseline characteristics are displayed in Table 1. The initial study group consisted of 1950 patients with pulmonary embolism. In all 1950 patients baseline weight was available, but in 39 patients (2.0%) body height was not known. Hence baseline BMI could be calculated in 1911 patients, comprising the study group for further analyses. Of these 1911, 493 (25.8%) patients had a normal BMI (Table 2). The majority of patients, i.e. 1389 (72.7%) had a BMI>25 and obesity (BMI>30) was present in 670 (35.1%). A small proportion, i.e. 29 (1.5%) patients was underweight.

**Table 1: Baseline characteristics.**

	Total		BMI <18.5		BMI 18.5-24.99		BMI >25	
	n	%	n	%	n	%	n	%
Included	1911	100	29	1.5	493	25.8	1389	72.7
<i>Clinical</i>								
Age (mean, SD)	56.9	16.6	56.6	23.9	55.7	18.8	57.3	15.5
Weight (mean, SD)	84.6	20.1	49.9	8.0	66.7	10.0	91.7	18.2
SBP mmHg (mean, SD)	128	16.5	118	15.4	126	16.8	129	16.3
DBP mmHg (mean, SD)	76	11.0	69	8.8	74	10.6	77	11.1
Heart Rate (mean, SD)	80	14.2	85	10.0	80	14.7	80	14.1
Age <50Y	629	32.9	11	37.9	190	38.5	428	30.8
Age > 65Y	696	36.4	14	48.3	183	37.1	499	35.9
Weight < 60 kg	187	9.8	24	82.8	144	29.2	19	1.4
Current alcohol use	741	38.8	10	34.5	199	40.4	532	38.3
Smoking	834	43.6	15	51.7	235	47.7	584	42.0
NT-proBNP > 600	504	27.3	12	42.9	115	23.9	377	28.2
sPESI* High Risk ≥1	1028	53.8	21	72.4	251	50.9	756	54.4
Unprovoked PE	1266	66.2	21	72.4	327	66.3	918	66.1
Concurrent DVT	447	23.4	3	10.3	102	20.7	342	24.6
<i>Risk Factors</i>								
Recent surgery, trauma, or immobilisation	364	19.0	5	17.2	76	15.4	283	20.4
Sitting > 4 hours	182	9.5	1	3.4	58	11.8	123	8.9
Oestrogen drugs use	193	10.1	8	27.6	73	14.8	112	8.1
Previous DVT/PE	405	21.2	1	3.4	85	17.2	319	23.0
Thrombophilia	94	4.9	1	3.4	32	6.5	61	4.4
<i>Concomitant Disease History</i>								
Hypertension	793	41.5	11	37.9	136	27.6	646	46.5
Diabetes	194	10.2	3	10.3	18	3.7	173	12.5
Cardiovascular Disease	306	16.0	6	20.7	82	16.6	218	15.7
Chronic Heart Failure	34	1.8	2	6.9	6	1.2	26	1.8
Cerebrovascular Disease	71	3.7	1	3.4	20	4.1	50	3.6
Stroke	34	1.8	1	3.4	11	2.2	22	1.6
Renal Disease	128	6.7	2	6.9	30	6.1	96	6.9
Hepatic Disease	207	10.8	3	10.3	47	9.5	157	10.8
Pulmonary Disease	391	20.5	12	41.4	91	18.5	288	20.7
COPD	100	5.2	7	24.1	35	7.1	58	4.2
Pulmonary hypertension	43	2.3	2	6.9	6	1.2	35	2.5
Cancer	221	11.6	6	20.7	65	13.2	150	10.8

Data are number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DBP – Diastolic Blood Pressure; DVT – Deep Vein Thrombosis; PE – Pulmonary Embolus; SBP – Systolic Blood Pressure; US – Ultrasound. \* sPESI- item on O2 considered positive if patient needed oxygen administration.

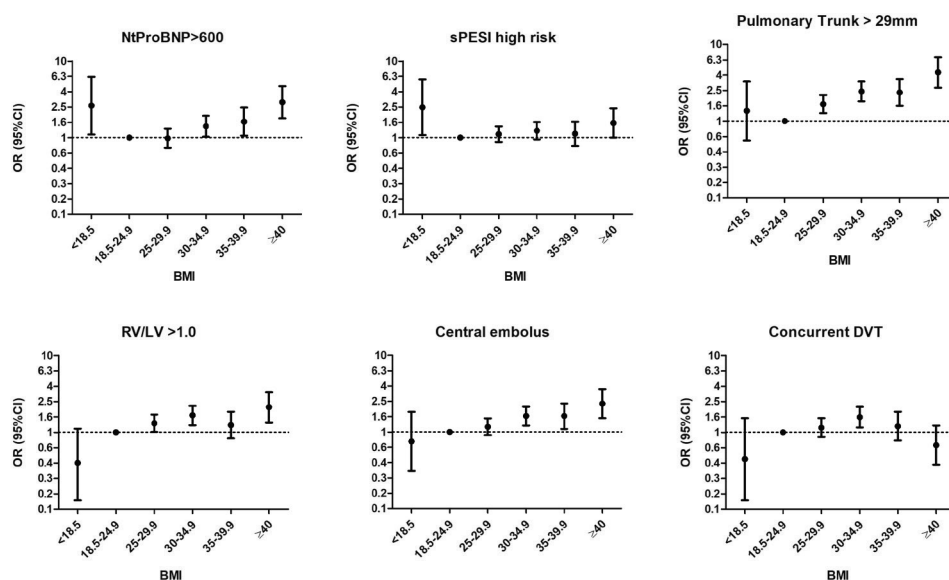
**Table 2: Distribution of patients according to WHO categories.**

Total BMI	1911	%
<18,5	29	1.5
18,5-24,9	493	25.8
25-29,9	717	37.5
30-34,9	414	21.7
35-39,9	154	8.1
≥40	104	5.4
<b>Complete</b>	<b>1950*</b>	

\* Body height was not available in 39 (2.0%) of 1950 patients, so in these patients BMI could not be calculated.

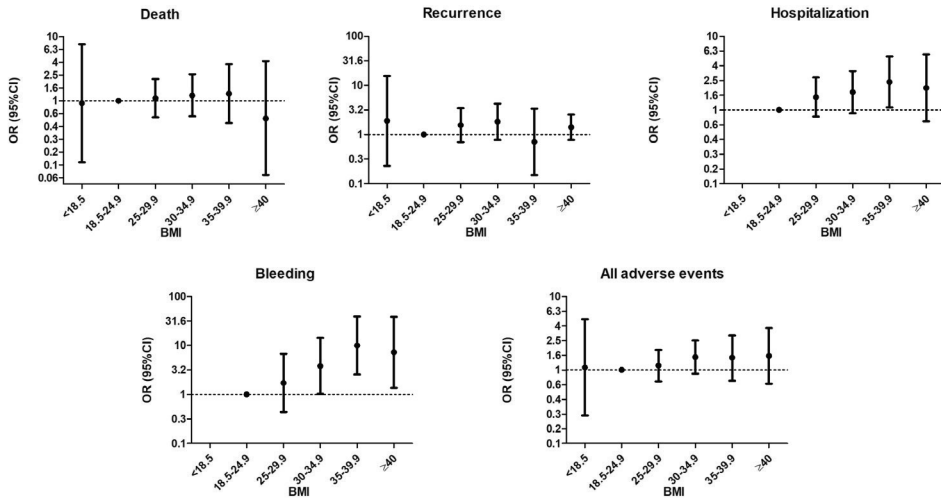
With regard to risk factors for VTE, 372 patients (19.5%) had undergone recent surgery and 415 patients (21.7%) had a history of VTE. Arterial cardiovascular risk factors (e.g. smoking, hypertension) were present in a substantial proportion of patients: hypertension was present in 810 (42.4%) patients, 199 (10.4%) had diabetes mellitus, and 314 (16.4%) patients had a history of cardiovascular disease.

The overall trend, clinical, radiological and outcome parameters are displayed in Figure 1 for all patients according to the BMI categories. Both patterns for NT-proBNP, sPESI and enlarged pulmonary trunk showed a U-shaped curve, with lowest percentages in the normal BMI-range, and were higher for overweight as well as underweight patients. Other parameters like enlarged right-to-left ventricular ratio and central embolus showed a direct association with increasing BMI.



**Figure 1:**

Association between body mass index (BMI) categories and clinical and radiological parameters with BMI 18.5–24.9 kg-m<sup>-2</sup> as a reference. Odds ratios for a) N-terminal pro-brain natriuretic peptide, b) high-risk simplified pulmonary embolism severity index score, c) pulmonary trunk >29 mm, d) right/left ventricular diameter ratio >1.0, e) central embolism and d) concurrent deep venous thrombosis are shown. Error bars present 95% confidence intervals.

**Figure 2:**

Association between body mass index (BMI) categories and outcomes with BMI 18.5–24.9 kg·m<sup>-2</sup> as reference. Odds ratios for a) death, b) recurrent venous thromboembolism, c) hospitalisation, d) bleeding and e) all adverse events are shown. Error bars represent 95% confidence intervals.

**Table 3: Odds ratios for clinical and radiological parameters and outcomes according to BMI categories.**

BMI	N (%)	OR	OR*
<b><i>NTProBNP &gt;600</i></b>			
<18.5	12(42.8)	2.38 (1.09-5.18)	2.62 (1.10-6.23)
18.5-24.9	115 (24.0)	1 (reference)	1 (reference)
25.0-29.9	162 (23.4)	0.97 (0.74-1.28)	0.98 (0.74-1.31)
30.0-34.9	124 (31.2)	1.44 (1.07-1.94)	1.41 (1.03-1.93)
35.0-39.9	50 (34.0)	1.64 (1.10-2.44)	1.62 (1.06-2.48)
>40	41 (41.0)	2.21 (1.41-3.46)	2.90 (1.79-4.70)
<b><i>sPESI high risk</i></b>			
<18.5	21 (72.4)	2.52 (1.10-5.80)	2.49 (1.08-5.75)
18.5-24.9	251 (51.0)	1 (reference)	1 (reference)
25.0-29.9	375 (52.4)	1.06 (0.84-1.33)	1.11 (0.88-1.40)
30.0-34.9	230 (55.7)	1.21 (0.93-1.57)	1.23 (0.95-1.60)
35.0-39.9	84 (54.5)	1.15 (0.80-1.66)	1.13 (0.78-1.62)
>40	66 (63.5)	1.67 (1.08-2.58)	1.55 (1.00-2.41)
<b><i>Pulmonary trunk &gt; 29 mm</i></b>			
<18.5	8 (27.6)	1.39 (0.60-3.22)	1.36 (0.56-3.28)
18.5-24.9	106 (21.5)	1 (reference)	1 (reference)
25.0-29.9	232 (32.4)	1.75 (1.34-2.28)	1.66 (1.27-2.19)
30.0-34.9	168 (40.7)	2.50 (1.87-3.34)	2.44 (1.81-3.28)
35.0-39.9	59 (38.3)	2.26 (1.53-3.34)	2.37 (1.59-3.53)
>40	49 (47.1)	3.24 (2.09-5.04)	4.32 (2.73-6.83)
<b><i>RV/LV&gt;1.0</i></b>			
<18.5	4 (13.8)	0.45 (0.15-1.31)	0.40 (0.13-1.12)
18.5-24.9	130 (26.4)	1 (reference)	1 (reference)
25.0-29.9	231 (32.3)	1.33 (1.03-1.71)	1.31 (1.01-1.70)
30.0-34.9	157 (38.0)	1.71 (1.29-2.27)	1.66 (1.24-2.21)
35.0-39.9	48 (31.2)	1.26 (0.85-1.88)	1.24 (0.83-1.85)
>40	41 (39.4)	1.81 (1.17-2.81)	2.12 (1.34-3.33)

**Table 3: Continued.**

BMI	N (%)	OR	OR*
<b>Central Embolus</b>			
<18.5	7 (24.1)	0.78 (0.33-1.86)	0.75 (0.31-1.82)
18.5-24.9	143 (29.1)	1 (reference)	1 (reference)
25.0-29.9	234 (32.7)	1.19 (1.19-0.92)	1.17 (0.91-1.50)
30.0-34.9	167 (40.4)	1.66 (1.26-2.19)	1.61 (1.22-2.13)
35.0-39.9	62 (40.3)	1.65 (1.30-2.40)	1.61 (1.10-2.36)
>40	49 (47.1)	2.17 (1.41-3.35)	2.34 (1.51-3.62)
<b>Concurrent DVT</b>			
<18.5	3 (10.3)	0.44 (0.13-1.49)	0.45 (0.13-1.52)
18.5-24.9	102 (20.7)	1 (reference)	1 (reference)
25.0-29.9	170 (23.7)	1.19 (0.90-1.57)	1.15 (0.87-1.52)
30.0-34.9	121 (29.3)	1.58 (1.17-2.15)	1.57 (1.16-2.14)
35.0-39.9	36 (23.4)	1.17 (0.76-1.80)	1.20 (0.78-1.85)
>40	15 (14)	0.64 (0.36-1.16)	0.68 (0.38-1.23)
<b>Death</b>			
<18.5	1 (3.4)	1.22 (0.16-9.61)	0.92 (0.11-7.59)
18.5-24.9	14 (2.8)	1 (reference)	1 (reference)
25.0-29.9	22 (3.1)	1.08 (0.55-2.14)	1.09 (0.55-2.18)
30.0-34.9	14 (3.4)	1.20 (0.56-2.54)	1.21 (0.57-2.60)
35.0-39.9	5 (3.2)	1.15 (0.41-3.23)	1.29 (0.45-3.71)
>40	1 (1.0)	0.33 (0.04-2.55)	0.53 (0.07-4.18)
<b>Recurrent VTE</b>			
<18.5	1 (3.4)	1.92 (0.24-15.67)	1.90 (0.23-15.57)
18.5-24.9	9 (1.8)	1 (reference)	1 (reference)
25.0-29.9	21 (2.9)	1.62 (0.74-3.57)	1.55 (0.70-3.42)
30.0-34.9	14 (3.4)	1.88 (0.81-4.40)	1.82 (0.78-4.25)
35.0-39.9	2 (1.3)	0.71 (0.15-3.30)	0.71 (0.15-3.34)
>40	3 (2.9)	1.59 (0.42-5.99)	1.41 (0.78-2.53)
<b>Hospitalisation</b>			
<18.5	0 (0)	0	0
18.5-24.9	16 (3.3)	1 (reference)	1 (reference)
25.0-29.9	34 (4.7)	1.48 (0.81-2.72)	1.49 (0.81-2.75)
30.0-34.9	23 (5.6)	1.75 (0.91-3.37)	1.74 (0.90-3.35)
35.0-39.9	11 (7.1)	2.29 (1.04-5.04)	2.39 (1.08-5.32)
>40	5 (4.8)	1.50 (0.54-4.20)	1.99 (0.70-5.67)
<b>Bleeding</b>			
<18.5	0 (0)	0	0
18.5-24.9	3 (0.6)	1 (reference)	1 (reference)
25.0-29.9	7 (1.0)	1.61 (0.41-6.25)	1.72 (0.44-6.74)
30.0-34.9	9 (2.2)	3.63 (0.98-13.50)	3.82 (1.02-14.34)
35.0-39.9	8 (5.2)	8.93 (2.34-34.10)	9.99 (2.56-38.92)
>40	3 (2.9)	4.84 (0.96-24.33)	7.26 (1.37-38.32)
<b>All Adverse Events</b>			
<18.5	2 (6.9)	1.23 (0.279-5.43)	1.08 (0.24-4.90)
18.5-24.9	28 (5.7)	1 (reference)	1 (reference)
25.0-29.9	47 (6.6)	1.16 (0.72-1.89)	1.15 (0.70-1.87)
30.0-34.9	35 (8.5)	1.53 (0.92-2.57)	1.50 (0.89-2.52)
35.0-39.9	12 (7.8)	1.40 (0.69-2.83)	1.47 (0.71-2.94)
>40	7 (6.7)	1.20 (0.51-2.82)	1.55 (0.65-3.72)

Odds ratios for clinical and radiological parameters (3a) and outcomes (3b) according to BMI categories (BMI <18.5 (29 patients); 18.5-24.9 (492); 25.0-29.9(716); 30.0-34.9(413); 35.0-39.9 (154) and >40 (104 patients), with BMI 18.5-24.9 as reference. Proportion was calculated per BMI category with follow-up up to 12 months. BMI -Body Mass Index; DVT – deep venous thrombosis; PT – pulmonary trunk, sPESI – simplified pulmonary embolism severity index, RV/LV – right-to-left ventricular ratio; VTE – venous thrombo-embolism \* Adjusted for age and sex; sPESI only adjusted for sex.

The associations between the prognostic characteristics and BMI categories are shown in Table 3. There was an apparent exposure-response relationship between BMI category and the proportion of patients with NT-ProBNP>600, sPESI high risk, pulmonary trunk > 29 mm, RV/VL>1 and presence of central emboli. The OR for NT-ProBNP>600 increased up to 2.90 (95%CI 1.79-4.70) at BMI>40. For the other prognostic characteristics the ORs for BMI>40 compared to normal BMI were OR 4.32 (95%CI 2.73-6.83) for pulmonary trunk>29mm, 2.12 (95%CI 1.34-3.33) for RV/LV>1.0, 2.34 (95%CI 1.51-3.62) for central location of the emboli and 1.55 (95%CI 1.00-2.41) for high sPESI risk category.

There were 57 deaths, 50 recurrent VTEs, 89 hospitalisations, 30 major bleedings, and 131 adverse events over all reported during one year. For the clinical outcomes an exposure-response relation for risk of hospitalisation, bleeding and adverse events was observed, with the risk of the event increasing with BMI (Table 3). The highest risk in the BMI category >40 was for bleeding (OR 7.26, 95%CI 1.37-38.3). Also for the other clinical outcomes, mortality and recurrent VTE, an increase for the higher BMI categories was observed, as well as for the overall risk of adverse events (Figure 1). Interestingly, risk of hospitalisation and major bleeding were not higher in patients with underweight, although the 95% CI for this point estimate was wide.

## Discussion

We demonstrated that prognostic characteristics of pulmonary embolism on CTPA are associated with BMI in a category-dependent manner, with highest risk at the extremes of BMI. Also for the most important clinical outcomes mortality and VTE recurrence an unfavourable trend for the high BMI categories was present, though not statistically significant. Our study highlights the potential importance of assessing BMI as a prognostic indicator when diagnosing and treating patients with pulmonary embolism. Contrary to many other determinants, common demographics like body size and height are easily obtainable, without any effort or costs, for regular use in daily clinical practice.

A strength of our study is the prospective and rigorous collection of all included data as part of a large international randomized clinical trial. Both imaging data and clinical outcomes were assessed before the data lock and the assessors were blinded for treatment and outcome. We evaluated a broad range of parameters in order to provide a complete, integral picture rather than limiting to a single factor with concurrent restricted impact.

Our study has some limitations. Despite the fact that the number of all included patients is large, the relatively low frequency of events with associated statistical uncertainty prohibits us from drawing firm or definite conclusions, even more so

for the underweight category. We did not further adjust for potential confounders like comorbidities and risk factors, as the power to do so was limited by the relatively low number of outcome events. Because of the paucity of literature on this increasingly prominent issue however, we nevertheless think it of contributing value, as an incentive for further exploration of this topic. Also, we are aware that patients included in a randomized controlled trial do not necessarily reflect all those presenting in daily clinical practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients and patients with a limited life expectancy. Lastly, we only used correlation with BMI categories. Although BMI as an obesity measure has been questioned, it is still the most widely used body-weight measurement, and easy to obtain. Apart from BMI also other measures for body size exists, such as body fat percentage, waist circumference or waist hip ratio (not registered in the trial).<sup>5</sup>

A classic U- or J-shaped curve for BMI categories has been reported in a wide variety of pathological and physiological conditions such as cardiovascular and respiratory disease, stroke, and cancer.<sup>10,13,14</sup> Our findings suggest that a similar pattern applies to prognostic indicators in patients with pulmonary embolism, with lowest prevalence of many investigated parameters for the normal weight group, and a higher prevalence at the extremes of body weight. BMI not only was predictive in several clinical and radiological prognostic characteristics associated with RV dysfunction, but also in a similar way with the relevant clinical outcomes. We are not aware of other studies that explored the association between a broad range of prognostic characteristics of pulmonary embolism and BMI categories; only for NT-proBNP one study reported that obese patients in general have reduced concentrations, despite higher left ventricular end diastolic pressures.<sup>15</sup> As such, it is even more interesting that in patients with pulmonary embolism, NT-proBNP levels tended to be higher in higher BMI categories. Notably, in obese patients adaptations in cardiac structure and function, more specifically differences of RV morphology could develop.<sup>16</sup> These alterations could e.g. be induced by increased RV afterload, increased blood volume, hormonal effects, or direct obesity-related myocardial effects.<sup>17</sup>

How do our findings fit into the current assessment of overweight patients with acute PE? In the Framingham study, women who had a fatal PE had higher body weight than those who died of other causes.<sup>18</sup> On the contrary, several investigators have reported a higher incidence of VTE in obese patients but a lower rate of mortality compared to non-obese patients, even despite the fact that obese patients have more comorbidities, a phenomenon referred to as the obesity paradox.<sup>19-23</sup> However, this is also in contrast with large autopsy studies where in each category of above-normal BMIs obese individuals were more likely to die from pulmonary embolism.<sup>24,25</sup>

Complex relationships exist between body mass indicators, metabolic function



and cardiovascular risk. Possibly, clot composition in obese individuals might be different from those with normal weight.<sup>26</sup> It has been hypothesized that these could become more resistant to fibrinolysis because of higher fibrinogen levels, polycythaemia, and other haematological changes related to obesity.<sup>27,28</sup> Our observation that patients with higher BMI categories had more central clots could also be a reflection of the different physical properties of the thrombi in obese.

For recurrent VTE several papers have been published, however also with conflicting results, as some found no association between obesity and the risk of VTE recurrence,<sup>29-32</sup> whereas others found a higher recurrence risk with higher BMI.<sup>33,34</sup> In our study confidence intervals for the estimates crossed unity and we therefore cannot give a definitive answer on this matter.

Reports on the other investigated clinical outcomes –hospitalisation, bleeding and overall adverse effects- are scarce, as most often they are used as a composite outcome, or focus on differences between treatment regimens.

Our finding of a trend for increased hospitalisation for obese patients is supported by the large Australian 45 and Up cohort study, where the risk of hospitalisation for a wide range of CVD subtypes increased with relatively fine increments in BMI. For PE, the age and sex adjusted hazard ratio was 1.39 (95% CI 1.25-1.55) compared to normal BMI.<sup>35</sup>

Bleeding complications during treatment of PE are more frequent than recurrent VTE.<sup>36</sup> In the current study a higher incidence of bleeding in the overweight was observed, underlining the importance of this complication. Both for weight and BMI, in the RIETE prospective registry,<sup>19,37</sup> as well as in subgroup analysis of the Matisse<sup>29</sup> and Einstein DVT/PE<sup>31</sup> anticoagulation RCT's no association between body weight or BMI and major bleeding was found. However, analysis was only performed using two or three large categories (patients weighing <50, 50–100 kg vs >100 kg, or BMI <30 vs ≥30 or <25, 25-30 and 30-35), and underweight patients were included in the normal weight category. Of note, in the RIETE study underweight patients with VTE(or weighing <50 kg) had a significantly higher rate of bleeding complications. This is in contradiction with our findings. A potential explanation could be the difference in selection of patients, or analysis and categorisation study.

For underweight patients studies on other clinical outcomes are scarce. For prognostic characteristics and RVD until now no data are published. Underweight patients had an increased mortality compared with those with normal weight,<sup>19</sup> but an equal number of fatal PE. Difficulty for this category is that it can reflect two different populations, those who have been always underweight, and those that due to underlying condition sustained a significant weight loss, such as in cancer, immobility or renal insufficiency making them susceptible to adverse events. As these people have less adipose tissue, probably drug pharmacokinetics could be different.

Our findings of a trend towards worse prognostics in obese patients underlines the importance of more patient centred care<sup>38</sup> in particular with respect to choosing the appropriate anticoagulant therapy for each individual patient. In this way, we can confirm the call for increased awareness on dedicated prophylactic and therapeutic anticoagulant regimens in obesity.<sup>7</sup> Reassuringly, a recent well-sized cohort study suggested similar efficacy and safety between direct oral anti-Xa inhibitors and warfarin in morbidly obese patients, although these retrospective findings warrant confirmation in prospective studies.<sup>39</sup>

Future directions for study should explore the interaction of obesity and other risk factors for VTE, both for development, presentation, therapeutics and outcomes.<sup>40</sup> Special attention should focus on clinical severity, RVD and risk stratification. As obesity can be regarded a pro-inflammatory condition, more fundamental research should be directed toward molecular, pathogenic and sex-specific mechanisms responsible for VTE onset, development, and recurrence.<sup>41</sup>

In conclusion, we found that several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism are not evenly distributed among the BMI categories. This is reflected in a trend toward worse outcomes in the over- and underweight patients compared to normal weights. This could be an incentive toward dedicated patient tailored evaluation and treatment.

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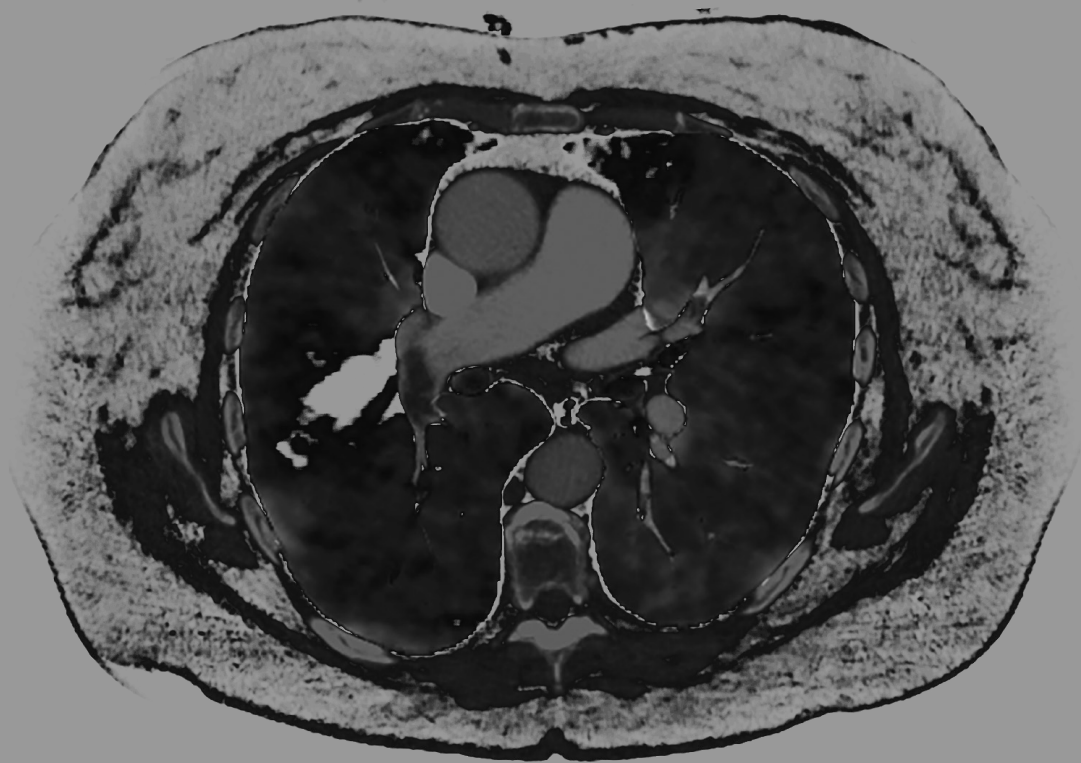
## References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018; **137**(12): e67-e492.
2. Wattanakit K, Lutsey PL, Bell EJ, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thrombosis and haemostasis* 2012; **108**(3): 508-15.
3. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis: A PRISMA-compliant systemic review and meta-analysis. *Medicine* 2016; **95**(32): e4495.
4. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. *The American journal of medicine* 2005; **118**(9): 978-80.
5. Gregson J, Kaptoge S, Bolton T, et al. Cardiovascular Risk Factors Associated With Venous Thromboembolism. *JAMA cardiology* 2019; **4**(2): 163-73.
6. Braekkan SK, Siegerink B, Lijfering WM, Hansen JB, Cannegieter SC, Rosendaal FR. Role of obesity in the etiology of deep vein thrombosis and pulmonary embolism: current epidemiological insights. *Seminars in thrombosis and hemostasis* 2013; **39**(5): 533-40.
7. Rocca B, Fox KAA, Ajjan RA, et al. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. *European heart journal* 2018; **39**(19): 1672-86f.
8. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH* 2016; **14**(6): 1308-13.
9. Konstantinides S, Torbicki A. Management of venous thrombo-embolism: an update. *European heart journal* 2014; **35**(41): 2855-63.
10. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *The Lancet* 2016; **388**(10046): 776-86.
11. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *The New England journal of medicine* 2013; **369**(15): 1406-15.
12. Beenen LFM, Bossuyt PMM, Stoker J, Middeldorp S. Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism. *The European respiratory journal* 2018; **52**(1): 1702611.
13. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. *Heart (British Cardiac Society)* 2015; **101**(20): 1631-8.
14. Qin W, Liu F, Wan C. A U-shaped association of body mass index and all-cause mortality in heart failure patients: A dose-response meta-analysis of prospective cohort studies. *Cardiovascular therapeutics* 2017; **35**(2).

15. Taylor JA, Christenson RH, Rao K, Jorge M, Gottlieb SS. B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide are depressed in obesity despite higher left ventricular end diastolic pressures. *American heart journal* 2006; **152**(6): 1071-6.
16. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arteriosclerosis, thrombosis, and vascular biology* 2006; **26**(5): 968-76.
17. Chahal H, McClelland RL, Tandri H, et al. Obesity and right ventricular structure and function: the MESA-Right Ventricle Study. *Chest* 2012; **141**(2): 388-95.
18. Goldhaber SZ, Savage DD, Garrison RJ, et al. Risk factors for pulmonary embolism. The Framingham Study. *The American journal of medicine* 1983; **74**(6): 1023-8.
19. Barba R, Zapatero A, Losa JE, et al. Body mass index and mortality in patients with acute venous thromboembolism: findings from the RIETE registry. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(4): 595-600.
20. Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation* 2008; **117**(13): 1711-6.
21. Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: the mounting evidence of risk and the mortality paradox. *Thrombosis research* 2011; **128**(6): 518-23.
22. Galyfos G, Geropapas GI, Kerasidis S, Sianou A, Sigala F, Filis K. The effect of body mass index on major outcomes after vascular surgery. *Journal of vascular surgery* 2017; **65**(4): 1193-207.
23. Elagizi A, Kachur S, Lavie CJ, et al. An Overview and Update on Obesity and the Obesity Paradox in Cardiovascular Diseases. *Progress in cardiovascular diseases* 2018; **61**(2): 142-50.
24. Saab J, Salvatore SP. Evaluating the cause of death in obese individuals: a ten-year medical autopsy study. *Journal of obesity* 2015; **2015**: 695374.
25. Rosenfeld HE, Tsokos M, Byard RW. The association between body mass index and pulmonary thromboembolism in an autopsy population. *Journal of forensic sciences* 2012; **57**(5): 1336-8.
26. Delluc A, Le Moigne E, Tromeur C, et al. Site of venous thromboembolism and prothrombotic mutations according to body mass index. Results from the EDITH study. *British journal of haematology* 2011; **154**(4): 486-91.
27. Egermayer P. Obesity, oral contraceptives, and fatal pulmonary embolism. *The New Zealand medical journal* 2001; **114**(1129): 170-1.
28. Sundell IB, Nilsson TK, Ranby M, Hallmans G, Hellsten G. Fibrinolytic variables are related to age, sex, blood pressure, and body build measurements: a cross-sectional study in Norsjo, Sweden. *Journal of clinical epidemiology* 1989; **42**(8): 719-23.
29. Davidson BL, Buller HR, Decousus H, et al. Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Matisse trials. *Journal of thrombosis and haemostasis : JTH* 2007; **5**(6): 1191-4.

30. Linnemann B, Zgouras D, Schindewolf M, Schwonberg J, Jarosch-Preusche M, Lindhoff-Last E. Impact of sex and traditional cardiovascular risk factors on the risk of recurrent venous thromboembolism: results from the German MAISTHRO Registry. *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* 2008; **19**(2): 159-65.
31. Di Nisio M, Vedovati MC, Riera-Mestre A, et al. Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. *Thrombosis and haemostasis* 2016; **116**(4): 739-46.
32. Vuckovic BA, Cannegieter SC, van Hylckama Vlieg A, Rosendaal FR, Lijfering WM. Recurrent venous thrombosis related to overweight and obesity: results from the MEGA follow-up study. *Journal of thrombosis and haemostasis : JTH* 2017; **15**(7): 1430-5.
33. Eichinger S, Hron G, Bialonczyk C, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. *Archives of internal medicine* 2008; **168**(15): 1678-83.
34. Prandoni P, Barbar S, Milan M, Vedovetto V, Pesavento R. The risk of recurrent thromboembolic disorders in patients with unprovoked venous thromboembolism: new scenarios and opportunities. *European journal of internal medicine* 2014; **25**(1): 25-30.
35. Joshy G, Korda RJ, Attia J, Liu B, Bauman AE, Banks E. Body mass index and incident hospitalisation for cardiovascular disease in 158 546 participants from the 45 and Up Study. *International journal of obesity (2005)* 2014; **38**(6): 848-56.
36. Jimenez S, Ruiz-Artacho P, Merlo M, et al. Risk profile, management, and outcomes of patients with venous thromboembolism attended in Spanish Emergency Departments: The ESPHERIA registry. *Medicine* 2017; **96**(48): e8796.
37. Barba R, Marco J, Martin-Alvarez H, et al. The influence of extreme body weight on clinical outcome of patients with venous thromboembolism: findings from a prospective registry (RIETE). *Journal of thrombosis and haemostasis : JTH* 2005; **3**(5): 856-62.
38. Cushman M, Creager MA. Improving Awareness and Outcomes Related to Venous Thromboembolism. *Jama* 2015; **314**(18): 1913-4.
39. Kushnir M, Choi Y, Eisenberg R, et al. Efficacy and safety of direct oral factor Xa inhibitors compared with warfarin in patients with morbid obesity: a single-centre, retrospective analysis of chart data. *The Lancet Haematology* 2019; **6**(7): e359-e65.
40. Yang G, De Staercke C, Hooper WC. The effects of obesity on venous thromboembolism: A review. *Open journal of preventive medicine* 2012; **2**(4): 499-509.
41. Drife J. Deep venous thrombosis and pulmonary embolism in obese women. *Best practice & research Clinical obstetrics & gynaecology* 2015; **29**(3): 365-76.





# Chapter 6

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Clinical impact of concomitant  
cardiopulmonary disease on CT  
pulmonary angiography in acute  
pulmonary embolism

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*In preparation*



## **Abstract**

### **Background**

The prognosis of acute pulmonary embolism varies depending on amongst other clot burden and concomitant conditions, usually assessed with prognostic scores of clinical variables. The aim of our study was to determine the impact of concomitant cardiopulmonary disease identified on the diagnostic CTPA on clinical outcome of acute pulmonary embolism.

### **Methods**

We studied a post hoc sample of patients with pulmonary embolism included in the Hokusai-VTE randomized clinical trial that compared two anticoagulant regimens (n=1950). We assessed occurrence and severity of cardiopulmonary diseases on CT (pleural fluid, pericardial fluid, consolidations, coronary and aortic calcifications) and clinical and radiological prognostic characteristics for right ventricular dysfunction. Primary outcome was one-year mortality; secondary outcomes were recurrent VTE, hospitalization, bleeding and overall adverse events.

### **Results**

Concomitant disease was present on CTPA in 1298 of 1950 patients (66.6%). One-year mortality was increased with presence of mild, moderate and severe disease on CTPA (OR 4.9, 10.4 and 32.2 (95%CI 1.4-16.8, 3.0-36.2 and 10.0-116)), also after adjustment for sPESI and age OR 3.4, 4.8 and 15.3 (0.99-11.9, 1.3-17.6 and 4.3-54.8)), compared to absence of concomitant disease. The exposure dependant association between disease severity and mortality was apparent in all evaluated CTPA findings.

### **Conclusions**

In patients with acute pulmonary embolism, concomitant disease observed on the baseline CTPA impacts mortality and may be of additional value in risk stratification and prognosis.

## Introduction

Computed tomography pulmonary angiography (CTPA) is the current state of the art diagnostic modality in the evaluation of patient with suspected pulmonary embolism (PE). The major advantage above other techniques is the ability to provide an alternative explanation for the patients' complaints, which can be encountered even more frequently than PE itself.<sup>1</sup> In clinical practice this can be very helpful, as signs and symptoms of PE are not specific and several other cardiopulmonary diseases can present with similar complaints. Also, the diagnosis of other cardiopulmonary diseases may have an impact on clinical course and outcome.

PE is a serious disease with overall mortality after 1 month of 9.1%.<sup>2</sup> The prognosis is determined by the impact it carries on the patients' cardiopulmonary status, more specifically how the clot burden affects right ventricular function, and by underlying diseases such as cancer.

Currently, risk assessment for pulmonary embolism is performed by first considering hemodynamic stability, followed by determination of several risk factors present in the simplified pulmonary embolism severity index (sPESI), and signs of right ventricular dysfunction as determined by NT-proBNP, echocardiography or on CTPA.<sup>3</sup> The additional burden of concomitant cardiopulmonary disease could negatively impact the chance for good recovery. Only a few, mostly retrospective single-centre studies have addressed this question, usually focusing on one aspect such as concomitant pleural effusion.<sup>4,6</sup> We investigated a variety of cardiopulmonary disease features on CTPA in a large prospective trial of patients with confirmed pulmonary embolism. The aim of our study was to determine the impact of concomitant cardiopulmonary disease as identified on the diagnostic CTPA on clinical outcome.

## Materials and Methods

### *Patients and study design*

The present study is a post hoc analysis of all patients that underwent CTPA for pulmonary embolism in the Hokusai-VTE study, a large multi-centre international randomized clinical trial in which two anticoagulant regimens were compared in patients with venous thromboembolism (VTE); ClinicalTrials.gov identifier: NCT00986154).<sup>7</sup> In this trial, eligible patients were aged 18 years or older and had acute symptomatic deep vein thrombosis (DVT) and/or PE. Patients were excluded in case of contraindication to heparin or warfarin, severely impaired renal function or pregnancy. The institutional review board at each participating centre approved the general study protocol, and all patients provided written informed consent. Follow-up was 12 months, covering the in-hospital period as well as regular outpatient clinic controls, and patients on and off anticoagulant treatment. Adverse events were

noted on separate forms, as well as whether these were PE-related. An independent committee adjudicated all predefined outcomes. For the current analysis all patients with PE, either with or without DVT, were included. Excluded were patients not evaluated by CTPA, or when images were not available in DICOM format or inaccessible for reading in the image viewer.

### ***Data collection***

All clinical and radiological data were anonymized and centrally registered with double data entry by an independent trial data management agency before the trial data lock. Clinical data were retrieved from the original CRFs. This included a broad range of risk factors at baseline as well as present and past diseases. In all patients NT-proBNP levels were measured at baseline. CTPA data were acquired from the participating centres, using local settings and protocols, with a wide variety of CT-scanners, from basic until high-end CT. Anonymized patient images from the central database were evaluated by a radiologist (LB) with 12 years of experience in cardiovascular imaging in cooperation with a dedicated research assistant, both blinded for patient details and clinical information. Data were registered on a CRF designed for the present analysis. For image reading a commercially available image viewer was used (eFilm Workstation for Windows Version 3.4.0, Build 10, Merge Technologies Inc., Milwaukee, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting (MPR). Standard CTPA, mediastinal and lung window settings were used, with individual adaptation if deemed necessary.

### ***Definitions and outcomes***

We defined concomitant disease as all pleuro-parenchymal and cardiovascular pathologies visible on the baseline CTPA, in line with the Fleischner glossary terms:<sup>8</sup> pleural fluid, pericardial fluid, lung parenchymal opacities, interstitial lung disease (ILD), and calcifications in the aorta and coronary arteries. All concomitant disease was assessed semi-quantitatively using the 4-ordinal scale “none – mild – moderate – severe in line with common clinical practice. Pericardial fluid was regarded pathological if > 5 mm. When all pathologies were regarded together, the highest graded pathology determined the overall severity grade.

Additionally, clinical (NT-proBNP, sPESI) and radiological prognostic characteristics for right ventricular dysfunction and adverse events were registered.<sup>9</sup> For NT-proBNP a value of  $\geq 600$  pg/ml at baseline was considered abnormal. For sPESI calculation the arterial oxyhaemoglobin saturation <90% was not registered; this item was considered positive if patient required oxygen administration. Radiological parameters assessed for right ventricular dysfunction (RVD) were: right-to-left ventricular (RV/LV) ratio >1.0 (transverse diameter of right and left ventricle (axial view), pulmonary trunk (PT) > 29 mm; bowing of the interventricular

septum (D-shaped/ straightened or curved toward the left ventricle) and reflux of contrast medium in the intrahepatic veins. All continuous variables were noted in millimetres were applicable.

The primary outcome for the present analysis was mortality after one year. Secondary outcomes were recurrent VTE, hospitalization, bleeding and overall adverse events during one year follow up.

### ***Statistical analysis***

Descriptive statistics are displayed as mean  $\pm$  standard deviation (SD) for normally distributed variables and median  $\pm$  interquartile ranges (IQR, 25<sup>th</sup> to 75<sup>th</sup> percentile) for not normally distributed variables. For comparison on binary outcomes the Chi-square test for dichotomous variables were used. Between the groups categorical variables were compared using the Chi-square test for trend; for continuous data by Students T test or Mann-Whitney U test if non-normally distributed. A p-value  $< 0.05$  was considered statistically significant. We used logistic regression models to estimate odds ratios (OR) with 95% confidence intervals (CI) to investigate the association between the outcome variables. In addition, we adjusted odds ratios for sPESI. All statistical analyses were performed in SPSS version 23 (SPSS Inc, Chicago Ill).

### **Results**

Baseline characteristics are displayed in Table 1. The study group consisted of 1950 patients with pulmonary embolism. Concomitant disease on CTPA was present in 1298 patients (66.6%), and was mild in 810 (41.5%), moderate in 327 (16.8%) and severe in 161 (8.3%) (Table 2). The odds ratios for mortality of sPESI $\geq 1$  was 4.3 (CI 2.1-8.5).

There was a severity-dependent increase both in occurrence as well as in odds ratios of mortality. When no concomitant disease was present, the 1-year mortality was 0.5%, which increased to 2.2% in mild, 4.6% in moderate, and to 13.7% in severe concomitant disease. With no concomitant disease as reference, the odds ratios and adjusted odds ratios for mortality in mild disease were 4.9 (CI 1.4-16.7) and 3.4 (1.0-11.9), and for moderate disease 10.4 (3.0-36.2) and 4.8 (1.3-17.6), respectively (Table 3). With absence of concomitant disease as reference (OR 1), the odds ratio for mortality with presence of any severe concomitant disease on CTPA was 32.24 [95%CI 10.0-116], and adjusted for sPESI 15.3 (4.3-54.8).

The stepwise association between concomitant disease severity and mortality was apparent in all evaluated CTPA findings. After adjustment for sPESI, the odds ratio for mortality in the most severe pathologies were 27.9 (CI 7.6-102.8) for ILD, 10.99 (CI 2.7-45.6) for pleural fluid and 8.4 (CI 1.6-44.5) for pulmonary consolidations.

**Table 1: Baseline characteristics.**

	All patients		Concomitant disease on CTPA	
	n	%	n	%
Included	1950	100	1298	66.6
<b>Clinical</b>				
Age (mean, SD)	57.0	16.6	60.0	16.4
Weight (mean, SD)	84.5	20.1	82.8	18.9
SBP mmHg (mean, SD)	128	17	129	17
DBP mmHg (mean, SD)	76	11	76	11
Heart Rate (mean, SD)	80	14	80	14
Age <50Y	638	32.7	355	26.0
Age > 65Y	154	7.9	143	10.5
Weight < 60 kg	190	9.7	144	10.5
Current alcohol use	754	38.7	528	38.7
Smoking	854	43.8	635	46.5
NT-proBNP > 600	515	27.4	378	28.8
sPESI* High Risk $\geq$ 1	1051	53.9	807	59.1
Concurrent DVT	456	23.4	275	20.1
<b>Risk Factors</b>				
Recent surgery, trauma, or immobilisation	372	19.1	273	20.0
Sitting > 4 hours	185	9.5	114	8.3
Oestrogen drugs use	196	10.1	100	7.3
Previous DVT/PE	415	21.3	282	20.6
Thrombophilia	94	4.8	62	4.5
<b>Concomitant Disease History</b>				
Hypertension	810	41.5	635	46.5
Diabetes	199	10.2	153	11.2
Cardiovascular Disease	314	16.1	256	18.7
Chronic Heart Failure	35	1.8	28	2.0
Cerebrovascular Disease	73	3.7	60	4.4
Stroke	35	1.8	29	2.1
Renal Disease	129	6.6	93	6.8
Hepatic Disease	212	10.9	155	11.3
Pulmonary Disease	401	20.6	322	23.6
COPD	103	5.3	96	7.0
Pulmonary hypertension	43	2.2	39	2.9
Cancer	228	11.7	190	13.9

Data are number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DVT – Deep Vein Thrombosis; PE – Pulmonary Embolism; sPESI – simplified pulmonary embolism severity index; US – Ultrasound; \* - 523/1950 included and 496/1531 excluded patients (mm: mean, SD); \*\* sPESI- item on O2 considered positive if patient needed oxygen administration.

**Table 2: Association between concomitant disease severity on CTPA and clinical outcomes.**

	N (%)	OR	OR Adjusted for sPESI
<b>Mortality</b>			
<i>Concomitant disease</i>			
No	3 (0.5)	1 (reference)	1 (reference)
Mild	18 (2.2)	4.9 (1.4-16.8)	3.4 (0.99-11.9)
Moderate	15 (4.6)	10.4 (3.0-36.2)	4.8 (1.3-17.6)
Severe	22 (13.7)	32.2 (10.0-115.9)	15.3 (4.3-54.8)
Total	58 (3.0)		
<b>Recurrent VTE</b>			
<i>Concomitant disease</i>			
No	12 (1.8)	1 (reference)	1 (reference)
Mild	21 (2.6)	1.4 (0.69-2.9)	1.3 (0.62-2.7)
Moderate	14 (4.3)	2.4 (1.1-5.2)	2.0 (0.82-4.7)
Severe	3 (1.9)	1.0 (0.28-3.6)	0.8 (0.21-3.1)
Total	50 (2.6)		
<b>All Bleeding</b>			
<i>Concomitant disease</i>			
No	6 (0.9)	1 (reference)	1 (reference)
Mild	12 (1.5)	1.6 (0.60-4.4)	1.1 (0.39-3.1)
Moderate	8 (2.4)	2.7 (0.93-7.9)	1.2 (0.37-3.9)
Severe	4 (2.5)	2.7 (0.77-9.8)	1.3 (0.32-5.1)
Total	30 (1.5)		
<b>Hospitalisation</b>			
<i>Concomitant disease</i>			
No	15 (2.3)	1 (reference)	1 (reference)
Mild	35 (4.3)	1.9 (1.04-3.5)	1.4 (0.76-2.7)
Moderate	26 (8.0)	3.4 (1.9-7.0)	2.0 (0.97-4.0)
Severe	14 (8.7)	4.0 (1.9-8.6)	2.2 (0.98-5.0)
Total	90 (4.6)		
<b>All Adverse Events</b>			
<i>Concomitant disease</i>			
No	20 (3.1)	1 (reference)	1 (reference)
Mild	50 (6.2)	2.1 (1.2-3.5)	1.6 (0.95-2.8)
Moderate	34 (10.4)	3.7 (2.8-6.5)	2.2 (1.2-4.0)
Severe	28 (17.4)	6.7 (3.6-12.2)	3.9 (2.0-7.4)
Total	132 (6.8)		

Odds ratios for concomitant disease severity and different clinical outcomes, with no disease as reference. Proportion was calculated per disease severity with follow-up up to 12 months. CI – confidence intervals, OR –Odds ratio; sPESI – simplified pulmonary embolism severity index, VTE – venous thromboembolism.

**Table 3: Association between concomitant cardiopulmonary diseases on CTPA and mortality.**

		N (%)	OR	OR Adjusted for sPESI
<b>Concomitant disease</b>				
No	652	3 (0.5)	1 (reference)	1 (reference)
Mild	810	18 (2.2)	4.9 (1.4-16.8)	3.4 (0.99-11.9)
Moderate	327	15 (4.6)	10.4 (3.0-36.2)	4.8 (1.3-17.6)
Severe	161	22 (13.7)	32.2 (10.0-115.9)	15.3 (4.3-54.8)
Total	1950	58 (3.0)		
<b>Coronary calcifications</b>				
No	1136	24 (1.8)	1 (reference)	1 (reference)
Mild	426	16 (3.8)	2.1 (1.1-4.1)	0.98 (0.49-2.0)
Moderate	161	15 (9.3)	5.6 (2.9-11.0)	2.0 (0.95-4.4)
Severe	27	3 (11.1)	6.8 (1.9-24.2)	2.9 (0.75-11.0)
<b>Aorta calcifications</b>				
No	1177	17 (1.4)	1 (reference)	1 (reference)
Mild	564	22 (3.9)	2.8 (1.5-5.3)	1.4 (0.65-2.8)
Moderate	192	15 (7.8)	5.8 (2.8-11.8)	1.9 (0.81-4.7)
Severe	17	4 (23.5)	21.0 (6.2-71.0)	5.5 (1.32-22.8)
<b>Pericardial fluid</b>				
No			1 (reference)	1 (reference)
Moderate/severe	52	6 (8.3)	3.2 (1.3-7.7)	2.3 (0.9-5.8)
<b>Pleural Fluid</b>				
No	1578	38 (2.4)	1 (reference)	1 (reference)
Mild	300	10 (3.3)	1.4 (0.69-2.8)	1.2 (0.6-2.6)
Moderate	59	7 (11.9)	5.5 (2.3-12.8)	4.3 (1.7-10.5)
Severe	13	3 (23.1)	12.2 (3.2-45.9)	11.0 (2.7-45.6)
<b>Consolidation</b>				
No	1121	25 (2.2)	1 (reference)	1 (reference)
Mild	604	25 (4.1)	1.9 (1.1-3.3)	1.8 (0.99-3.2)
Moderate	211	6 (2.8)	1.3 (0.52-3.2)	1.5 (0.58-3.8)
Severe	14	2 (14.3)	7.3 (1.6-34.4)	8.4 (1.6-44.5)
<b>Emphysema</b>				
No	1513	29 (1.9)	1 (reference)	1 (reference)
Mild	291	14 (4.8)	2.6 (1.4-4.9)	1.7 (0.9-3.3)
Moderate	109	8 (7.3)	4.1 (1.8-9.1)	2.4 (1.02-5.6)
Severe	37	7 (18.9)	11.9 (4.8-29.4)	4.5 (1.6-12.6)
<b>ILD</b>				
No	1905	50 (2.6)	1 (reference)	1 (reference)
Mild	21	1 (4.8)	1.9 (0.24-14.1)	1.2 (0.15-9.5)
Moderate	13	1 (7.7)	3.1 (0.4-24.2)	2.9 (0.35-24.1)
Severe	11	6 (54.5)	44.5 (13.2-150.1)	28.0 (7.6-102.8)

Odds ratios for different concomitant diseases and 1 year mortality, with no disease as reference. Proportion was calculated per disease severity with follow-up up to 12 months. CI – confidence intervals, OR –Odds ratio; sPESI – simplified pulmonary embolism severity index, VTE – venous thromboembolism \* Adjusted for sPESI.

For the secondary outcomes hospitalisation and overall adverse events association was apparent ( $p < 0.001$ ) (Table 4), but recurrent VTE ( $p = 0.165$ ) and bleeding ( $p = 0.244$ ) were not associated with presence of concomitant disease.

## Discussion

In this study we showed that in patients with acute pulmonary embolism concomitant disease present on the baseline CTPA is associated with poor clinical outcome. Both pulmonary and cardiovascular manifestations of disease were associated with mortality in a severity-dependent manner, also when adjusted for sPESI.

A strength of our study is the prospective and rigorous collection of all included data as part of a large international randomized clinical trial. Both imaging data and clinical outcomes were assessed before the data lock and the assessors were blinded for allocation of treatment and for clinical outcome during follow-up. We evaluated a broad range of parameters and biomarkers in order to provide a complete radiological assessment rather than limiting us to a single factor.

Our study has some limitations. We did not further adjust for potential confounders like known comorbidities. Yet, we think that with age and sPESI parameters the most important confounders are covered. Also, we are aware that patients included in a randomized controlled trial do not necessarily reflect all those presenting in daily practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients and patients with a limited life expectancy.

Acute PE can interfere with both circulation and gas exchange. It therefore seems biologically plausible that concomitant pathology affects primary cardiopulmonary reserve, and consequently could lead to worse clinical outcomes of acute PE<sup>3</sup>.

Although sPESI has been validated as risk assessment tool, its ingredients represent to a great deal static information on known diseases. The imaging findings assessed in this study can be regarded as a more direct reflection of the actual health status of the individual patient. As this is supplementary information not present in other scores, additional value can be derived which could possibly impact on prognostics of the individual patient.

This is reflected in our findings of a general higher odds ratio for mortality with increasing severity of concomitant disease, even after correcting for sPESI. Interestingly, the odds ratios were even a little bit higher for the overall radiological pathologies than for overall sPESI, although confidence intervals did overlap. It seems logical that also with higher degrees of disease severity, the number of adverse events and hospitalisation increase.

In our study manifestations of concomitant pathology apparently had no effect on the risk of major bleeding or recurrent VTE.



A variety of cardiopulmonary pathologies had impact on mortality, each with a different pathophysiological background, which will be discussed shortly.

Pleural fluid is the pulmonary manifestation most widely studied in conjunction with pulmonary embolism, with widely varying estimates of prevalence between 2 and 50%.<sup>4,10-16</sup> Conversely, pulmonary embolism should be considered as a possible cause of any pleural effusion, as it is the most commonly overlooked disorder in patients with pleural effusion.<sup>17</sup> In our study mortality was about 11-fold higher in patients with large effusions.

Consolidations and atelectasis are frequent diagnoses in patients presenting to the emergency department with chest pain or dyspnoea.<sup>1</sup> However, it does not exclude presence of PE. In fact, in our study severe consolidations were associated with increased mortality, whereas for less severe consolidations and atelectasis no impact on mortality was found.

COPD and PE can both present with dyspnoea. Mortality and length of hospital admission seem to be increased in patients with unexplained acute exacerbation of COPD and PE.<sup>18,19</sup> Also, in patients with ILD and pulmonary hypertension a RV/LV ratio  $\geq 1$  is predictive for mortality or transplantation.<sup>20</sup> This is in line with our observations of increasing odds ratios for mortality in the more severe cases of emphysema and ILD.

Pericardial fluid had a moderate effect on mortality in our study, which is in line with other studies in different settings.<sup>21,22</sup> Occurrence of pericardial fluid during PE ranges between 3-9%. Presence of pericardial fluid may lead to hemodynamic deterioration during both acute right ventricular pressure load and subsequent volume loading, and has been proposed as contributing factor for risk estimation in prognostic scores.<sup>23,24</sup>

Coronary and aortic calcifications may not have implications for acute clinical management but may be important for incident cardiovascular risk prediction<sup>25</sup>. Prevalence in CTPA is rather high with ranges between 44 - 54%.<sup>4,26</sup> Of note, these findings are often not reported.<sup>26</sup> We observed higher mortality with increasing severity of coronary and/or aorta calcifications, which underlines the need for adequate reporting.

How do our findings fit into the current assessment of patients with acute PE?

Many parameters have been suggested as potentially valuable for prognostication, yet are not integrated in clinical practice as they are too difficult for regular handling.<sup>27</sup> Concomitant abnormalities on CTPA are not yet incorporated, and can probably be regarded as risk modifiers for both the intermediate and low risk categories of the ESC guidelines on PE, with impact on either the decision for home treatment or on the other spectrum close monitoring. In this perspective, standardized reporting of radiological, clinical and biochemical parameters into a format which could be integrated into an artificial intelligence algorithm could be of

additional value. Future directions for study should explore imbedding these findings in artificial intelligence algorithms.

In conclusion, we found that in patients with acute pulmonary embolism concomitant disease observed on CTPA is associated with mortality and may be of additional value in risk stratification and prognosis.

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Dr Beenen declared no conflict of interest related to this work.

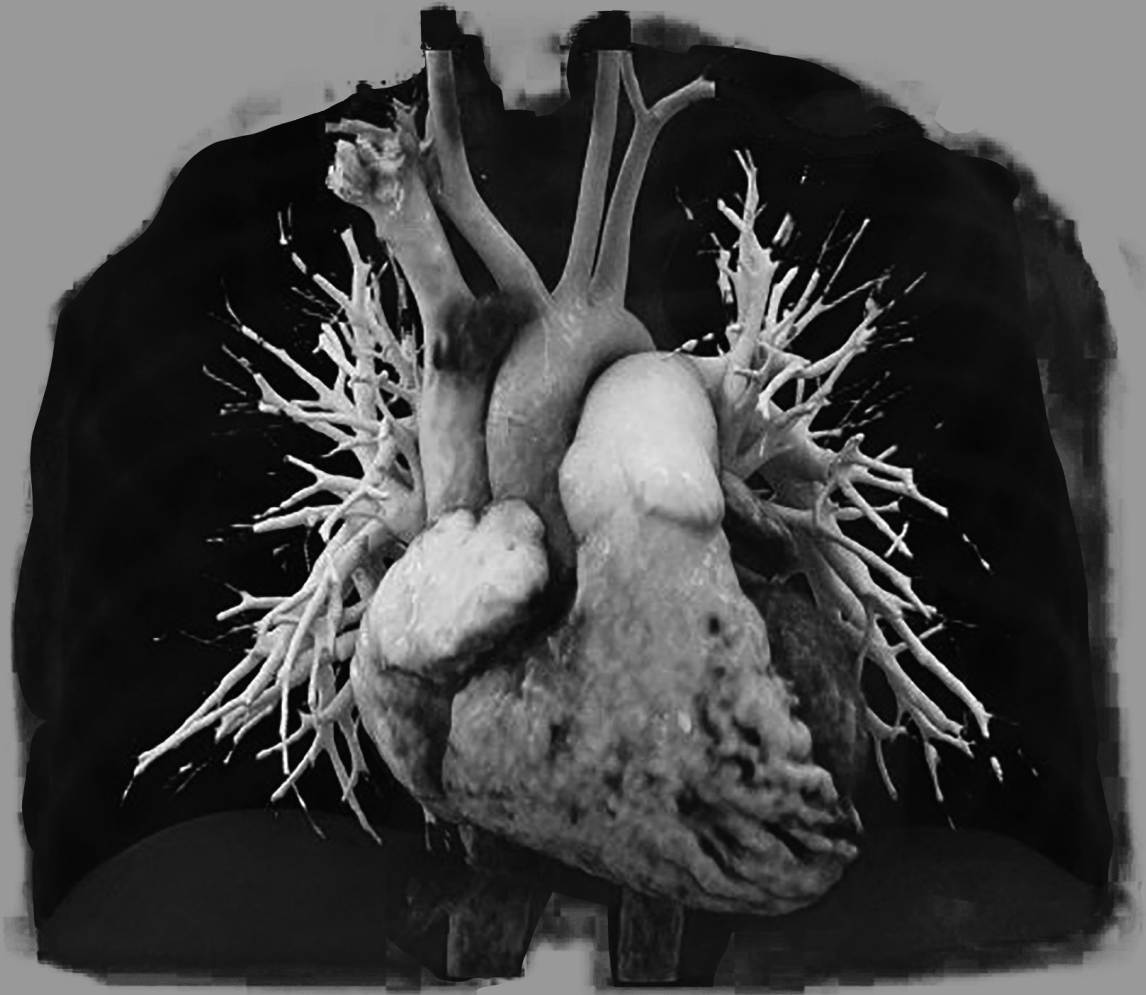
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## References

1. van Es J, Douma RA, Schreuder SM, et al. Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism. *Chest* 2013; **144**(6): 1893-9.
2. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020; **141**(9): e139-e596.
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *European heart journal* 2020; **41**(4): 543-603.
4. Foley PW, Hamaad A, El-Gendi H, Leyva F. Incidental cardiac findings on computed tomography imaging of the thorax. *BMC research notes* 2010; **3**: 326.
5. Groth M, Henes FO, Mayer U, Regier M, Adam G, Begemann PG. Age-related incidence of pulmonary embolism and additional pathologic findings detected by computed tomography pulmonary angiography. *European journal of radiology* 2012; **81**(8): 1913-6.
6. Kiris T, Yazici S, Koc A, et al. Prognostic impact of pleural effusion in acute pulmonary embolism. *Acta radiologica (Stockholm, Sweden : 1987)* 2017; **58**(7): 816-24.
7. Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *The New England journal of medicine* 2013; **369**(15): 1406-15.
8. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**(3): 697-722.
9. Beenen LFM, Bossuyt PMM, Stoker J, Middeldorp S. Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism. *The European respiratory journal* 2018; **52**(1): 1702611.
10. Bynum LJ, Wilson JE, 3rd. Radiographic features of pleural effusions in pulmonary embolism. *The American review of respiratory disease* 1978; **117**(5): 829-34.
11. Ghaye B, Ghuysen A, Willems V, et al. Severe pulmonary embolism: pulmonary artery clot load scores and cardiovascular parameters as predictors of mortality. *Radiology* 2006; **239**(3): 884-91.
12. Johnson PT, Wechsler RJ, Salazar AM, Fisher AM, Nazarian LN, Steiner RM. Spiral CT of acute pulmonary thromboembolism: evaluation of pleuroparenchymal abnormalities. *Journal of computer assisted tomography* 1999; **23**(3): 369-73.
13. Karabulut N, Kiroglu Y. Relationship of parenchymal and pleural abnormalities with acute pulmonary embolism: CT findings in patients with and without embolism. *Diagnostic and interventional radiology (Ankara, Turkey)* 2008; **14**(4): 189-96.
14. Pfeil A, Schmidt P, Hermann R, Bottcher J, Wolf G, Hansch A. Parenchymal and pleural findings in pulmonary embolism visualized by multi-channel detector computed tomography. *Acta radiologica (Stockholm, Sweden : 1987)* 2010; **51**(7): 775-81.
15. Yap E, Anderson G, Donald J, Wong CA, Lee YC, Sivakumaran P. Pleural effusion in patients with pulmonary embolism. *Respirology (Carlton, Vic)* 2008; **13**(6): 832-6.

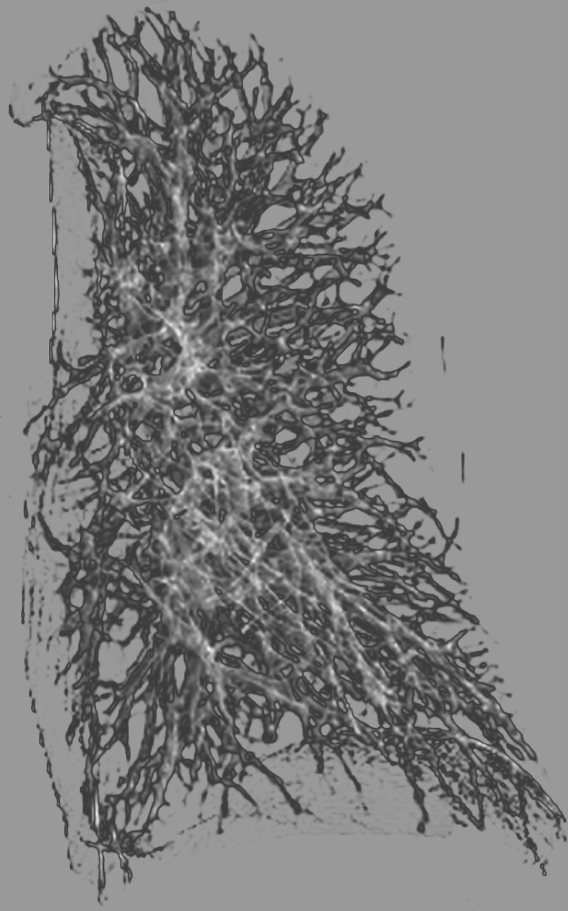
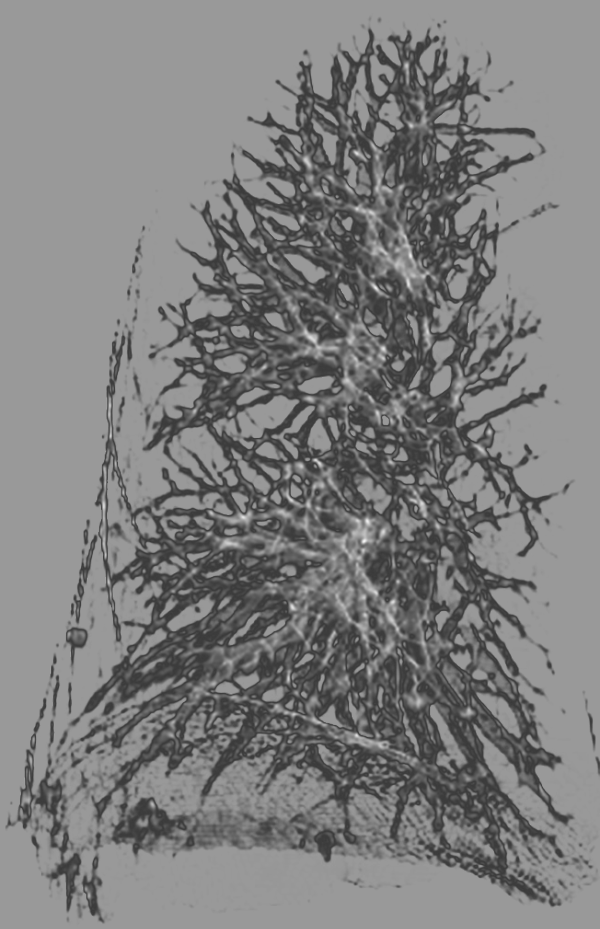
16. Zhou X, Zhang Z, Zhai Z, et al. Pleural effusions as a predictive parameter for poor prognosis for patients with acute pulmonary thromboembolism. *Journal of thrombosis and thrombolysis* 2016; **42**(3): 432-40.
17. Findik S. Pleural effusion in pulmonary embolism. *Current opinion in pulmonary medicine* 2012; **18**(4): 347-54.
18. Aleva FE, Voets L, Simons SO, de Mast Q, van der Ven A, Heijdra YF. Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-analysis. *Chest* 2017; **151**(3): 544-54.
19. Couturaud F, Bertoletti L, Pastre J, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. *Jama* 2021; **325**(1): 59-68.
20. Bax S, Jacob J, Ahmed R, et al. Right Ventricular to Left Ventricular Ratio at CT Pulmonary Angiogram Predicts Mortality in Interstitial Lung Disease. *Chest* 2020; **157**(1): 89-98.
21. Liu M, Guo X, Zhu L, et al. Computed Tomographic Pulmonary Angiographic Findings Can Predict Short-Term Mortality of Saddle Pulmonary Embolism: A Retrospective Multicenter Study. *Journal of computer assisted tomography* 2016; **40**(3): 327-34.
22. Olgun Yildizeli S, Kasapoglu US, Arikan H, et al. Pleural effusion as an indicator of short term mortality in acute pulmonary embolism. *Tuberkuloz ve toraks* 2018; **66**(3): 185-96.
23. Kumamaru KK, Saboo SS, Aghayev A, et al. CT pulmonary angiography-based scoring system to predict the prognosis of acute pulmonary embolism. *Journal of cardiovascular computed tomography* 2016; **10**(6): 473-9.
24. Vasil'tseva OY, Vorozhtsova IN, Lavrov AG, Karpov RS. [Estimation of poor prognostic factors in patients with pulmonary artery thromboembolism]. *Terapevticheskii arkhiv* 2016; **88**(12): 28-32.
25. Hoffmann U, Massaro JM, D'Agostino RB, Sr., Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular Event Prediction and Risk Reclassification by Coronary, Aortic, and Valvular Calcification in the Framingham Heart Study. *Journal of the American Heart Association* 2016; **5**(2).
26. Johnson C, Khalilzadeh O, Novelline RA, Choy G. Coronary artery calcification is often not reported in pulmonary CT angiography in patients with suspected pulmonary embolism: an opportunity to improve diagnosis of acute coronary syndrome. *AJR American journal of roentgenology* 2014; **202**(4): 725-9.
27. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Jama* 1999; **282**(15): 1458-65.



# **PART III**

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## **Venous thromboembolism and COVID-19**



# Chapter 7

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## Incidence of venous thromboembolism in hospitalized patients with COVID-19

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## **Abstract**

### **Background**

Coronavirus disease 2019 (COVID-19) can lead to systemic coagulation activation and thrombotic complications. Objective of this study was to investigate the incidence of objectively confirmed venous thromboembolism (VTE) in hospitalized patients with COVID-19.

### **Methods**

Single-centre cohort study of 198 hospitalized patients with COVID-19.

### **Results**

Seventy-five patients (38%) were admitted to the intensive care unit (ICU). At time of data collection, 16 (8%) were still hospitalized and 19% had died. During a median follow-up of 7 days (IQR, 3-13), 39 patients (20%) were diagnosed with VTE of whom 25 (13%) had symptomatic VTE, despite routine thrombosis prophylaxis. The cumulative incidences of VTE at 7, 14 and 21 days were 16% (95% CI, 10-22), 33% (95% CI, 23-43) and 42% (95% CI 30-54) respectively. For symptomatic VTE, these were 10% (95% CI, 5.8-16), 21% (95% CI, 14-30) and 25% (95% CI 16-36). VTE appeared to be associated with death (adjusted HR, 2.4; 95% CI, 1.02-5.5). The cumulative incidence of VTE was higher in the ICU (26% (95% CI, 17-37), 47% (95% CI, 34-58), and 59% (95% CI, 42-72) at 7, 14 and 21 days) than on the wards (any VTE and symptomatic VTE 5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21), and 9.2% (2.6-21) at 7, 14, and 21 days).

### **Conclusions**

The observed risk for VTE in COVID-19 is high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or PE. Future research should focus on optimal diagnostic and prophylactic strategies to prevent VTE and potentially improve survival.

## Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and can lead to systemic coagulation activation. Initial studies from China report increased D-dimers (0.5 mg/L or higher) in 46% to 63% of patients, as well as other signs of coagulation activation including mild thrombocytopenia and a moderately prolonged prothrombin time.<sup>1,2</sup> Additionally, more pronounced coagulation activation seems to be correlated with a severe disease course, including admission to the intensive care unit (ICU) and death. For example, patients who died of COVID-19 had higher D-dimers on admission compared with those who survived, whereas D-dimer levels increased further during hospital stay in patients who died, but not in survivors.<sup>3</sup> In another study, patients with D-dimer levels of 1.0 µg/L or higher had an 18-fold increased risk of death.<sup>2</sup> One study used the International Society on Thrombosis and Haemostasis definition of disseminated intravascular coagulation and found that a score of  $\geq 5$  points was present in 71% of those who died compared with 0.6% in survivors.<sup>4</sup> None of these studies reported on the number of patients with thrombotic complications.

Since the pandemic spread of SARS-CoV-2, there have been several anecdotal reports from colleagues on a high incidence of thrombotic complications, including thrombosis of extracorporeal circuits for continuous veno-venous hemofiltration, central venous catheter-associated thrombosis, and deep venous thrombosis (DVT) and pulmonary embolism (PE). Most but not all of these complications occurred in patients admitted to the ICU, with most patients receiving routine thrombosis prophylaxis.

Diagnosis of DVT and PE may be particularly challenging in patients with COVID-19. Symptoms of PE overlap with symptoms of COVID-19 and mild symptoms may be overlooked in a patient already suffering from shortness of breath. Similarly, clinical signs and symptoms of DVT may be harder to detect, especially in ICU patients, and when treating clinicians primarily focus on respiratory status and do not systematically assess lower extremities for signs of DVT.

In early April 2020, a large number of venous thromboembolic events were diagnosed in COVID-19 patients admitted to our ICU, based on a clinical suspicion of DVT in the lower extremities. These observations have led us to intensify the dose of low-molecular-weight heparin to prevent VTE in COVID-19 patients in the ICU. In the present study, we report on the incidence and risk factors of VTE in COVID-19 patients admitted to the ICU or general ward.

## Methods

### *Patients*

We identified consecutive patients admitted for COVID-19 to the Amsterdam University Medical Centres, location Academic Medical Centre, until April 12, 2020. COVID-19 was confirmed by a reverse transcription polymerase chain reaction (RT-PCR) test on a nose/throat swab or sputum sample positive for SARS-CoV-2. Given the sensitivity of RT-PCR of only 50% to 80%,<sup>5</sup> a daily multidisciplinary team also considered COVID-19 confirmed in patients with a negative RT-PCR but with symptoms and disease course consistent with COVID-19, the absence of an alternative diagnosis, as well as a computed tomography (CT) scan of the chest showing abnormalities highly suspicious of typical pulmonary involvement of COVID 19 (COVID-19 Reporting and Data System [CO-RADS] 4 or 5 per the Dutch Radiology Society).<sup>6,7</sup> We did not include patients who were diagnosed with COVID-19 during hospital stay for other medical conditions.

Hospitalized patients were categorized as ICU patients or as ward patients. Patients were categorized as ward patients if they had not been transferred to the ICU at any time during the course of their disease. All ICU patients were admitted on the ICU for mechanical ventilation.

Thrombosis prophylaxis was part of standard of care in all COVID-19 patients. Ward patients received thrombosis prophylaxis with nadroparin 2850 IU once daily or 5700 IU for patients with a body weight of  $\geq 100$  kg. From April 3 onwards, patients in ICU received a double dose of nadroparin compared with patients on the wards, which was nadroparin 2850 IU twice daily for patients with a body weight  $< 100$  kg and 5700 IU twice daily for those  $\geq 100$  kg.

### *Outcomes*

The primary outcome was an objectively confirmed diagnosis of distal or proximal DVT, PE, or venous thrombosis at other sites including catheter-related thrombosis. The secondary outcome was symptomatic VTE, excluding events detected by bilateral leg ultrasound screening. All outcomes were adjudicated by two of the authors (M.C. and N.v.E.). We did not adjudicate deaths to identify fatal PE because almost all deaths were due to hypoxemic respiratory failure, which can be indistinguishable from fatal PE, whereas autopsies were rarely performed in COVID-19 patients.

### *Data collection*

Patient data were retrospectively reviewed from the day of admission to our hospital (also in case a patient was transferred from another hospital) until death, hospital discharge, transfer to another hospital, or end of data collection on April 30, 2020. We collected data on demographics and blood tests on admission. D-dimer levels

were included if measured on or within 72 hours of admission. Formal approval from the Medical Ethics Review Committee was not required as the Medical Research Involving Human Subjects Act does not apply for this observational study.

### ***Statistical analysis***

Patient characteristics were compared between ICU and ward patients using standard descriptive statistics. The proportion of ICU and ward patients with VTE was assessed, with 95% confidence intervals (CI) calculated using Wilson's score interval. In addition, the cumulative incidence, overall and for symptomatic VTE only, was calculated at 7, 14, and 21 days using a competing risk approach considering death as a competing risk. Risk factors for VTE were evaluated by calculating subdistribution hazard ratios (SHR) in Fine & Gray competing risk regression models. A sensitivity analysis was performed in which missing values were imputed 20 times using multiple imputation with chained equations, assuming a missing at random pattern. The multiple imputation model included all patient characteristics, laboratory values, radiology information, and outcome data. Estimates across the imputation datasets were combined using Rubin's rule. The association between VTE and mortality and between ICU stay and VTE were analysed by calculating a time-varying hazard ratio in Cox proportional hazards model. Analyses were performed in R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

## **Results**

Between March 2 and April 12, 2020, 199 patients who were hospitalized because of COVID-19 were identified. One patient was excluded because he was immediately transferred to another hospital from the emergency department. Of the remaining 198 patients, 148 (75%) were hospitalized after an emergency department visit, whereas 50 (25%) were transferred from another hospital. Seventy-five patients (38%) were admitted to the ICU after being transferred from the ICU of another hospital ( $n = 44$ ), our general ward ( $n = 20$ ), or directly from the emergency department ( $n = 11$ ). COVID-19 was confirmed by a positive RT-PCR in 173 patients (87%) and considered confirmed by clinical features consistent with COVID-19 in combination with a CT of the chest with highly suspicious or typical features (CO-RADS 4 or 5) and no alternative diagnosis in 25 (13%).

### ***Characteristics***

Patient characteristics are shown in Table 1. Mean age was 61 years (standard deviation, 14) and 130 (66%) were male. Median body mass index was 27 kg/m<sup>2</sup> (interquartile range [IQR], 24, 31). Compared with ward patients, ICU patients were more often male (77% vs 59%;  $P = .011$ ) and had higher D-dimer levels on

admission (median 2.0 vs 1.1 mg/L;  $P = .006$ ). The median time between symptom onset and admission to our hospital was 7 days (IQR, 5, 10) for patients presenting at the emergency department and 11 days (IQR, 6, 14) for those transferred from another hospital. Thrombosis prophylaxis was initiated in 167 patients (84%), whereas 19 (9.6%) continued therapeutic anticoagulation for an indication that was present at the time of admission (e.g., atrial fibrillation).

**Table 1: Baseline characteristics.**

	All Patients N = 198	Patients Admitted to ICU N = 75	Patients Admitted to Regular Ward N = 123	P value
Mean age, y (SD)	61 (14)	62 (10)	60 (16)	0.28
Male sex, n (%)	130 (66)	58 (77)	72 (59)	0.011
Body weight $\geq$ 100 kg, n (%)	22/157 (14)	12/73 (16)	10/84 (12)	0.56
Median body mass index, kg/m <sup>2</sup> (IQR)	27 (24, 31)	27 (24, 29)	28 (25, 31)	0.17
History of venous thromboembolism, n (%)	11 (5.6)	2 (2.7)	9 (7.3)	0.27
Active cancer, n (%)	7 (3.5)	3 (4.0)	4 (3.3)	1.0
Anticoagulant therapy at admission	19 (9.6)	7 (9.3)	12 (9.8)	1.0
Antiplatelet therapy at baseline	29 (15)	8 (11)	21 (17)	0.30
<b>Platelet count</b>				
Mean, $\times 10^9$ /L (SD)	239 (93)	251 (89)	231 (95)	0.15
<150 $\times 10^9$ /L, n (%)	27/196 (14)	7 (9.5)	20/122 (16)	0.23
<b>D-dimer</b>				
Median, mg/L (IQR)	1.1 (0.7, 2.3)	2.0 (0.8, 8.1)	1.1 (0.7, 1.6)	0.006
>0.5 mg/L, n (%)	110/131 (84)	40/48 (83)	70/83 (84)	1.0
>1.0 mg/L, n (%)	75/131 (57)	31/48 (65)	44/83 (53)	0.27

**Table 2: Clinical outcomes.**

	All Patients (N = 198) n (%)	ICU Patients (N = 75) n (%)	Patients in Wards (N = 123) n (%)
<b>Venous thromboembolism</b>			
Pulmonary embolism	39 (20)	35 (47)	4 (3.3)
Central or lobar	13 (6.6)	11 (15)	2 (1.6)
Segmental	1 (0.5)	1 (1.3)	0
Subsegmental	10 (5.1)	9 (12)	1 (0.8)
DVT	2 (1.0)	1 (1.3)	1 (0.8)
<b>DVT</b>			
Proximal leg DVT	26 (13)	24 (32)	2 (1.6)
Distal leg DVT	14 (7.1)	14 (19)	0
Upper extremity DVT	11 (5.6)	9 (12)	2 (1.6)
	1 (0.5)	1 (1.3)	0
<b>Symptomatic VTE</b>			
Pulmonary embolism	25 (13)	21 (28)	4 (3.3)
Proximal DVT	13 (6.6)	11 (15)	2 (1.6)
Distal DVT	8 (4.0)	8 (11)	0
	4 (2.0)	2 (2.7)	2 (1.6)

At the end of data collection (April 30, 2020), 136 patients (69%) had been discharged, 8 (4.0%) transferred to another hospital, 38 had died (19%), and 16 (8%) were still hospitalized. All patients still hospitalized were followed for at least 17 days. The median times from admission to discharge or death were 5 days (IQR, 3, 9) and 9 days (IQR, 5, 14), respectively. Thirteen patients (6.6%) were re-hospitalised after a median of 4 days (IQR, 2, 16) after discharge.

### ***Venous thromboembolism***

During a median follow-up of 7 days (IQR, 3, 13; range, 1-43), 39 patients (20%; 95% CI, 15-26) were diagnosed with VTE and 2 (1.0%; 95% CI, 0.28-3.6) with extensive symptomatic thrombophlebitis for which therapeutic anticoagulation was initiated. Type of VTE was PE with or without DVT in 13 patients (6.6%), proximal DVT in 14 (7.1%), distal DVT in 11 (5.6%), and upper extremity DVT in 1 (0.5%) (Table 2). VTE was symptomatic in 25 patients (13%) and detected incidentally or by screening in 14 (7.1%). Of note, screening for lower extremity DVT was performed in 55 patients (28%) during hospital stay (ICU, n = 38; ward, n = 17), whereas CT pulmonary angiography for PE was only performed on indication (e.g., sudden worsening hypoxemia). VTE was diagnosed after a median of 7 days after admission (IQR, 4, 10) and symptomatic VTE also after a median of 7 days (IQR, 5, 9).

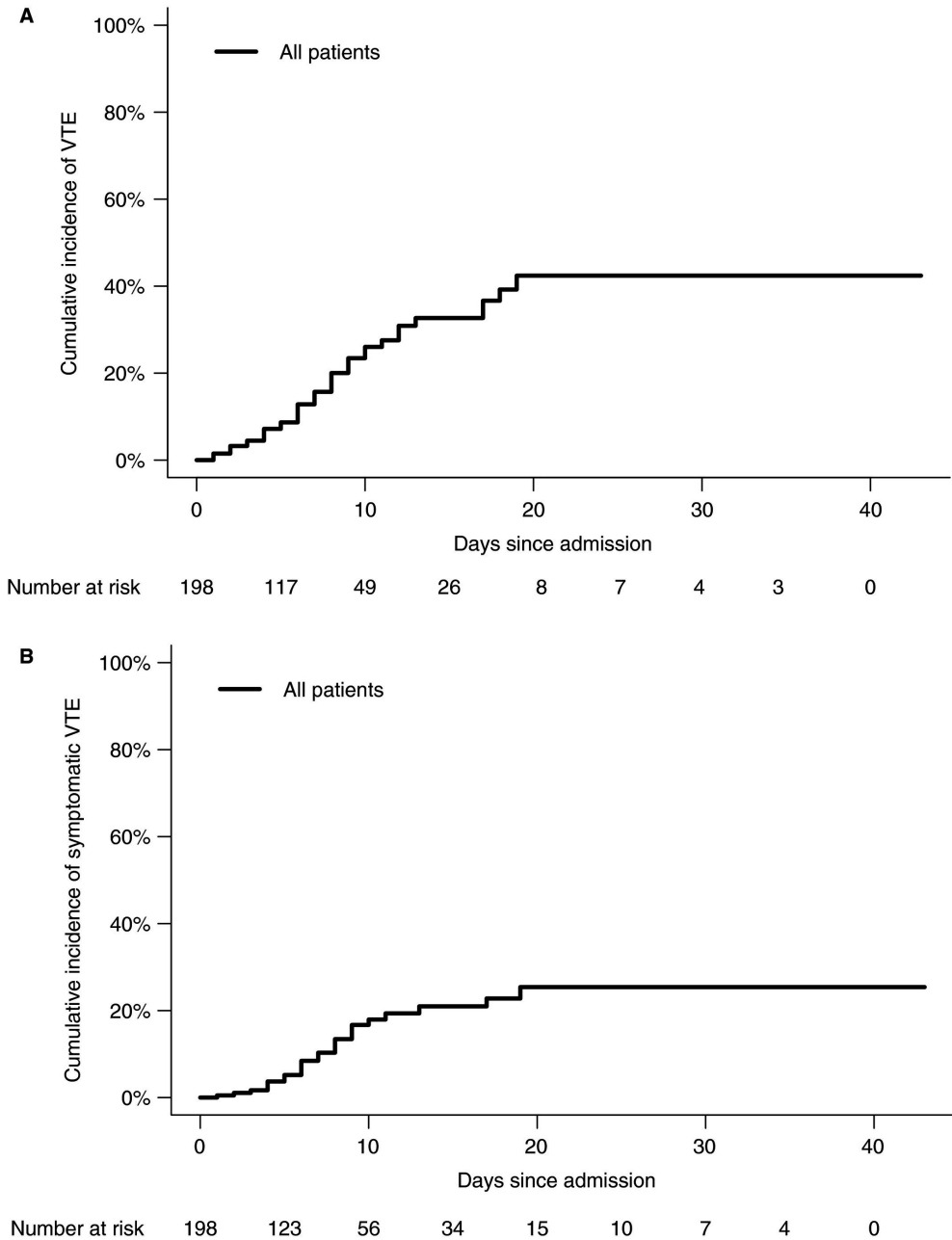
In the competing risk model, the cumulative incidences of VTE at 7, 14, and 21 days were 16% (95% CI, 10-22), 33% (95% CI, 23-43), and 42% (95% CI, 30-54), respectively (Figure 1A). When only considering symptomatic VTE, the cumulative incidences were 10% (95% CI, 5.8-16), 21% (95% CI, 14-30), and 25% (95% CI, 16-36) at 7, 14, and 21 days, respectively (Figure 1B). When analysed as a time-varying variable, VTE was significantly associated with death (hazard ratio [HR], 2.7; 95% CI, 1.3-5.8), also when adjusted for age, sex, and ICU stay as time-varying variable (adjusted HR, 2.4; 95% CI, 1.02-5.5).

All VTE were diagnosed in patients receiving thrombosis prophylaxis. The risk of VTE in ICU patients was not lower during the period when the standard dose of nadroparin prophylaxis was doubled (58%) vs in the first follow-up period (41%).

### ***ICU vs ward patients***

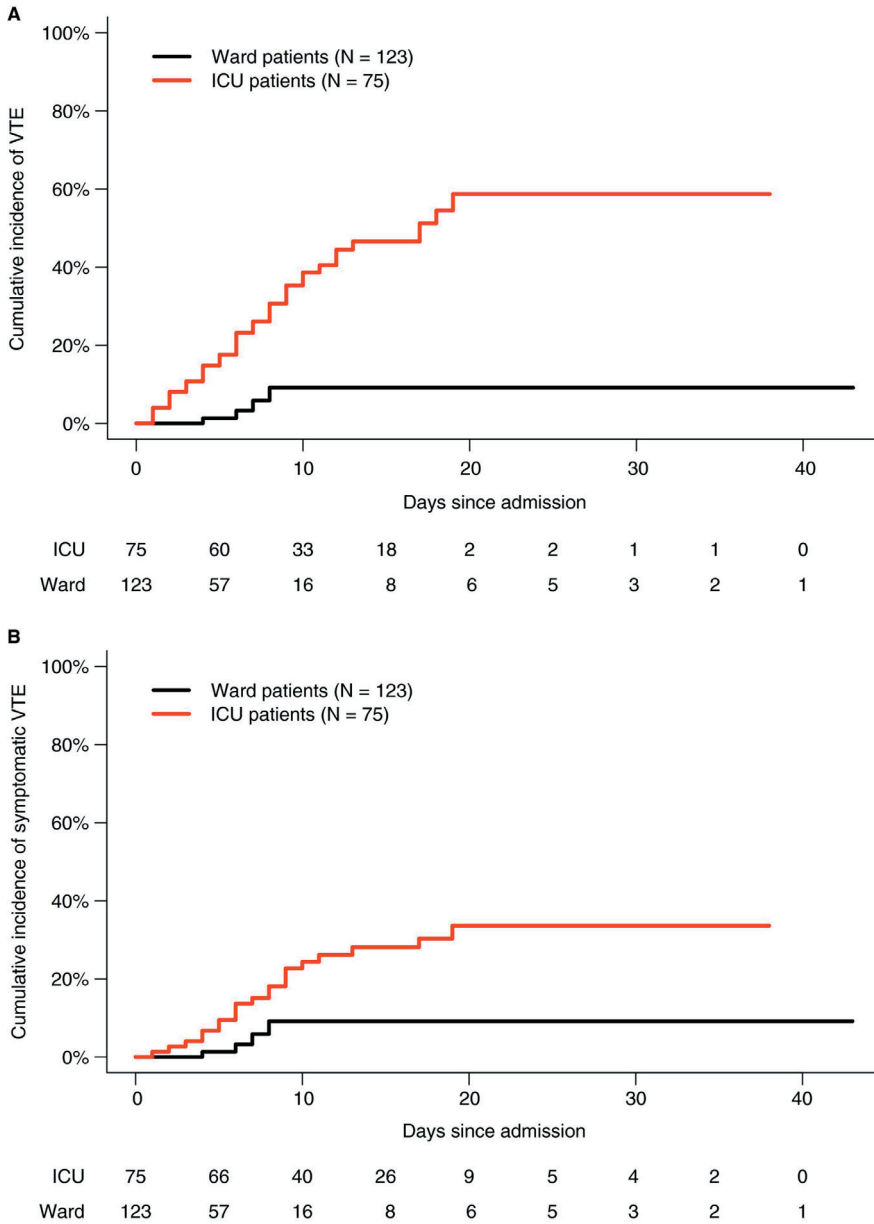
Median follow-up duration was 15 days in ICU patients (IQR, 9, 20) and 4 days in ward patients (IQR, 2, 7). The proportion of patients with VTE was significantly higher in ICU patients (47%; 95% CI, 36-58) than in ward patients (3.3%; 95% CI, 1.3-8.1), corresponding to an SHR of 7.9 (95% CI, 2.8-23). The cumulative incidences of any VTE in ICU patients at 7, 14, and 21 days were 26% (95% CI, 17-37), 47% (95% CI, 34-58), and 59% (95% CI, 42-72), respectively (Figure 2A).

Symptomatic VTE was detected in 21 (28%) ICU patients and 4 (3.3%) ward patients (SHR, 3.9; 95% CI, 1.3-12). The cumulative incidences of symptomatic VTE in ICU patients at 7, 14, and 21 days were 15% (95% CI, 8.0-24), 28% (95% CI, 18-39), and 34% (95% CI, 21-46) (Figure 2B). The cumulative incidences of both any VTE and symptomatic VTE in ward patients at 7, 14, and 21 days were 5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21), and 9.2% (2.6-21) (Figure 2).



**Figure 1:**

A, Venous thromboembolism. B, Symptomatic venous thromboembolism. ICU, intensive care unit; VTE, venous thromboembolism.



**Figure 2:**

A, Venous thromboembolism in ICU and ward patients. B, Symptomatic venous thromboembolism in ICU and ward patients. ICU, intensive care unit; VTE, venous thromboembolism.

The difference between ICU and ward patients was comparable when ICU stay was modelled as a time-varying variable (HR for any VTE, 7.1; 95% CI, 3.1-16). The higher risk in ICU patients was consistent in the sensitivity analysis excluding patients transferred from another hospital (50% vs 3.4%; SHR, 7.2; 95% CI, 2.3-23).



**Table 3: Risk factors for venous thromboembolism.**

	VTE (N = 39)	No VTE (N = 159)	Univariable SHR (95% CI) <sup>c</sup>	Multivariable SHR (95% CI) <sup>d</sup>
Mean age, years (SD)	62 (10)	60 (15)	0.98 (0.8-1.2) <sup>a</sup>	1.05 (0.82-1.4) <sup>a</sup>
Male sex	27 (69)	103 (65)	0.7 (0.4-1.5)	0.53 (0.27-1.0)
Intensive care unit	35 (89)	40 (25)	7.9 (2.8-23)	8.9 (3.2-25)
Median body weight, kg/m <sup>2</sup> (IQR)	82 (74, 93)	84 (75, 95)	0.6 (0.2, 2.3) <sup>b</sup>	0.9 (0.2, 3.9) <sup>b</sup>
History of venous thromboembolism	3 (7.9)	8 (5.2)	1.1 (0.3-3.0)	1.6 (0.4-7.2)
Anticoagulant use at admission	0 (0)	19 (12)		
Mean hemoglobin, mmol/L (SD)	8.0 (1.4)	7.9 (1.2)	1.04 (0.8-1.4) <sup>b</sup>	1.1 (0.8-1.5) <sup>b</sup>
Median white blood cell count, ×10 <sup>9</sup> /L (IQR)	7.6 (5.9, 11)	6.9 (5.4, 9.3)	1.9 (1.1, 3.2)	1.9 (0.9, 4.1) <sup>b</sup>
Median neutrophil count, ×10 <sup>9</sup> /L	6.0 (4.4-8.1)	5.2 (3.8-7.1)	2.0 (0.99-4.0)	1.7 (0.8-3.7) <sup>b</sup>
Median lymphocyte count, ×10 <sup>9</sup> /L	0.59 (0.47-0.83)	1.0 (0.8-1.3)	0.66 (0.43-1.02)	0.7 (0.4-0.95) <sup>b</sup>
Median neutrophil-to-lymphocyte ratio	11 (7.0-15)	5.4(3.5-8.1)	2.0 (1.3-3.1) <sup>b</sup>	1.7 (1.2-2.5) <sup>b</sup>
Mean platelet count, ×10 <sup>9</sup> /L	246 (87)	237 (95)	1.02 (0.99-1.1) <sup>a</sup>	1.002 (0.97-1.04) <sup>a</sup>
Median D-dimer, mg/L (IQR)	2.6 (1.1, 18)	1.0 (0.7, 1.7)	1.6 (1.2, 2.1) <sup>b</sup>	1.4 (1.1, 1.9)

Abbreviations: IQR, interquartile range; SD, standard deviation; SHR, subdistribution hazard ratio; VTE, venous thromboembolism. <sup>a</sup> Per 10-unit increase. <sup>b</sup> Per 1-unit increase. <sup>c</sup> Variables with a non-normal distribution (i.e., body weight, white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, and D-dimer) were analysed log-transformed. <sup>d</sup> Multivariable analysis were adjusted for age, sex, and intensive care unit admission.

### ***Risk factors for venous thromboembolism***

Besides ICU stay, other risk factors associated with VTE in univariable regression analyses were a higher white blood cell count (SHR, 1.9 for every log-transformed unit increase; 95% CI, 1.1-3.2), higher neutrophil-to-lymphocyte ratio (SHR, 2.0 for every log-transformed unit increase; 95% CI, 1.3-3.1), and a higher D-dimer level (SHR, 1.6 for every log-transformed unit increase; 95% CI, 1.2-2.1) (Table 3). These associations remained materially unchanged when adjusted for age, sex, and ICU stay (Table 3), when excluding patients transferred from another hospital (data not shown), and when missing values were imputed (data not shown). Notably, none of the 19 patients (0%) who continued therapeutic anticoagulation that they used for other indications developed VTE compared with 39 of 179 of the remaining patients (22%; SHR, not estimable; Fisher exact test  $P = 0.03$ ).

### **Discussion**

We observed a very high risk of VTE in patients with COVID-19. Although the profound coagulopathy associated with COVID-19 has been described soon after start of the pandemic, few data on clinical VTE have been reported. In a cohort of 81 ICU patients in China, in which routine thromboprophylaxis was not the standard of care, the proportion of patients who were diagnosed with DVT was 25%; a follow-up

duration or cumulative incidence was not reported.<sup>8</sup> In a study of 184 ICU patients in 3 Dutch hospitals, where routine low-molecular-weight heparin prophylaxis was applied, 68 (37%) patients had VTE, with a reported cumulative incidence of 49%.<sup>9</sup> Similar observations have now been reported in ICU patients in France and Italy.<sup>10,11</sup> In our hospital, where thrombosis prophylaxis in patients admitted with COVID-19 is standard of care, VTE was observed in 35 of 75 (47%) ICU patients, with a cumulative incidence of 59% at 21 days. The very high incidence in ICU patients in the present study may partially be explained by the initiation of a screening approach, although the risk remained high if only symptomatic VTE was considered (28% of patients; cumulative incidence 34% at 21 days). In non-ICU COVID-19 patients admitted to the regular ward, 4 of 123 patients (3%) were diagnosed with symptomatic VTE despite thrombosis prophylaxis.

Our study has some limitations and strengths. First, this was a single-centre cohort study with a relatively small sample size, and 8% of patients were still hospitalized at the time of data collection. Second, including patients transferred from other hospitals may lead to immortal time bias because they need to survive until transfer, thereby potentially biasing the VTE cumulative incidence. However, restricting the analysis to patients admitted directly from our own emergency department did not substantially affect the results. Although immortal time bias could also have been introduced by placing patients who were transferred from the ward to the ICU in the ICU group, results were consistent when analysing ICU stay in a time-varying model. There appeared to be a considerable difference between the crude proportion of patients with VTE and the cumulative incidence estimate from the survival model, despite the use of a competing risk model to mitigate the influence of death. Likely explanations include the relatively short median follow-up duration, the number of patients still hospitalized, and the (informative) censoring of patients when discharged from the hospital; the risk of VTE in the latter group is likely to be lower than that of patients remaining in the cohort. Finally, based on concerns of a high risk of (fatal) VTE following early observations, we changed our practice during the follow-up period by performing screening compression ultrasound in the ICU every 5 days, while also performing a single cross-sectional round of compression ultrasounds at the ward in the 10 days before data collection. This screening led to diagnosis of asymptomatic DVT, all in the ICU group, which may be clinically less relevant than symptomatic DVT. Strengths include the inclusion of consecutive patients, the follow-up duration of at least 17 days, no loss to follow-up, and the objectively confirmed and adjudicated diagnosis of VTE.

Whether the high incidence of VTE observed in the ICU justifies higher or therapeutic doses of pharmacological prophylaxis at an acceptable bleeding risk and whether this would improve the outcome of severe COVID-19 pneumonia is unknown. One observational study from China that included 449 hospitalized

COVID-19 patients suggested that thrombosis prophylaxis was associated with a 56% to 63% reduction in mortality in patients with sepsis-induced coagulopathy, but not in other patients.<sup>12</sup> Only 22% of COVID-19 patients received thrombosis prophylaxis, which is much less than expected according to guidelines on thrombosis prophylaxis in medical patients.<sup>13</sup> Currently, several randomized controlled trials are being planned or have started in which the optimal dose of thrombosis prophylaxis will be investigated. Some of these trials use an elevated D-dimer level as an entry criterion (e.g., Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care [RAPID COVID COAG]; clinicalTrials.gov identifier NCT04362085). This approach is supported by the present observation that higher D-dimer levels at baseline are associated with VTE during follow-up. It is not known whether VTE contributes to respiratory deterioration or death in COVID-19 pneumonia, although VTE during the course of disease appeared to be associated with mortality in an exploratory analysis in our cohort. Interestingly, none of the patients who were receiving therapeutic anticoagulation at admission (for other indications) developed VTE.

The 3% risk of VTE among patients who were not admitted to ICU is considerable, despite the standard use of thrombosis prophylaxis. In an Italian single-centre retrospective cohort study, the proportion of COVID-19 patients with VTE was 6% in ward patients, corresponding to a cumulative incidence of 7%.<sup>11</sup> These reported risks appear to be higher than expected in medical hospitalized patients who are not critically ill.<sup>13</sup>

Based on the present findings, we believe the threshold of suspicion of VTE in COVID-19 patients should be low and elicit appropriate diagnostic testing and treatment if VTE is diagnosed. The clinical value of ultrasound screening of the lower extremities in ICU patients with COVID-19 is a matter of debate. However, given the high risk of symptomatic VTE in ICU patients, screening followed by initiating therapeutic anticoagulation may be justified in patients diagnosed with asymptomatic (proximal) DVT to prevent extension and embolization. It is possible that a higher intensity of thrombosis prophylaxis, both in ICU and ward patients, not only decreases VTE but also decreases mortality. Future research should therefore focus on optimal diagnostic and prophylactic strategies for VTE in hospitalized patients with COVID-19.

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### **Conflict of interest**

Dr. Middeldorp reports grants and fees paid to her institution, outside the present work, from Abbvie, BMS/Pfizer, Aspen, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Sanofi, and Portola. Dr. Coppens reports research support and lecturing or consultancy fees, outside the present work, from Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk, Sanquin Blood Supply, Sobi, and Portola. Dr. van Es reports fees paid to his institution, outside the present work, from Bayer, LEO Pharma, and Daiichi Sankyo. The other authors have no disclosures.

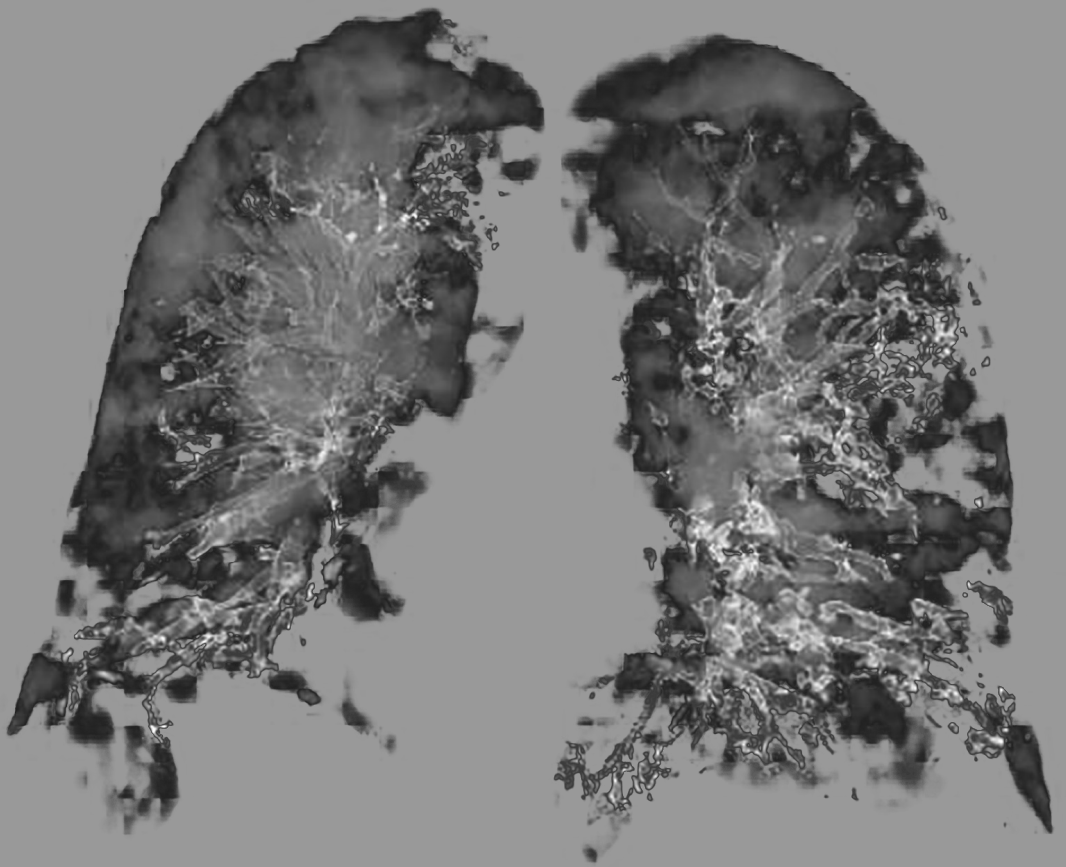
### **Author contributions**

All authors contributed substantially to the study design, acquisition, analysis, and interpretation of the data. Saskia Middeldorp, Michiel Coppens, and Nick van Es drafted the first version of the manuscript. All authors revised the manuscript critically and approved the final version.

## References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine* 2020; **382**(18): 1708-20.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)* 2020; **395**(10229): 1054-62.
3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 2020; **323**(11): 1061-9.
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(4): 844-7.
5. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *Jama* 2020; **323**(18): 1843-4.
6. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**(2): E32-e40.
7. Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**(2): E97-E104.
8. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(6): 1421-4.
9. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis research* 2020; **191**: 148-50.
10. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive care medicine* 2020; **46**(6): 1089-98.
11. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis research* 2020; **191**: 9-14.
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(5): 1094-9.
13. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2018; **2**(22): 3198-225.





# Chapter 8

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## Extensive pulmonary perfusion defects compatible with microthrombosis and thromboembolic disease in severe Covid-19 pneumonia

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## **Abstract**

### **Background**

It is unclear why some patients with progression to severe COVID-19 pneumonia require invasive mechanical ventilation while others can be managed with supplemental oxygen. We hypothesized that pulmonary perfusion defects consistent with microthrombosis are common in COVID-19 patients requiring mechanical ventilation.

### **Methods**

We studied 20 consecutive PCR confirmed COVID-19 pneumonia patients who were admitted to the hospital due to acute respiratory failure and who had a clinical suspicion of pulmonary embolism. We compared 10 ICU patients who required invasive mechanical ventilation to 10 patients who were managed on the ward. All patients underwent dual energy CT Pulmonary Angiography (CTPA). Lung analysis for iodine distribution maps was used to evaluate pulmonary perfusion and were compared between groups.

### **Results**

Median duration between disease onset and CTPA was 16 (IQR 11) vs. 13.5 (IQR 10) days for the ICU and ward-groups, respectively. Pulmonary emboli were diagnosed in 8 ICU patients and 2 ward patients ( $p < 0.005$ ). All ICU patients showed bilateral extensive scattered perfusion defects while ward patients only showed small perfusion defects near the pleura or directly associated with a pulmonary embolism (mean area  $52.5\% \pm 14.8$  vs.  $17.5\% \pm 7.5$  of total lung volume;  $p < 0.0001$ ). No significant differences in right ventricular dysfunction signs were observed.

### **Conclusions**

Mechanically ventilated ICU patients with severe COVID-19 pneumonia associated respiratory failure have both a high incidence of pulmonary embolism as well as scattered large areas of severely diminished lung perfusion, resulting in a pulmonary ventilation perfusion mismatch, most likely reflecting pulmonary microcirculatory dysfunction due to inflammatory response with microthrombosis.

## Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) can result in severe COVID-19 pneumonia and poses unprecedented health care problems, both on a global scale and for many individual patients.<sup>1,2</sup> Acute respiratory failure is the most common reason for hospital admission. Many patients can be managed with supplementary oxygen on the ward, but in up to 20% respiratory failure progresses and requires admission to an intensive care unit (ICU) for mechanical ventilation.<sup>3</sup> The mortality of these patients is particularly high, ranging up to 50%.<sup>4</sup>

Several hypotheses have been proposed to explain the differences in clinical course between patients. One hypothesis is that pulmonary embolism results in severe hypoxemia. Observational studies suggest a high incidence of deep vein thrombosis in COVID-19, up to 25% in ICU patients compared to 6.5% in ward patients,<sup>5</sup> which may progress to pulmonary embolism. Pulmonary oedema as a result of dysbalance of the bradykinin-kallikrein system is also suggested to contribute.<sup>6</sup> Another hypothesis is the onset of local thrombosis in the pulmonary microvasculature due to an inflammatory thrombotic microangiopathy.<sup>7,8</sup> All entities are observed in some autopsy reports of COVID-19 patients.<sup>9-11</sup> A better understanding of why gas exchange worsens is important as this could set the stage for intervention studies.<sup>12,13</sup>

We performed a cross-sectional study comparing advanced functional imaging findings on dual energy CT Angiography (CTPA) between patients with COVID-19 pneumonia who were admitted to the ICU for invasive ventilation and patients who were admitted to the ward with supplemental oxygen. We hypothesized that patients requiring invasive mechanical ventilation for COVID-19 related acute respiratory failure have more extensive perfusion defects compared to patients not requiring invasive ventilation.

## Materials and Methods

### *Patients and study design*

This was an observational study in 20 patients who were admitted after March 15<sup>th</sup> 2020 to a university hospital in the Netherlands with RT-PCR confirmed COVID-19 and in the course of the disease had a clinical suspicion of pulmonary embolism. We compared 10 consecutive patients with severe COVID-19 pneumonia who were admitted to the ICU requiring mechanical ventilation to 10 consecutive patients who were managed on the COVID-19 ward with supplemental oxygen with a maximum of 15 L/min via non-rebreathing mask but no need for positive pressure ventilation. All ICU patients were admitted because of type I respiratory failure. We do not perform high flow nasal oxygen therapy or continuous positive airway pressure ventilation in patients with severe COVID-19 pneumonia and all ICU-patients are

intubated and mechanically ventilated. All patients had radiological characteristics of COVID-19, scored as CORADS 5 according to the CO-RADS system, the “COVID-19 Reporting and Data System”.<sup>14</sup> CO-RADS 5 implies a very high level of suspicion for pulmonary involvement of COVID-19 based on typical CT findings (multifocal bilateral ground-glass opacities, with or without consolidations, in lung regions close to visceral pleural surfaces). All patients underwent a dual energy CT Pulmonary Angiography for clinical suspicion of pulmonary embolism, for the ICU patients primarily on clinical grounds, for the ward patients according to the YEARS-criteria.<sup>15</sup> Informed consent was waived by the institutional ethics committee.

### ***Data collection***

Clinical data were obtained through review of medical records. Patient characteristics (age, gender, comorbidities), clinical follow up, including multidisciplinary conferences, and RT-PCR results were extracted from electronic patient records. The data reported here are those available through May 15<sup>th</sup>, 2020. Results are reported according to the STROBE guideline.

### ***Imaging***

CT-images were acquired from a high-end dual source CT (CT Somatom Force, Siemens Healthineers, Forchheim, Germany) in the emergency department solely dedicated to COVID-19 (suspected) patients. A non-enhanced Chest CT (NECT) scan followed by a dual energy CT Pulmonary Angiography (CTPA) in deep inspiration was obtained from all 20 patient with the following scan parameters: for NECT: 100/Sn150 kVp, Qref mAs 200 mA, pitch 1.8, rotation time 0.25 sec, careDose4D, and for CTPA: collimation 2 \* 192 \* 0.6 mm, 80/Sn150 kVp, Qref mAs 90/50, pitch 0.55, rotation time 0.25 sec, after injection of 50 mL contrast medium (Iomeron 300, Bracco Imaging, Germany) at 5 mL/s in the right antecubital vein. Reconstructions were done in 1 and 3 mm lung and soft kernel. Post-processing was performed on a dedicated software platform (Syngo via, VB30, Siemens Healthineers, Forchheim, Germany). Iodine maps were constructed from Lung Analysis; both axial, sagittal and coronal iodine multiplanar reconstructions (MPR) were made with 1 and 5 mm slice thickness and increment.

All images were evaluated independently by two radiologists (LB and MS) with respectively 15 and 7 years of experience in chest imaging, differences were settled in consensus. Images were primarily read in PACS (Enterprise Imaging, AGFA-Gevaert, Mortsel, Belgium) in 3 orientations (axial, coronal and sagittal) with additional MPR if deemed necessary. Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation when necessary. Pulmonary embolism was defined as a constant intravascular filling defect on CTPA. Location of a filling defect was registered for each lobe until

most distal subsegmental levels, occurrence of an isolated subsegmental defect and central emboli were also noted separately. Severity of the COVID-19 pneumonia was assessed semi-quantitatively, scored for each lobe in steps of 25% (0: normal; 1: <25%; 2: <50%; 3: <75% and 4>75% of lobe volume involved) with a maximum score of 20. Iodine maps were calculated for Pulmonary Blood Volume (PBV) using a dedicated software program (Lung analysis).<sup>16</sup> Pulmonary blood volume perfusion defects were visually assessed semi-quantitatively on the orange coloured iodine distribution maps in steps of 10% for each lung, and a composite volume for both lungs. The following parameters suggestive of right ventricular dysfunction were assessed: right-to-left ventricular (RV/LV) ratio, pulmonary trunk diameter, bowing of the interventricular septum and reflux of contrast medium into intrahepatic veins > 3 cm.<sup>17</sup> All data were registered on a specially designed CRF.

### ***Statistical analysis***

Data are presented as mean  $\pm$  standard deviation (SD) for normally distributed variables and median  $\pm$  interquartile ranges (IQR, 25<sup>th</sup> to 75<sup>th</sup> percentile) for non-normally distributed variables. For comparison on binary outcomes Chi-square or Fisher's exact test for dichotomous variables was used and for continuous data between groups by Students T test or Mann-Whitney U test where applicable. Significance of differences were evaluated with two-sided p-values; a p-value <0.05 was considered to imply statistical significance. All statistics were performed in SPSS version 26 (SPSS Inc, Chicago Ill).

## **Results**

Patients demographics are displayed in Table 1. The mean ( $\pm$ SD) age of patients was 63.9 $\pm$ 7.8 for patients admitted to the ICU and 61.7 $\pm$ 9.1 years for patients who were managed on the ward.

Duration of symptoms to the moment of CTPA imaging was not different between the two groups (16 vs. 13.5 days, P=0.24). CT severity scores indicative of the extent of parenchymal involvement were higher in the ICU patient compared to the ward patients (17.7 $\pm$ 2.0 vs 8.5 $\pm$ 3.8 of max. 20 points; p<0.001).

**Table 1: Patient characteristics of ICU and ward patients with severe COVID-19 pneumonia.**

	ICU N=10		Ward N=10		<i>p</i> -value
<b>Baseline</b>					
Age years (Mean; SD)	63.6	8.2	61.7	10.2	0.60
<b>Sex (N; %)</b>					
Male	6	(60)	5	(50)	0.37
Female	4	(40)	5	50)	
Weight <i>kg</i> (Median; IQR)	87.0	(25.0)	97.0	(32.0)	0.21
BMI (Median; IQR)	28.3	(4.8)	33.3	(18.8)	0.081
<b>Co-morbidities</b>					
Obesity (N; %)	4	(40)	4	(40)	
Diabetes (N; %)	3	(30)	3	(30)	
Hypertension (N; %)	2	(20)	4	(40)	
Cancer (N; %)	0	(0)	0	(0)	
Cardiovascular Disease (N; %)	2	(20)	1	(10)	
Cerebrovascular Disease (N; %)	2	(20)	0	(0)	
Obstructive Pulmonary Disease (N; %)	3	(30)	2	(20)	
History of DVT/PE (N; %)	1	(10)	2	(20)	
<b>Clinical course of COVID-19</b>					
Duration symptoms to hospitalization <i>days</i> (Median; IQR)	6	(5)	8	11	0.03
Duration symptoms to CTPA <i>days</i> (Median; IQR)	16	(11)	13.5	10	0.24
Mortality (N; %)	6	(60)	0	(0)	0.003
Discharged (N; %)	0	(0)	8	(80)	0.000
<b>Use of anticoagulation</b>					
Use of therapeutic anticoagulation at time of CTPA (N; %)	1	(10)	0	(0)	
Antiplatelet use (N; %)	3	(30)	0	(0)	
LMWH prophylaxis (N; %)	9	(90)	9	(90)	
Concomitant DVT (N; %)	6	(60)	1	(10)	
<b>Laboratory values at day of CTPA</b>					
CRP <i>mg/L</i> (median; IQR)	227.9	(138.5)	77.5	(147.6)	0.27
Hb <i>mmol/L</i> (mean; SD)	6.9	(1.1)	7.9	(2.3)	0.74
WBC $\times 10^9/L$ (median; IQR)	7.8	(9.8)	4.9	(2.5)	0.006
Lymphocytes $\times 10^9/L$ (median; IQR)	0.49	(0.09)	0.68	(0.36)	0.11
Platelet count $\times 10^9/L$ (median; IQR)	261	(212)	148	(67)	0.016
Fibrinogen <i>g/L</i> (median; IQR)	8.3	(2)	NA		0.37
APTT <i>seconds</i> (median; IQR)	44.5	(23)	23	(4)	0.002
PT <i>seconds</i> (median; IQR)	11.3	(0.74)	10.9	(0.6)	0.64
D-dimer <i>mg/L</i> (median; IQR)	7.4	(10.5)	1.3	(3.7)	0.017
Creatinin <i>umol/L</i> (median; IQR)	77.0	(25)	81.0	(64)	0.65
LDH <i>U/L</i> (median; IQR)	616	(180)	353	(298)	0.09
<b>Ventilation parameters</b>					
PEEP <i>cmH2O</i> (Median; IQR)	8.9	(2.9)			
Driving pressure <i>cmH2O</i> (Median; IQR)	12.2	(8.1)			
Plateau pressure <i>cmH2O</i> (Median; IQR)	21.1	(8.0)			
Tidal Volume <i>mL/kg</i> (Median; IQR)	5.8	(2.1)			
PaO <sub>2</sub> /Fio <sub>2</sub> <i>mmHg</i> (Median; IQR)	114	(39)			
Compliance <i>mL/cmH2O</i> (Median; IQR)	56.6	(33.9)			

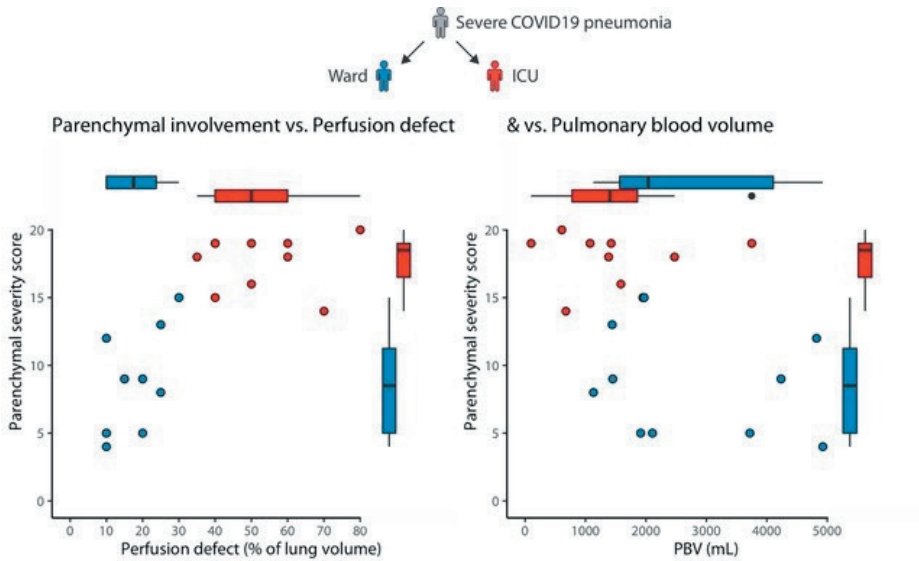
**Table 2: Radiological characteristics of ICU and ward patients with severe COVID-19 pneumonia who underwent CT Pulmonary Angiography.**

	ICU N=10	Ward N=10	<i>p</i> -value
<b><i>CORADS &amp; Disease Severity</i></b>			
CORADS	5	5	1
CT Severity points (max20; mean, SD)	17.7 (2.0)	8.5 (3.8)	<0.001
Ascending aorta <i>HU</i> (median, IQR)	261 (109)	256 (151)	0.65
Pulmonary trunk <i>HU</i> (median, IQR)	295 (156)	365 (138)	0.33
Aorta/pulmonary trunk <i>HU</i> (mean, SD)	0.94 (0.48)	0.74 (0.36)	0.35
<b><i>CT angiography results</i></b>			
Pulmonary embolism			
Present (N; %)	8 (80)	2 (20)	0.007
Bilateral (N; %)	5 (50)	1 (10)	<0.001
<b><i>Most proximal clot location</i></b>			
Central (N; %)	2 (20)	1 (10)	
Segmental (N; %)	4 (40)	0 (0)	
Subsegmental (N; %)	1 (10)	1 (10)	
Isolated subsegmental (N; %)	1 (10)	0 (0)	
<b><i>Signs of right ventricular dysfunction</i></b>			
Right/Left Ventricular ratio > 1.0 (N; %)	3 (30)	3 (30)	1
Pulmonary Trunk > 29 mm (N; %)	4 (40)	2 (20)	0.068
Septal flattening (N; %)	2 (20)	1 (10)	0.53
Reflux of contrast medium (N; %)	2 (20)	1 (10)	0.53
<b><i>Perfusion defects Iodine map</i></b>			
Right lung % of lung (mean, SD)	52.0 (16.2)	21.0 (5.7)	0.009
Left lung % of lung (mean, SD)	52.0 (16.2)	20.0 (10.5)	<0.001
Total % of both lungs (mean, SD)	52.5 (14.8)	17.5 (7.5)	<0.001
Total perfusion defect >1/3 lung volume (N; %)	10 (100)	0 (0)	<0.001
Pulmonary blood volume right lung	838 (669)	1209 1527	0.049
Pulmonary blood volume left lung	536 (490)	895 (1289)	0.023
Pulmonary blood volume lungs	1404 (1423)	2039 (2934)	0.034

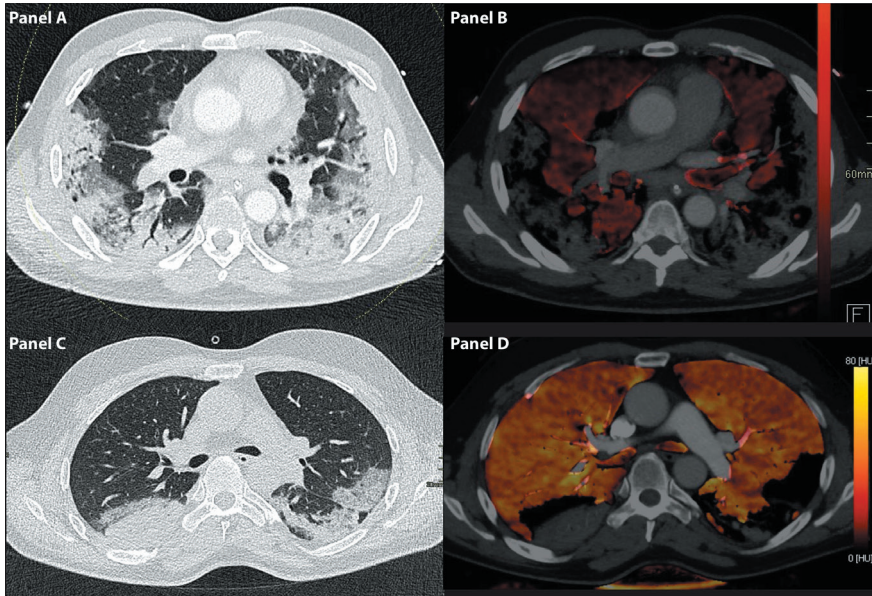
Pulmonary embolism was found more often in ICU patients compared to patients managed on the ward: 80% (n=8) versus 20% (n=2;  $p<0.005$ ; Table 2). Central emboli were observed in 2 ICU patients and 1 ward patient.

Analysis of the iodine pulmonary blood volume maps showed strikingly different appearances between the two groups (Figure 1).

ICU patients displayed large areas of scattered perfusion defects throughout both lungs, not only at the subpleural regions but also in the deeper parts of the lungs remote from the pleura or fissures. The areas with perfusion defects were anatomically not completely explainable by pulmonary embolism and parenchymal involvement. Estimated mean percentage of perfusion defects was  $52.5\% \pm 14.8$  in ICU patients and  $17.5\% \pm 7.5$  in COVID-19 ward patient ( $p<0.001$ ; Figure 2).

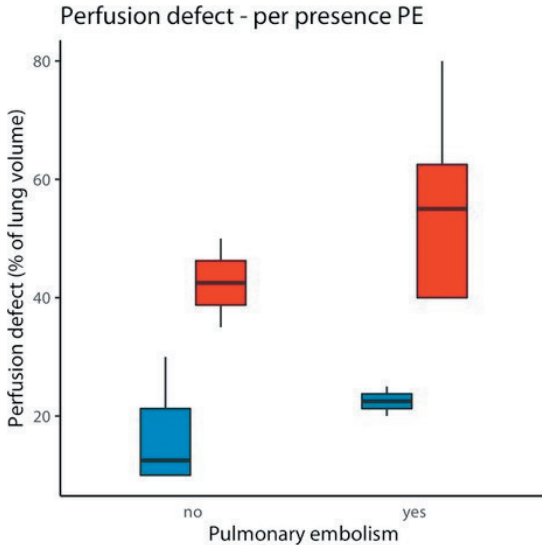


**Figure 1:** Relationship between parenchymal involvement, perfusion defect, pulmonary blood volume for intubated ICU patients (red) and ward patients (blue). Y-axis: Parenchymal involvement with maximal score 20. Left panel, x-axis: perfusion defect as percentage of lung volume. Right panel, x-axis: pulmonary perfused blood volume (PBV) in mL.



**Figure 2:** CT and Dual energy CTPA Pulmonary Blood Volume maps in two COVID-19 patients. Top panels: ICU patient with mechanical ventilation. Bottom panels: ward patient. Left panels: CT images in lung setting. Right panels: Perfusion reconstructions. (a) example of extensive involvement of the lung parenchyma (b) pulmonary embolus in the right lower lobe, with bilateral large areas of perfusion defects, also without associated pulmonary emboli. Note the limited areas of normal perfusion (orange) even in visually rather normal appearing lung zones. (c) bilateral posterior consolidations and areas of ground glass. (d) CTPA showed no pulmonary embolism. Homogeneous perfused blood volume in both lungs, with restriction only in the consolidated areas.

A lower pulmonary blood volume was seen in ICU patients (1404 mL) compared to patients managed on the ward (2039 mL,  $p=0.03$ ; Figure 3, Table 2). Enhancement of pulmonary trunk and aorta was not different between the 2 groups. No significant differences were present between the groups with respect to signs of right ventricular dysfunction.



**Figure 3:** Perfusion defect as percentage of lung volume stratified for the presence of pulmonary embolism for intubated ICU patients (red) and ward patients (blue).

## Discussion

The main findings of our study can best be summarized as follows: (1) intubated and mechanically ventilated ICU patients with COVID-19 related acute respiratory failure show extensive bilateral patchy areas of perfusion defects, which are not seen in patients who do not require invasive mechanical ventilation; (2) pulmonary embolism is also more frequent in ICU patients (3) perfusion defects occur also in normally aerated areas without adjacent pulmonary embolism, possibly due to microthrombi. The observed extensive pulmonary perfusion defects might contribute to the severity in respiratory failure in concert with increased shunt due to the loss of aeration as a result of parenchymal involvement.

The remarkably higher incidence of pulmonary embolism we observed is in line with the reported incidences of venous thromboembolic events in several cohorts of COVID-19 patients.<sup>18-20</sup> Deep vein thrombosis, both in the distal and proximal veins of the lower extremities as well as in the upper limbs or jugular veins, is frequently observed in COVID-19 patients on the ICU.<sup>5,21-23</sup> Despite this fact, our



observation that the minority of cases had central pulmonary embolism suggest that the pulmonary emboli are not all the result of deep vein thrombosis migrating to the pulmonary vasculature. Local microthrombi might better explain our observations and might result from diffuse alveolar damage and local thrombotic microangiopathy, which is in line with a case series of post mortem COVID-19 sections of the lungs.<sup>11,24</sup> This is not unique for COVID-19 pneumonia as acute infections in general are associated with a transient increased risk of venous thromboembolic events. The pathophysiology of thrombotic coagulopathy is complex and multifactorial, involving an interplay between cellular and plasmatic elements of the haemostatic system and components of the innate immune response to the infecting pathogen.<sup>25,26</sup> This study emphasized the need for a better understanding of this interplay in severe COVID-19 pneumonia.<sup>27</sup>

The scattered areas of diminished pulmonary perfusion as encountered in the COVID-19 ICU patients included in this study are strikingly different from the perfusion defects that are commonly seen on these scans.<sup>28-30</sup> The currently available evidence suggests that these perfusion defects cannot only be attributed to acute lung injury or mechanical ventilation,<sup>31,32</sup> but are rather unique for severe COVID-19 pneumonia. Peripheral perfusion defects were also seen in the included ward patients with pulmonary embolism but occurred adjacent to the embolism. Pulmonary embolism only partly explained the perfusion defects in ICU patients, as these also occurred without any adjacent intravascular filling defects. Perfusion defects have long been known to emerge after pulmonary embolism as they were frequently observed on regular nuclear V/Q scans.<sup>33</sup> Clinically, over the last decade dual energy CT scanners proved to provide comparable functional imaging by iodine density maps as surrogates of lung perfusion.<sup>28,29,34</sup> In pulmonary embolism the imaging defects are regularly confined to the periphery, and only infrequently cover more than a third of the normal pulmonary area.

In our study perfusion defects extended in some areas beyond the boundaries of consolidations and ground glass opacities into quite normal appearing lung tissue. Absent perfusion in normally aerated lung tissue is detrimental, certainly in the context of pneumonia, as it will cause additional dead space ventilation and may redirect pulmonary blood flow to poorly- or non-aerated lung tissue resulting in additional shunt and therefore hypoxemia. In pulmonary embolism outside the context of COVID-19, the thrombotic burden and diminished lung perfusion areas could result in an increase in the afterload of the right ventricle, which then could lead to right ventricular dysfunction and acute heart failure,<sup>17,35</sup> however between our two groups no significant differences were seen with regard to signs of right ventricular dysfunction. A possible explanation may be that regulatory vasodilatation occurs in other regions, which aggravates shunt, although we are uncertain about the mechanism through which this is regulated. The large areas of severely diminished

perfusion most likely reflect diffuse pulmonary microcirculation dysfunction that is irrespective of the presence of pulmonary embolism. Pinpointing the exact location of the microcirculatory blood flow disturbances is challenging, yet important to better understand the pathophysiological substrate of our findings. Our findings are consistent with a recent case report that also suggested vascular and perfusion abnormalities in severe COVID-19 pneumonia,<sup>7</sup> although the extent of the perfusion defects is much more evident in this present study.

The strength of our study is that all patients underwent advanced imaging using a high-end dual source CT-scanner dedicated to COVID-19 patients. This limits the chance of measuring artefacts, although even then technical challenges remain. Our study also has several limitations. First, this is a single centre study using a cross sectional design which does not allow to make any causal inferences with regard to the pathophysiology or order of events. Second, we used semi-quantitative scores for single pass CT perfusion evaluation. Quantitative measurements for image analysis require a time-consuming procedure, and above that are not validated for the investigated questions. Also, we did not prospectively calculate the dead-space and shunt fractions in the included patients and were unable to link the imaging results with gas-exchange.<sup>36</sup> Finally, we cannot assess the impact of positive pressure ventilation on the observed perfused blood volumes and perfusion defects. Although the effect of positive pressure ventilation on lung perfusion is well known, little data is available on the changes in regional perfusion defects like we observed. Two animal studies applying positive pressure ventilation did not report any perfusion defects similar to what we describe here.<sup>31,37</sup>

In conclusion, Invasively mechanically ventilated ICU patients with severe COVID-19 frequently develop pulmonary embolism and also show large scattered areas of severely diminished perfusion consistent with diffuse pulmonary microcirculatory dysfunction. These defects are independent of the presence of pulmonary embolism, possibly reflective of microthrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

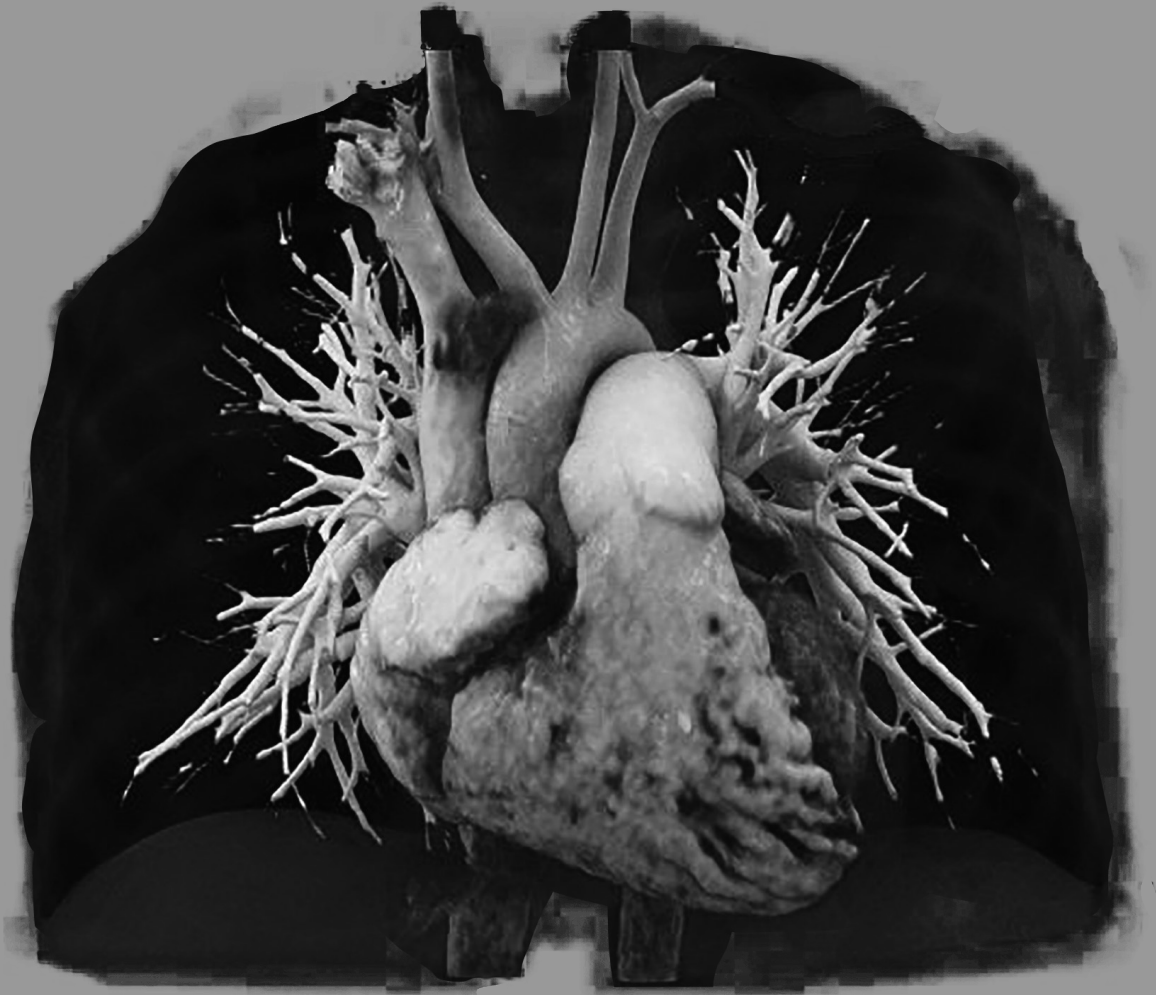
## References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)* 2020; **395**(10223): 497-506.
2. Arabi YM, Murthy S, Webb S. COVID-19: a novel coronavirus and a novel challenge for critical care. *Intensive care medicine* 2020; **46**(5): 833-6.
3. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama* 2020; **323**(16): 1574-81.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)* 2020; **395**(10229): 1054-62.
5. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(8):1995-2002
6. van de Veerdonk FL, Netea MG, van Deuren M, et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. *eLife* 2020; **9**:e57555.
7. Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *The Lancet Infectious diseases* 2020; **20**(12):1365-1366
8. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thrombosis and haemostasis* 2020; **120**(6): 998-1000.
9. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *American journal of clinical pathology* 2020; **153**(6): 725-33.
10. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2020; **15**(5): 700-4.
11. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Annals of internal medicine* 2020; **173**(4): 268-77.
12. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *British journal of haematology* 2020; **189**(5): 846-7.
13. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive care medicine* 2020; **46**(6): 1099-102.
14. Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**(2): E97-E104.
15. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected

- pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet (London, England)* 2017; **390**(10091): 289-97.
16. Masy M, Giordano J, Petyt G, et al. Dual-energy CT (DECT) lung perfusion in pulmonary hypertension: concordance rate with V/Q scintigraphy in diagnosing chronic thromboembolic pulmonary hypertension (CTEPH). *European radiology* 2018; **28**(12): 5100-10.
  17. Beenen LFM, Bossuyt PMM, Stoker J, Middeldorp S. Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism. *The European respiratory journal* 2018; **52**(1): 1702611
  18. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research* 2020.
  19. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis research* 2020; **191**: 9-14.
  20. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(7): 1743-6.
  21. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research* 2020; **191**: 145-7.
  22. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(6): 1421-4.
  23. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive care medicine* 2020; **46**(6): 1089-98.
  24. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020; **77**(2): 198-209.
  25. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(4): 844-7.
  26. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(4): 786-7.
  27. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive care medicine* 2020; **46**(6): 1105-8.
  28. Meinel FG, Graef A, Sommer WH, Thierfelder KM, Reiser MF, Johnson TR. Influence of vascular enhancement, age and gender on pulmonary perfused blood volume quantified by dual-energy-CTPA. *European journal of radiology* 2013; **82**(9): 1565-70.
  29. Singh R, Nie RZ, Homayounieh F, Schmidt B, Flohr T, Kalra MK. Quantitative lobar pulmonary perfusion assessment on dual-energy CT pulmonary angiography: applications in pulmonary embolism. *European radiology* 2020; **30**(5): 2535-42.

30. Otrakji A, Digumarthy SR, Lo Gullo R, Flores EJ, Shepard JA, Kalra MK. Dual-Energy CT: Spectrum of Thoracic Abnormalities. *Radiographics : a review publication of the Radiological Society of North America, Inc* 2016; **36**(1): 38-52.
31. Kay FU, Beraldo MA, Nakamura MAM, et al. Quantitative Dual-Energy Computed Tomography Predicts Regional Perfusion Heterogeneity in a Model of Acute Lung Injury. *Journal of computer assisted tomography* 2018; **42**(6): 866-72.
32. Schuster DP, Anderson C, Kozlowski J, Lange N. Regional pulmonary perfusion in patients with acute pulmonary edema. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2002; **43**(7): 863-70.
33. Thieme SF, Becker CR, Hacker M, Nikolaou K, Reiser MF, Johnson TR. Dual energy CT for the assessment of lung perfusion--correlation to scintigraphy. *European journal of radiology* 2008; **68**(3): 369-74.
34. Abdellatif W, Ebada MA, Alkanj S, et al. Diagnostic Accuracy of Dual-Energy CT in Detection of Acute Pulmonary Embolism: A Systematic Review and Meta-Analysis. *Canadian Association of Radiologists journal = Journal l'Association canadienne des radiologistes* 2021; **72**(2): 285-92.
35. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *European heart journal* 2020; **41**(4): 543-603.
36. Ospina-Tascon GA, Bautista DF, Madrinan HJ, et al. Microcirculatory dysfunction and dead-space ventilation in early ARDS: a hypothesis-generating observational study. *Annals of intensive care* 2020; **10**(1): 35.
37. Chai X, Zhang LJ, Yeh BM, Zhao YE, Hu XB, Lu GM. Acute and subacute dual energy CT findings of pulmonary embolism in rabbits: correlation with histopathology. *The British journal of radiology* 2012; **85**(1013): 613-22.





# **PART IV**

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**General Discussion and Appendix**





# **Chapter 9**

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**General discussion & future aspects**



## General discussion

In this thesis I examined the possibilities of improving the diagnostic management strategy and risk assessment of patients suspected to have pulmonary embolism (PE). With computed tomography pulmonary angiography (CTPA) not only the presence of pulmonary emboli can be established, but also risk estimation can be derived from various radiological parameters. In this way, use of imaging can be further optimized.

This thesis is divided into three parts. *Part I* focuses on the improvements in diagnostic decision support for patients with the suspicion of a pulmonary embolism. In *Part II*, for patients with confirmed pulmonary emboli the additional value of findings on CTPA in risk assessment and prognosis is explored. In *Part III*, the interaction between COVID-19 and VTE is discussed.

### ***PART I - DIAGNOSIS***

An important step in the evaluation of the suspicion of pulmonary embolism is the decision whether a patient has to undergo imaging to confirm or exclude the diagnosis. To this end, several diagnostic strategies have been developed, that include both a clinical decision rule and d-dimer test to assess the probability of pulmonary embolism. A ‘pulmonary embolism unlikely’ clinical decision rule with a negative D-dimer result safely excludes pulmonary embolism in 30% of presenting patients.

In **chapter 2** we aimed to simplify this diagnostic approach and to increase its efficiency. Data of two large prospective multicentre cohort studies in the Netherlands with consecutive patients suspected of pulmonary embolism were used for derivation and subsequent validation. After constructing a logistic regression model with the known D-dimer test result and items from the Wells clinical decision rule, we identified the most prevalent combinations of informative items and selected new D-dimer thresholds. In addition to a given D-dimer test result only three Wells items showed significant incremental value: haemoptysis, signs of deep vein thrombosis and ‘pulmonary embolism most likely diagnosis’. Two groups were identified in whom pulmonary embolism could be excluded without CTPA: (1) none of these three items positive and a d-dimer lower than 1000 ng/mL D-dimer; (2) one or more of these items positive and a d-dimer lower than 500 ng/mL. In this post-hoc analysis, pulmonary embolism could be excluded without CTPA in 36%, at a false-negative rate of 1.2%. (95% CI 0.04-3.3%). Combining the D-dimer test result with items of the Wells score resulted in a simple clinical decision rule with a high sensitivity and a significantly higher specificity compared to the previously most widely used diagnostic algorithm, i.e. the Wells score-D-dimer combination. We called this algorithm the YEARS algorithm, after Café De Jaren (Dutch for “years”)

where the investigators met to discuss these findings.

This newly developed YEARS clinical decision rule that incorporates differential D-dimer cut-off values at presentation has been developed to reduce the number of CTPA investigations in all age groups. Before its implementation in clinical practice could be considered, a prospective validation study of this clinical decision rule was needed; the results are described in **chapter 3**. In this prospective multicentre study in 12 hospitals in the Netherlands 3465 patients were assessed of whom 13% were diagnosed with pulmonary embolism. Of the 85% in whom pulmonary embolism was ruled out according to the YEARS algorithm and remained untreated, 0.6% (95% CI 0.36–0.96) of these patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up. CTPA was not indicated in 48% of patients, i.e. a 14% absolute decrease of CTPA examinations compared to the Wells' rule and fixed D-dimer threshold of less than 500 ng/mL.

## ***PART II - PROGNOSIS***

Prognosis of pulmonary embolism is determined primarily by the hemodynamic status of the patient. In general, the burden of embolic clots exerts a negative impact on the heart leading to right ventricular dysfunction (RVD). According to the ESC guidelines, in intermediate and low risk patients, prognosis is further refined by assessing the (simplified) PESI- pulmonary embolism severity index, combined with signs of right ventricular dysfunction. Apart from laboratory tests (NT-pro BNP) or echocardiography, information on right ventricular dysfunction also can be derived from the CTPA establishing the diagnosis of pulmonary embolism, although no general consensus exists on which of the parameters should be used.

In **chapter 4** the value of various cardiovascular CTPA parameters for prognosis and risk stratification on short- and long-term clinical outcomes were evaluated. Radiological and clinical data of 1950 patients with acute pulmonary embolism who participated in an international randomized clinical trial on anticoagulants (Hokusai VTE) were used. Studied parameters were right/left ventricular ratio, septal bowing, cardiothoracic ratio, diameters of pulmonary trunk and aorta, and intrahepatic/azygos vein contrast medium backflow. Associations with mortality, recurrent venous thromboembolism, hospitalization, bleeding and adverse events were assessed over the short term and long term. Pulmonary trunk enlargement was the only parameter significantly associated with mortality over both the short and long term, as well as with recurrent VTE and hospitalization.

In **chapter 5** the association of body mass index (BMI) with prognostic indicators and clinical outcomes in patients with pulmonary embolism was studied. Patients were analysed with regard to World Health Organization (WHO) BMI categories at the time of inclusion in the trial. We found that several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism

were not evenly distributed among BMI categories. The relationship between BMI categories and both prognostic parameters and clinical outcomes showed U-shaped curves, reflected in a trend towards worse outcomes in patients who are either overweight or underweight.

Apart from excluding or confirming a diagnosis of pulmonary embolism, CTPA also can provide an alternative diagnosis. When such a pathology is present together with pulmonary embolism this could increase the disease burden a patient has to cope with, and potentially could negatively influence survival. In **chapter 6** we aimed to determine the impact of concurrent cardiac and pulmonary disease identified on the diagnostic CTPA on clinical outcome of acute pulmonary embolism. We assessed occurrence and severity of a variety of comorbidities (pleural fluid, pericardial fluid, consolidations, coronary and aortic calcifications) and clinical and radiological prognostic characteristics for right ventricular dysfunction. Concomitant disease was present in 66.6% of all patients. Compared to patients without concomitant diseases, the odds for mortality with presence of mild, moderate and severe disease on CTPA was 4.9, 10.4 and 32 (95% CI 1.4-16.8, 3.0-36.2 and 10.0-115.9; and adjusted for sPESI and age 3.4, 4.8 and 15.3; (95% CI 1.0-11.9, 1.3-17.6 and 4.3-54.8). This stepwise association between disease severity and mortality was apparent in all evaluated CTPA findings. Concomitant disease observed on the baseline CTPA in patients with acute pulmonary embolism thus impacts mortality and may be of additional value in risk stratification and prognosis.

### ***PART III - COVID***

At present, Coronavirus disease 2019 (COVID-19) is dominating medicine and the world. Thrombosis, both VTE and arterial has proven to be a striking complication of COVID-19, as a consequence of marked coagulation activation and coagulopathy. In **chapter 7** we investigated the incidence of venous thromboembolism in 198 hospitalized patients with COVID-19 during the first wave of the pandemic. During a median follow-up of seven days 20% of patients were diagnosed with VTE, of whom 13% had symptomatic VTE, despite routine thrombosis prophylaxis. The cumulative incidence of VTE at 21 days was 42%, and was much higher in the ICU than on the wards. So, the observed risk for VTE in COVID-19 is high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or pulmonary embolism.

In **chapter 8** we evaluated pulmonary perfusion characteristics of COVID-19 patients with a suspicion of pulmonary embolism using dual energy CTPA. We found that invasively mechanically ventilated ICU patients with severe COVID-19 not only can develop pulmonary embolism but also show large scattered areas of severely diminished perfusion consistent with diffuse pulmonary microcirculatory dysfunction. These defects seem to be independent of the presence of pulmonary

embolism, possibly reflecting microthrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

## Future aspects

A clinical decision rule should be robust, reliable, intuitive, and easy to use. The YEARS algorithm allows the physician to exclude pulmonary embolism in a large proportion of patients without using imaging. For the future it seems however challenging to further optimize this algorithm. To further increase efficiency, probably more parameters should be incorporated, which in turn would complicate the decision process, and thus compromises the user-friendliness and willingness to use it in clinical practice. The role of the YEARS algorithm in different subgroups and populations is of interest, such as inpatients, patients with cancer and patients with COPD. Also for critical care patients it would be of value, as in this population an additional downside of the need for imaging is the disadvantage of transporting such patients with associated risk for complications. After publication of the YEARS algorithm, it has been investigated for pregnant women in the Artemis study and confirmed to be a safe and useful strategy, with a small adaptation with compression ultrasonography in case of signs of DVT. At present the multicentre HYDRA study is including patients with cancer and a suspicion of pulmonary embolism.

With respect to assessing prognosis, large scale prospective studies on the role of radiological cardiovascular parameters in risk stratification, both separately as well as in combination with other biomarkers, will be needed to confirm the findings and clinical impact presented in this thesis. This could be approached from two sides: looking at the negative predictive value, or focussing on the prognostic value: which patients carry a very low risk and can be discharged home safely, and in which patients is a more aggressive therapeutic approach warranted?

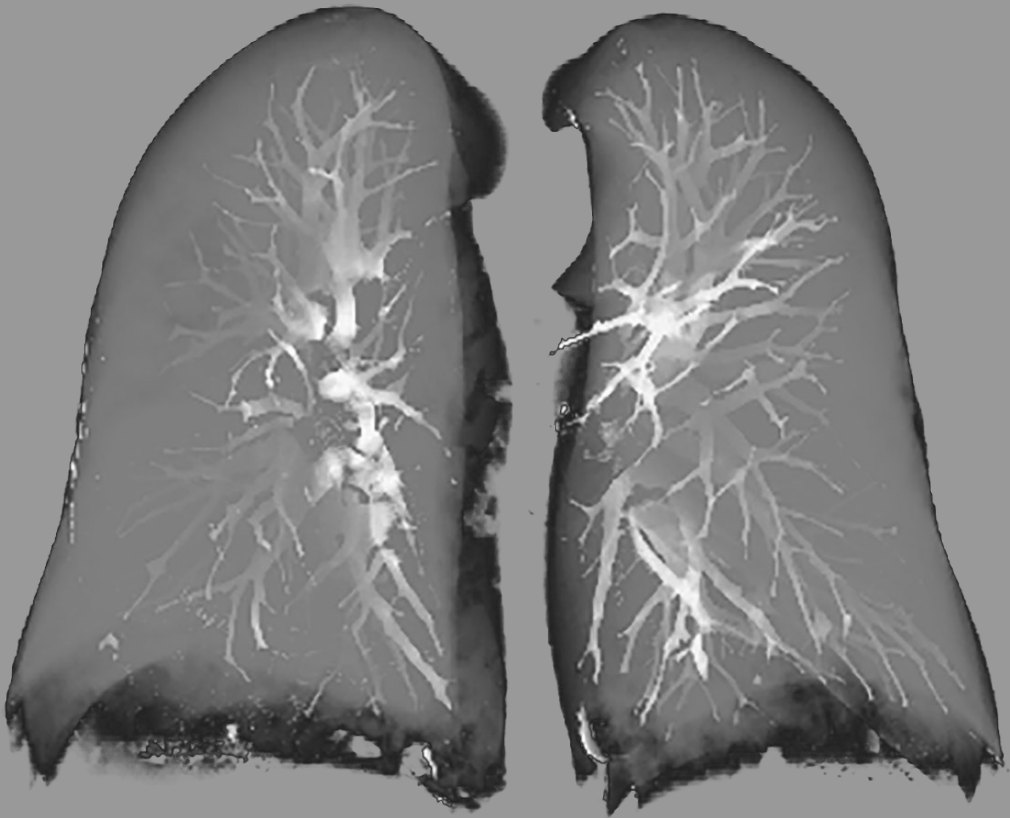
Concomitant pathologies on CTPA can probably be regarded as modifiers in risk estimation for both the intermediate and low risk categories, with impact on either the decision about home treatment, or close clinical monitoring on the other side of the spectrum.

Many potential parameters have been suggested for prognostication, yet are not integrated in clinical practice as these are too difficult in the daily work flow. Meta-analyses of individual patient data with pooling of (un)published results from large registries and clinical trials could potentially provide opportunities for subgroup analyses and adjustment for confounders in prognostication. Standardized reporting

of radiological, clinical and biochemical parameters into an integral format could be of additional value. Future studies should explore imbedding these uniformly reported findings in artificial intelligence programmes integrated into electronic patient data programs.

In Covid-19, future research should focus on optimal diagnostic and prophylactic strategies of VTE that may potentially improve survival of patients. Characterization of the different pulmonary and extra-pulmonary manifestations on CT both with and without associated pulmonary embolism could be supported by AI algorithms to better understand the time course of the disease. Evaluation of the prevalence and the extent of pulmonary perfusion defects observed in CTPA and their effect on physiology and outcome should be studied both in ward and ICU patients. Its influence on microcirculation and gas exchange could be a factor in choosing the appropriate ventilation strategy in critical care patients, but this has to be proven in larger prospective studies. Even though the pandemic of COVID-19 is improving, the lessons learned may be of benefit to optimize use of radiological assessments in other pneumonias.





# **Chapter 10**

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Appendix



## Summary

In this thesis the possibilities of improving the clinical workflow and risk assessment of patients with the suspicion of a pulmonary embolism in general, and in specific populations and circumstances have been explored.

Part I of this thesis focuses on the improvements in diagnostic decision support for patients with the suspicion of a pulmonary embolism. In Part II, for patients with proven pulmonary embolism, the additional value of findings on CTPA in risk assessment and prognosis is explored. In Part III, the interaction between COVID-19 and pulmonary embolism and deep vein thrombosis is discussed.

### *Part I*

In **chapter 2** we aimed to simplify the diagnostic approach for the use of CTPA in patients with a suspicion of pulmonary embolism. Data of 723 consecutive patients were analysed post hoc, and the results validated in 2785 consecutive patients suspected of pulmonary embolism of two prospective multicentre cohort studies in the Netherlands, respectively. Of the regular used clinical decision rule, only three Wells items significantly added incremental value to the D-dimer test: haemoptysis, signs of deep vein thrombosis and ‘pulmonary embolism most likely’. We identified two groups: (i) none of these three items positive and a 1000 ng/L D-dimer threshold; (ii) one or more of these items positive and 500 ng/L threshold. Combining Wells items with the D-dimer test resulted in a simplified decision rule, which reduces the need for CTPA in patients with suspected pulmonary embolism.

This YEARS algorithm that incorporates differential D-dimer cut-off values at presentation has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. In **chapter 3** we prospectively evaluated this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism in 3465 patients in 12 hospitals in the Netherlands. We concluded that pulmonary embolism could be safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients was the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

### *Part II*

In part II different perspectives on prognostication of patients with pulmonary embolism were studied, by using radiological and clinical data of 1950 patients with acute pulmonary embolism who participated in the Hokusai VTE-trial, an international randomized clinical trial on anticoagulants.

In **chapter 4** we evaluated the impact of specific cardiovascular radiological parameters on short and long-term clinical outcomes. Most of the evaluated

radiological parameters did not have strong effects on outcome in patients with acute pulmonary embolism. Only an enlarged pulmonary trunk diameter had an increased risk of mortality with odds ratio after 1 week of 4.2 (95% CI 1.04–16.8) and recurrent VTE up to 12 months, and can be used for risk stratification.

In **chapter 5** we explored the impact of body mass index (BMI) on prognostic indicators and clinical outcomes in patients with pulmonary embolism. We observed that several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism are not evenly distributed among the BMI categories. This is reflected in a trend towards worse outcomes in patients who are overweight and those who are underweight, giving it an impression of U-shaped curves.

In **chapter 6** the impact of concurrent cardiopulmonary disease identified on the diagnostic CTPA on clinical outcome of acute pulmonary embolism was determined. Concomitant disease observed on the baseline CTPA in patients with acute pulmonary embolism impacts mortality in a severity dependent manner, and may be of additional value in risk stratification and prognosis.

### ***Part III***

Coronavirus disease 2019 (COVID-19) can lead to systemic coagulation activation and thrombotic complications. In **chapter 7** we investigated the incidence of objectively confirmed venous thromboembolism in 198 hospitalized patients with COVID-19. The observed risk for VTE in COVID-19 is very high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or pulmonary embolism.

In **chapter 8** we observed that invasively mechanically ventilated ICU patients with severe COVID-19 not only can develop pulmonary embolism but also show large scattered areas of severely diminished perfusion on dual energy CTPA, consistent with diffuse pulmonary microcirculatory dysfunction. These defects seem to be independent of the presence of pulmonary embolism, possibly reflective of micro thrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

## Samenvatting

In dit proefschrift heb ik mogelijkheden voor de verbetering van de klinische evaluatie en risicoschatting bij patiënten die van een longembolie verdacht worden onderzocht. Dit niet alleen in algemene zin, maar ook voor specifieke subgroepen en omstandigheden.

Deel I van het proefschrift richt zich op de verbeteringen in de beslisondersteuning bij patiënten met verdenking op een longembolie. In deel II werd bij patiënten met een bewezen longembolie de aanvullende waarde van CT voor de inschatting van de prognose bekeken. In deel III werd de samenhang tussen COVID-19 en longembolie en diepe veneuze trombose onderzocht.

### *Deel I*

In **hoofdstuk 2** hebben we ons gericht op de verbetering van de diagnostiek met behulp van een CT bij patiënten met de verdenking op een longembolie. Daarbij werden uit twee grote Nederlandse cohorten data van 723 patiënten achteraf geanalyseerd, en vervolgens gevalideerd in 2785 opeenvolgende patiënten die verdacht werden van een longembolie. Van de regulier gebruikte Wells criteria bleken slechts drie een toegevoegde waarde te hebben als een d-dimeer reeds bekend was: bloed ophoesten, tekenen van een trombosebeen, en inschatting dat een longembolie de meest waarschijnlijke diagnose was. Daarbij konden twee groepen onderscheiden worden: 1) geen enkele van deze items was aanwezig; hierbij was een grens van 1000 ng/mL d-dimeer gesteld; of 2) een of meer van de drie items aanwezig, waarbij er een grens van 500 ng/mL voor de d-dimeer gehanteerd wordt. Op deze manier kon door een combinatie van de d-dimeer met genoemde items een makkelijk toepasbare beslisregel worden ontwikkeld.

Dit YEARS algoritme met verschillende D-dimeer afkapwaarden bij presentatie heeft tot doel om vlot, de klinische praktijk volgend, het aantal onnodige CT-scans te reduceren voor alle leeftijdscategorieën. In **hoofdstuk 3** werd deze simpele beslisregel prospectief gevalideerd in 3465 patiënten met de verdenking op een longembolie in 12 Nederlandse ziekenhuizen. We zagen dat longembolie veilig kon worden geëxcludeerd door YEARS. Het belangrijkste voordeel was de absolute afname met 14% van het aantal CT-scans in alle leeftijdscategorieën en in de verschillende subgroepen.

### *Deel II*

In deel II werden verschillende gezichtspunten t.a.v. het prognosticeren van patiënten met bewezen longembolie bestudeerd. Daartoe werden data gebruikt van 1950 patiënten uit een grote internationale gerandomiseerde trial van anticoagulantia, de Hokusai-VTE.

In **hoofdstuk 4** werd de impact van specifieke cardiovasculaire parameters bestudeerd op zowel de korte als de lange termijn uitkomsten. De meeste van de onderzochte parameters bleken niet van waarde te zijn bij de prognosevorming. Alleen een verbrede longslagader bleek geassocieerd met een verhoogde sterftkans (na 1 week Odds ratio van 4.2 met 95% betrouwbaarheidsinterval 1.04-16.8) en recidief trombo-embolie tot 12 maanden, en kan dus voor risicostratificatie ingezet worden.

In **hoofdstuk 5** werd de impact van de lichaamscompositie op basis van de BMI (body mass index) op de prognostische indicatoren en klinische uitkomsten bij longembolie bestudeerd. We zagen dat enkele klinische en radiologische prognostische karakteristieken en dysfunctie van de rechterhartkamer niet gelijkmatig verdeeld waren tussen de verschillende BMI-categorieën. Slechtere uitkomsten werden vaker gezien bij mensen met overgewicht of ondergewicht, resulterend in U-vormige curve.

In **hoofdstuk 6** werd de invloed van diverse andere cardiopulmonale afwijkingen op de CT longembolie ten aanzien van de klinische uitkomsten geanalyseerd. Het bleek dat gelijktijdige aanwezigheid van deze afwijkingen en longembolie op de CT effecten hebben op de sterfte, met een sterker effect bij ernstiger afwijkingen. Dit kan van belang zijn bij de risico stratificatie en prognose.

### ***Deel III***

Coronavirus ziekte-19 kan leiden tot stollingsstoornissen en trombotische complicaties. In **hoofdstuk 7** onderzochten we het voorkomen van trombosebenen en longembolieën bij 198 opgenomen patiënten met COVID-19. Het risico op veneuze trombo-embolie is zeer hoog, met name bij IC-patiënten, en zal derhalve tot een hoge mate van verdenking moeten leiden, en tot een laagdrempelig gebruik van aanvullende diagnostiek.

In **hoofdstuk 8** stelden we vast dat bij beademde IC-patiënten met ernstige COVID-19 op een zogenaamde dual energy CT er niet alleen longembolieën maar ook grote perfusiedefecten zichtbaar zijn. Dit bleek ook los van longembolieën op te treden, vermoedelijk door stoornissen in de microcirculatie van de longen. De combinatie van uitgebreide doorbloedingsdefecten en grote afwijkingen in het longweefsel kan de ernstige en aanhoudende ademhalingsproblemen verklaren zoals die vaak optreden bij beademde patiënten met een ernstige COVID-19 longontsteking.

**List of abbreviations**

CDR	Clinical Decision Rule
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CTPA	CT Pulmonary Angiography
DECT	Dual Energy CT
DVT	Deep Venous Thrombosis
ESC	European Society of Cardiology
IQR	Interquartile Range
LV	Left Ventricle
NPV	Negative Predictive Value
OR	Odds Ratio
PE	Pulmonary Embolism
PESI	Pulmonary Embolism Severity Index
PET	Positron Emission Tomography
PPV	Positive Predictive Value
PT	Pulmonary Trunk
RA	Right Atrium
RV	Right Ventricle
RVD	Right Ventricular Dysfunction
sPESI	Simplified PESI
US	Ultrasound
V/Q	Ventilation/perfusion
VTE	Venous Thromboembolism



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	Institute/location	Year	Workload (ECTS)
<b><i>General courses – 8.4 ECTS</i></b>			
AMC World of Science	AMC Graduate School	2014	0.7
Embase/Medline via OVID	AMC Graduate School	2014	0.1
Endnote	AMC Graduate School	2014	0.1
Medical Literature: Searching for a Systematic Review	AMC Graduate School	2014	0.1
Clinical Epidemiology: Evaluation of Medical Tests	AMC Graduate School	2014	0.9
Practical Biostatistics	AMC Graduate School	2014	1.4
Randomized Controlled Trials		2014	0.6
Clinical Epidemiology 2: Observational Epidemiology, Effects and Effectiveness	AMC Graduate School	2014	0.6
Evaluation of Medical Tests	AMC Graduate School	2014	0.1
Systematic Reviews	AMC Graduate School	2014	0.7
The Art of Scientific Writing	AMC Graduate School	2014	1.5
Oral Presentation in English	AMC Graduate School	2014	0.5
<b><i>Specific courses</i></b>			
BROK-GCP Herregistratie	VUMC	2015	0.1
EBRO Cursus	Utrecht	2016	0.2
Sprekerstraining Spies	NVVR, Nijmegen	2017	0.2
Teach The Teacher Good Practice Opleiden	Laren	2018	0.1
Teach the Teacher - KPБ	AMC Amsterdam	2018	0.1
Teach the Teacher - Voortgangsgesprek	AMC Amsterdam	2019	0.1
Symposium Update Regelgeving Klinisch Onderzoek - Herregistratie BROK	AMC Amsterdam	2019	0.1
Sprekerstraining Herreboot	NVVR, Hilversum	2020	0.2
<b><i>Conferences and symposia (selected) – 34.4 ECTS</i></b>			
RSNA 100 <sup>th</sup> Scientific Assembly & Annual meeting	RSNA, Chicago	2014	1.4
ECR	ESR, Wenen	2015	1.0
16 <sup>th</sup> European Congress of Trauma & Emergency Surgery	ECTES, Amsterdam	2015	0.5

4 <sup>th</sup> Congress International Society of Forensic Radiology and Imaging	Isfri, Leicester	2015	0.6
Ultra-Low Dose Cardiopulmonary CT Imaging – The State of the Art	UMC Utrecht	2015	0.1
26 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASE, Miami	2015	1.1
Platform Medisch Leiderschap Tweede Masterclass	Schola Medica, Utrecht	2015	0.1
Sectiedag Cardiovasculaire Radiologie, Cardiale beeldvorming middels CT en MRI: stand van zaken uitgelicht	Utrecht	2015	0.1
DECT in Radiology and Radiobiology	Maastricht	2015	0.2
5e NTVG-Dag. Kunst en Kunde	NTvG Amsterdam	2015	0.1
RSNA 101 <sup>th</sup> Scientific Assembly & Annual meeting	Chicago, USA	2015	1.4
Symposium Heart for women	Radboud UMC Nijmegen	2016	0.2
Sectiedag MSK	NVvR, Amersfoort	2016	0.1
9e Symposium Complicaties in de Traumachirurgie	AMC Amsterdam	2016	0.2
Radiologie Festival CT en de toekomst: CT bij MCI	VUmc Amsterdam	2016	0.2
Jaarlijkse sectiedag Acute Radiologie	NVvR, Hilversum	2016	0.1
5 <sup>th</sup> Congress International Society of Forensic Radiology and Imaging	ISFRI, Amsterdam	2016	0.5
27 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, San Francisco	2016	1.1
Patient symposium World Thrombosis Day	AMC Amsterdam	2016	0.1
Openingssymposium SEH van de Toekomst	AMC Amsterdam	2016	0.1
ESGAR Workshop Acute Abdomen	ESGAR Amsterdam	2016	0.4
Rembrandt symposium Longembolie	Amsterdam	2016	0.4
LNAZ symposium Improving trauma care: trauma system evaluations in an international perspective	Utrecht	2016	0.2
6e NTVG-Dag. Kunst en Kunde	NTvG, Amsterdam	2016	0.1
Sectievergadering Cardiovasculaire Radiologie	NVVR, Utrecht	2016	0.1
Symposium Advances in Intra-arterial Treatment of Acute Ischemic Stroke	Amsterdam	2016	0.1
Sectievergadering Abdomen Radiologie oncologische beeldvorming een handleiding voor de dagelijkse praktijk	AvL, Amsterdam	2016	0.1
Sectiedag thorax	NVVR, Utrecht	2016	0.1
RSNA 102 <sup>nd</sup> Scientific Assembly & Annual meeting	RSNA, Chicago	2016	1.4
ESER/BSER Annual Scientific Meeting	ESER, Londen	2017	0.5
6 <sup>th</sup> ISFRI Congress	ISFRI, Denemarken	2017	0.6
Symposium Mens in Beeld: Beeldvorming van infectie en inflammatie in de longen.	UMC Utrecht	2017	0.1
28 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Toronto	2017	1.1

Sectiedag Cardiovasculaire Radiologie	NVVR, Utrecht	2017	0.1
RSNA 103 <sup>rd</sup> Scientific Assembly & Annual meeting	RSNA, Chicago	2017	1.4
Jaarlijkse sectiedag Thorax Radiologie	NVvR, Utrecht	2017	0.1
SWC op weg naar de toekomst - stip op de horizon	NVVR, Utrecht	2018	0.1
KNMG Masterclass Calamiteiten in de regio	UMC Utrecht	2018	0.1
Congres opgeschaalde zorg	LNAZ, Amsterdam	2018	0.2
ESTI/ESCR Joint Meeting	ESTI/ESCR Geneve	2018	0.6
ESSR Annual Scientific Meeting	ESSR, Amsterdam	2018	0.5
4th Annual ACS symposium, Oosterkerk	ACS Amsterdam	2018	0.2
Sectiedag Forensische Radiologie	NVVR, Den Bosch	2018	0.1
Amstol symposium	AMC Amsterdam	2018	0.2
28 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Virginia	2018	1.1
Jaarlijkse sectiedag Thorax Radiologie	NVvR, Utrecht	2018	0.1
Sectiedag Cardiovasculaire Radiologie	NVVR Amsterdam	2018	0.1
Sectiedag Abdomen Radiologie	NVVR, Den Haag	2018	0.1
RSNA 104 <sup>th</sup> Scientific Assembly & Annual Meeting	RSNA, Chicago	2018	1.4
Hora Est Minisymposium	AMC Amsterdam	2018	0.1
Sandwichcursus Nucleaire geneeskunde	NVvR, Ede	2019	0.2
ECR	ESR, Wenen	2019	1.0
Sectiedag Cardiovasculaire Radiologie	NVvR, UMC Utrecht	2019	0.1
Contrast Stroke consortium meeting	UMCG Groningen	2019	0.2
Sectiedag MSK NL-BE Radiologie	NVvR, Leiden	2019	0.2
Spoedzorgnet Thema avond reanimatie ECMO en eCPR		2019	0.1
ESCR 2019 Cardiac Imaging Annual Scientific Meeting	ESCR, Antwerpen	2019	0.6
Sectiedag thorax	NVVR, Utrecht	2019	0.1
RSNA 105 <sup>th</sup> Scientific Assembly & Annual meeting	RSNA, Chicago	2019	1.4
Trauma Complicatiecongres2.9	AMC, Amsterdam	2020	0.2
SWC Zichtbaar Leiderschap	NVVR, Ede	2020	0.1
Sandwichcursus Thoraxradiologie	NVVR, Ede	2020	0.2
31 <sup>st</sup> ESGAR Annual Meeting and Postgraduate Course	ESGAR Amsterdam	2020	0.7
Radiologendagen bij je thuis	NVVR	2020	0.3
Postcovid care Live Event: Post-COVID-19 care and research at Amsterdam UMC	Amsterdam UMC	2020	0.2
ISTH 2020 Virtual Congress	ISTH, Online	2020	0.2

ECR European Congress of Radiology	ESR, Online	2020	1.0
ECR Highlights AI	ESR, Online	2020	0.2
ESC Congress 2020- The Digital Experience.	ESC, Online	2020	0.9
ECR Highlights: Abdomen, MSK, Cardio, Chest, Radiation, Children, Radiographers, Emergency Radiology, Interventional Radiology	ESR, Online	2020	1.4
Sectie Forensische en Postmortale Radiologie	NVVR, Online	2020	0.1
29 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Online	2020	1.2
43 <sup>rd</sup> Annual Meeting ESNR	ESNR, Online	2020	0.5
ESCR Congress	ESCR, Online	2020	0.5
Sectiedag Cardiovasculaire Radiologie	NVVR, Online	2020	0.1
FMS Symposium zorgevaluatie: de oogst van 5 jaar zorgevaluatie	FMS, Online	2020	0.1
Sectiedag Thorax Radiologie	NVvR, Online	2020	0.1
Amsterdam UMC & COVID-19: unorthodox teams, accelerating science	Amsterdam UMC	2020	0.2
EACVI online	ESC, Online	2020	0.2

### ***Seminars & Webinars***

ISTH Academy Webinar Acute PE: Administering Reperfu- sion Therapy		2016
ESCR Webinar Pulmonary Hypertension		2017
ACS Symposium The Female Factor in Thrombosis and Pulmonary Hypertension		2017
Venticare Live 2018, Jaarbeurs Utrecht		2018
Webinar ESR Artificial Intelligence		2019
Webinar FMS: COVID-19		2020
Webinar NIV: Dilemma rond behandeling en plaats CT-thorax bij COVID-19		2020
Webinar ISTH:Thrombosis, Thromboprophylaxis and Coagulopathy in COVID 19 Infections,		2020
Webinar ISTH thrombotic and hemostatic issues in critical care units managing COVID-19		2020
Webinar ESER   Post-Peak COVID: Where are we now		2020
Webinar ESCR "The role of the cardiovascular radiologist during the COVID-19 pandemic		2020
Webinar ISTH/EHA Coagulopathy in COVID-19 Patients: Latest Data, Recommendations, and Perspectives		2020
Webinar BIR: COVID-19 imaging		2020
Webinar ESCR Advanced Webinar "Imaging in vasculitis: MR, CT and more		2020
Webinar ISTH /Royal Society of Medicine.COVID-19 Series: Thrombotic complications		2020

ESCR Webinar Panta Rei	2020
Webinar Kansen voor machine learning in de acute keten	2020
ESCR Webinar Upcoming trends and techniques in cardiac CT	2020

***Presentations (selected)***

Sandwichcursus Acute & NeuroRadiologie	NVVR, Ede	2016	0.5
Radiologie Festival CT en de toekomst: CT bij MCI	VUMC Amsterdam	2016	0.2
27 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, San Francisco	2016	1.0
ESGAR Workshop Acute Abdomen	Amsterdam	2016	0.4
Rembrandt symposium Longembolie	Amsterdam	2016	0.4
28 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	Toronto, Canada	2017	1.1
Rembrandt symposium Longembolie CTEPH	Amsterdam	2017	0.4
Vaatlabcursus IVG	AMC Amsterdam	2017	0.2
Sandwichcursus Kinder - & Acute Radiologie	NVvR, Ede	2017	0.4
Sandwichcursus Acute & interventieradiologie	NVvR, Ede	2019	0.4
Radiologendagen NVVR	NVvR, Hilversum	2019	0.4
ECR	ESR, Wenen	2019	1.0
29 <sup>th</sup> ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Scottsdale	2019	1.1
Sandwichcursus Cardiovasculaire Radiologie	NVVR, Ede	2020	0.4
ACS Symposium Pulmonary hypertension, Update on the derivation and validation of the CO-RADS classification	AMC Amsterdam	2020	0.1
Amstel academie CTP/DECT	Amsterdam	2020	0.2
Nationale antistollingsdag,	Online	2020	0.1
NVTH COVID and VTE, PE and pulmonary perfusion	NVTH, Online	2020	0.2
RSNA 106 <sup>th</sup> Scientific Assembly & Annual meeting;	Online	2020	1.5

***Teaching***

	<b>Year</b>
<b><i>Teaching</i></b>	
Residents, students, technicians, radiologists, other physicians	2014-2021
<b><i>Supervising</i></b>	
Residents, students, technicians	2014-2021

***Awards/recognitions***

	<b>Year</b>
<b><i>Awards and Prizes</i></b>	
ASER Best oral presentation "cum laude"	2016
Fellow of American Society of Emergency Radiology	2020

## List of Publications

### 1990

1. Beenen LF, Scholten HG.  
Guillain-Barré syndrome following *Campylobacter jejuni* enteritis.  
Ned Tijdschr Geneeskd. 1990 May 19;134(20):1010-2.

### 1997

2. Roos YB, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M.  
Timing of surgery in patients with aneurysmal subarachnoid haemorrhage: rebleeding is still the major cause of poor outcome in neurosurgical units that aim at early surgery.  
J Neurol Neurosurg Psychiatry. 1997 Oct;63(4):490-3. doi: 10.1136/jnnp.63.4.490.

### 1999

3. Beenen LF, Lindeboom J, Kasteleijn-Nolst Trenité DG, Heimans JJ, Snoek FJ, Touw DJ, Adèr HJ, van Alphen HA.  
Comparative double blind clinical trial of phenytoin and sodium valproate as anticonvulsant prophylaxis after craniotomy: efficacy, tolerability, and cognitive effects.  
J Neurol Neurosurg Psychiatry. 1999 Oct;67(4):474-80. doi: 10.1136/jnnp.67.4.474.

### 2000

4. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M.  
Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands.  
J Neurol Neurosurg Psychiatry. 2000 Mar;68(3):337-41. doi: 10.1136/jnnp.68.3.337.
5. Postma TJ, Heimans JJ, Luykx SA, van Groeningen CJ, Beenen LF, Hoekstra OS, Taphoorn MJ, Zonnenberg BA, Klein M, Vermorken JB.  
A phase II study of paclitaxel in chemo-naïve patients with recurrent high-grade glioma.  
Ann Oncol. 2000 Apr;11(4):409-13. doi: 10.1023/a:1008376123066.
6. Beenen LF, Touw DJ, Hekker TA, Haring DA.  
Pharmacokinetics of intraventricularly administered teicoplanin in *Staphylococci* ventriculitis.  
Pharm World Sci. 2000 Aug;22(4):127-9. doi: 10.1023/a:1008719806949.



**2001**

7. Roos YB, Levi M, Carroll TA, Beenen LF, Vermeulen M.  
Nimodipine increases fibrinolytic activity in patients with aneurysmal subarachnoid hemorrhage.  
Stroke. 2001 Aug;32(8):1860-2. doi: 10.1161/01.str.32.8.1860.
8. Thomeer M, Vanbeckevoort D, Bielen D, Beenen L, Gevers A, Rutgeerts R, Marchal G.  
Virtual colonoscopy: a new screening tool for colorectal cancer?  
JBR-BTR. 2001 Aug;84(4):155-63.

**2002**

9. Roos YB, Dijkgraaf MG, Albrecht KW, Beenen LF, Groen RJ, de Haan RJ, Vermeulen M.  
Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis.  
Stroke. 2002 Jun;33(6):1595-9. doi: 10.1161/01.str.0000016401.49688.2f.

**2008**

10. Saltzherr TP, Fung Kon Jin PH, Bakker FC, Ponsen KJ, Luitse JS, Scholing M, Giannakopoulos GF, Beenen LF, Henny CP, Koole GM, Reitsma HB, Dijkgraaf MG, Bossuyt PM, Goslings JC.  
An evaluation of a Shockroom located CT scanner: a randomized study of early assessment by CT scanning in trauma patients in the bi-located trauma center North-West Netherlands (REACT trial).  
BMC Emerg Med. 2008 Aug 22;8:10. doi: 10.1186/1471-227X-8-10.

**2009**

11. Saltzherr TP, Goslings JC; multidisciplinary REACT 2 study group.  
Effect on survival of whole-body CT during trauma resuscitation.  
Lancet. 2009 Jul 18;374(9685):198; author reply 198-9. doi: 10.1016/S0140-6736(09)61324-6.
12. Saltzherr TP, Fung Kon Jin PH, Beenen LF, Vandertop WP, Goslings JC.  
Diagnostic imaging of cervical spine injuries following blunt trauma: a review of the literature and practical guideline.  
Injury. 2009 Aug;40(8):795-800. doi: 10.1016/j.injury.2009.01.015. Epub 2009 Jun 11.

**2010**

13. Rosmulder RW, Krabbendam JJ, Kerkhoff AH, Schinkel ER, Beenen LF, Luitse JS. ['Advanced triage' improves patient flow in the emergency department without affecting the quality of care]. *Ned Tijdschr Geneeskd.* 2010;154:A1109.
14. Aukema TS, Hietbrink F, Beenen LF, Leenen LP. Does thoracic injury impair the predictive value of base deficit in trauma patients? *Injury.* 2010 Apr 26. doi: 10.1016/j.injury.2010.04.003.
15. Saltzherr TP, Beenen LF, Reitsma JB, Luitse JS, Vandertop WP, Goslings JC. Frequent computed tomography scanning due to incomplete three-view X-ray imaging of the cervical spine. *J Trauma.* 2010 May;68(5):1213-7. doi: 10.1097/TA.0b013e3181b28aa4.
16. Lemmers M, Saltzherr TP, Beenen LF, Ponsen KJ, Goslings JC. Are routine repeat chest x-rays before leaving the trauma room useful? *Emerg Med J.* 2010 Jul;27(7):522-5. doi: 10.1136/emj.2009.078519. Epub 2010 Apr 1.

**2011**

17. Saltzherr TP, van der Vlies CH, van Lienden KP, Beenen LF, Ponsen KJ, van Gulik TM, Goslings JC. Improved outcomes in the non-operative management of liver injuries. *HPB (Oxford).* 2011 May;13(5):350-5. doi: 10.1111/j.1477-2574.2011.00293.x. Epub 2011 Mar 29.
18. Beenen LF, Adams R, Koster RW, Otto T. Computed tomography scanning during a traumatic resuscitation. *Am J Emerg Med.* 2011 Jun;29(5):572.e1-2. doi: 10.1016/j.ajem.2010.05.006. Epub 2010 Aug 1.
19. Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, van Houten AA, Hofstee HM, Klok FA, ten Cate H, Ullmann EF, Büller HR, Kamphuisen PW, Huisman MV; Prometheus Study Group. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. *Ann Intern Med.* 2011 Jun 7;154(11):709-18. doi: 10.7326/0003-4819-154-11-201106070-00002.

20. Paulus F, Veelo DP, de Nijs SB, Beenen LF, Bresser P, de Mol BA, Binnekade JM, Schultz MJ.  
Manual hyperinflation partly prevents reductions of functional residual capacity in cardiac surgical patients--a randomized controlled trial.  
Crit Care. 2011 Aug 5;15(4):R187. doi: 10.1186/cc10340.
21. Aukema TS, Beenen LF, Hietbrink F, Leenen LP.  
Validation of the Thorax Trauma Severity Score for mortality and its value for the development of acute respiratory distress syndrome.  
Open Access Emerg Med. 2011 Aug 23;3:49-53. doi: 10.2147/OAEM.S22802.  
eCollection 2011.
22. Fung Kon Jin PH, Dijkgraaf MG, Alons CL, van Kuijk C, Beenen LF, Koole GM, Goslings JC.  
Improving CT scan capabilities with a new trauma workflow concept: simulation of hospital logistics using different CT scanner scenarios.  
Eur J Radiol. 2011 Nov;80(2):504-9. doi: 10.1016/j.ejrad.2009.11.026. Epub 2010 Mar 12.
23. Kruyt ND, Beenen LF, van den Berg Vos RM, Dippel DW, Imanse JG, Kwa VI, de Leeuw FE, Luijckx GJ, Nederkoorn PJ, van Oostenbrugge RJ, Visser MC, van der Worp HB, Wermer MJ, Zinkstok SM, Roos YB  
Door-to-needle time bij intraveneuze trombolysie: interpretatie en registratie.  
Tijdschrift voor Neurologie en Neurochirurgie 2011;112 (5) :226-231.

## 2012

24. Wittenberg R, Berger FH, Peters JF, Weber M, van Hoorn F, Beenen LF, van Doorn MM, van Schuppen J, Zijlstra IA, Prokop M, Schaefer-Prokop CM.  
Acute pulmonary embolism: effect of a computer-assisted detection prototype on diagnosis--an observer study.  
Radiology. 2012 Jan;262(1):305-13. doi: 10.1148/radiol.11110372.
25. Saltzherr TP, Bakker FC, Beenen LF, Dijkgraaf MG, Reitsma JB, Goslings JC; REACT Study Group.  
Randomized clinical trial comparing the effect of computed tomography in the trauma room versus the radiology department on injury outcomes.  
Br J Surg. 2012 Jan;99 Suppl 1:105-13. doi: 10.1002/bjs.7705.

26. Sierink JC, Saltzherr TP, Edwards MJ, Beuker BJ, Patka P, Goslings JC; REACT-2-studiegroep.  
[Direct total body CT scan in multi-trauma patients].  
Ned Tijdschr Geneesk. 2012;156(30):A4897.
27. Aukema TS, Beenen LF, Hietbrink F, Leenen LP.  
Initial assessment of chest X-ray in thoracic trauma patients: Awareness of specific injuries.  
World J Radiol. 2012 Feb 28;4(2):48-52. doi: 10.4329/wjr.v4.i2.48.
28. Sierink JC, Saltzherr TP, Beenen LF, Luitse JS, Hollmann MW, Reitsma JB, Edwards MJ, Hohmann J, Beuker BJ, Patka P, Suliburk JW, Dijkgraaf MG, Goslings JC; REACT-2 study group.  
A multicenter, randomized controlled trial of immediate total-body CT scanning in trauma patients (REACT-2).  
BMC Emerg Med. 2012 Mar 30;12:4. doi: 10.1186/1471-227X-12-4.
29. Sierink JC, Saltzherr TP, Beenen LF, Luitse JS, Hollmann MW, Reitsma JB, Edwards MJ, Patka P, Beuker BJ, Suliburk JW, Hohmann J, Dijkgraaf MG, Goslings JC; REACT-2 Study Group.  
Randomised, controlled trial of immediate total-body computed tomography scanning in trauma patients.  
Emerg Med Australas. 2012 Jun;24(3):350-1. doi: 10.1111/j.1742-6723.2012.01558.x.
30. Zinkstok SM, Roos YB; ARTIS investigators.  
Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial.  
Lancet. 2012 Aug 25;380(9843):731-7. doi: 10.1016/S0140-6736(12)60949-0. Epub 2012 Jun 28.
31. Giannakopoulos GF, Saltzherr TP, Beenen LF, Reitsma JB, Bloemers FW, Goslings JC, Bakker FC; REACT Study Group.  
Missed injuries during the initial assessment in a cohort of 1124 level-1 trauma patients.  
Injury. 2012 Sep;43(9):1517-21. doi: 10.1016/j.injury.2011.07.012. Epub 2011 Aug 4.

32. Fahmi F, Marquering HA, Streekstra GJ, Beenen LF, Velthuis BK, VanBavel E, Majoie CB.  
Differences in CT perfusion summary maps for patients with acute ischemic stroke generated by 2 software packages.  
AJNR Am J Neuroradiol. 2012 Dec;33(11):2074-80. doi: 10.3174/ajnr.A3110. Epub 2012 May 3.
33. van Es J, Beenen LF, Gerdes VE, Middeldorp S, Douma RA, Bossuyt PM.  
The accuracy of D-dimer testing in suspected pulmonary embolism varies with the Wells score.  
J Thromb Haemost. 2012 Dec;10(12):2630-2. doi: 10.1111/jth.12037.
34. Purmer IM, van Iperen EP, Beenen LF, Kuiper MJ, Binnekade JM, Vandertop PW, Schultz MJ, Horn J.  
Brain computer tomography in critically ill patients--a prospective cohort study.  
BMC Med Imaging. 2012 Dec 12;12:34. doi: 10.1186/1471-2342-12-34.
35. Marquering H, Engelberts J, Groot P, Majoie C, Beenen L, van Kampen A, Olabarriaga SD.  
Optimization and Parallelization of the Matched Masked Bone Elimination Method for CTA.  
Proceedings of the DCICTIA-MICCAI 2012 Workshop : Data- and Compute-Intensive Clinical and Translational Imaging Applications. S.l: s.n; 2012. p. 31-40.

### 2013

36. Saltzherr TP, Goslings JC, Bakker FC, Beenen LF, Olf M, Meijssen K, Asselman FF, Reitsma JB, Dijkgraaf MG; REACT study group.  
Cost-effectiveness of trauma CT in the trauma room versus the radiology department: the REACT trial.  
Eur Radiol. 2013 Jan;23(1):148-55. doi: 10.1007/s00330-012-2593-0. Epub 2012 Aug 11.
37. Lucassen WA, Beenen LF, Büller HR, Erkens PM, Schaefer-Prokop CM, van den Berk IA, van Weert HC.  
Concerns in using multi-detector computed tomography for diagnosing pulmonary embolism in daily practice. A cross-sectional analysis using expert opinion as reference standard.  
Thromb Res. 2013 Feb;131(2):145-9. doi: 10.1016/j.thromres.2012.11.027. Epub 2012 Dec 13.

38. Garssen FP, Goslings JC, Bouman CS, Beenen LF, Visser CE, de Jong VM. [Necrotising soft-tissue infections: diagnostics and treatment]. *Ned Tijdschr Geneeskd.* 2013;157(31):A6031.
39. Beenen LF, Koolen MK, Hoogerwerf JJ, Schep NW. A large soft tissue mass of the chest wall. *Neth J Med.* 2013 Mar;71(2):86, 89.
40. Moos SI, Stoker J, Beenen LF, Flobbe K, Bipat S. The prevention of contrast-induced nephropathy in Dutch hospitals. *Neth J Med.* 2013 Mar;71(2):97-103.
41. van der Made AD, Maas M, Beenen LF, Oostra RJ, Kerkhoffs GM. Postmortem imaging exposed: an aid in MR imaging of musculoskeletal structures. *Skeletal Radiol.* 2013 Apr;42(4):467-72. doi: 10.1007/s00256-012-1515-1. Epub 2012 Sep 14.
42. Sierink JC, van Lieshout WA, Beenen LF, Schep NW, Vandertop WP, Goslings JC. Systematic review of flexion/extension radiography of the cervical spine in trauma patients. *Eur J Radiol.* 2013 Jun;82(6):974-81. doi: 10.1016/j.ejrad.2013.02.009. Epub 2013 Mar 13.
43. Boers AM, Marquering HA, Jochem JJ, Besselink NJ, Berkhemer OA, van der Lugt A, Beenen LF, Majoie CB; MR CLEAN investigators. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. *AJNR Am J Neuroradiol.* 2013 Aug;34(8):1522-7. doi: 10.3174/ajnr.A3463. Epub 2013 Mar 7.
44. Marquering HA, Nederkoorn PJ, Beenen LF, Lycklama à Nijeholt GJ, van den Berg R, Roos YB, Majoie CB. Carotid pseudo-occlusion on CTA in patients with acute ischemic stroke: a concerning observation. *Clin Neurol Neurosurg.* 2013 Sep;115(9):1591-4. doi: 10.1016/j.clineuro.2013.02.008. Epub 2013 Mar 1.

45. Niesten JM, van der Schaaf IC, Biessels GJ, van Otterloo AE, van Seeters T, Horsch AD, Luitse MJ, van der Graaf Y, Kappelle LJ, Mali WP, Velthuis BK; DUTch acute Stroke Trial (DUST).  
Relationship between thrombus attenuation and different stroke subtypes.  
*Neuroradiology*. 2013 Sep;55(9):1071-9. doi: 10.1007/s00234-013-1217-y. Epub 2013 Jun 21.
46. Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwöcho L, Segers A, Shi M, Verhamme P, Wells P.  
Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism.  
*N Engl J Med*. 2013 Oct 10;369(15):1406-15. doi: 10.1056/NEJMoa1306638. Epub 2013 Aug 31.
47. Sierink JC, Saltzherr TP, Wirtz MR, Streekstra GJ, Beenen LF, Goslings JC.  
Radiation exposure before and after the introduction of a dedicated total-body CT protocol in multitrauma patients.  
*Emerg Radiol*. 2013 Dec;20(6):507-12. doi: 10.1007/s10140-013-1147-3. Epub 2013 Aug 16.
48. Fahmi F, Beenen LF, Streekstra GJ, Janssen NY, de Jong HW, Riordan A, Roos YB, Majoie CB, Vanbavel E, Marquering HA.  
Head movement during CT brain perfusion acquisition of patients with suspected acute ischemic stroke.  
*Eur J Radiol*. 2013 Dec;82(12):2334-41. doi: 10.1016/j.ejrad.2013.08.039. Epub 2013 Aug 30.
49. van Es J, Douma RA, Schreuder SM, Middeldorp S, Kamphuisen PW, Gerdes VEA, Beenen LFM.  
Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism.  
*Chest*. 2013 Dec;144(6):1893-1899. doi: 10.1378/chest.13-0157.

## 2014

50. Olthof DC, van der Vlies CH, Scheerder MJ, de Haan RJ, Beenen LF, Goslings JC, van Delden OM.  
Reliability of injury grading systems for patients with blunt splenic trauma.  
*Injury*. 2014 Jan;45(1):146-50. doi: 10.1016/j.injury.2012.08.013. Epub 2012 Sep 21.

51. van Schuppen J, Olthof DC, Wilde JC, Beenen LF, van Rijn RR, Goslings JC.  
Diagnostic accuracy of a step-up imaging strategy in pediatric patients with blunt abdominal trauma.  
*Eur J Radiol.* 2014 Jan;83(1):206-11. doi: 10.1016/j.ejrad.2013.09.024.
52. Fahmi F, Marquering HA, Streekstra GJ, Beenen LF, Janssen NN, Majoie CB, van Bavel E.  
Automatic detection of CT perfusion datasets unsuitable for analysis due to head movement of acute ischemic stroke patients.  
*J Healthc Eng.* 2014;5(1):67-78. doi: 10.1260/2040-2295.5.1.67.
53. Fahmi F, Riordan A, Beenen LF, Streekstra GJ, Janssen NY, de Jong HW, Majoie CB, van Bavel E, Marquering HA.  
The effect of head movement on CT perfusion summary maps: simulations with CT hybrid phantom data.  
*Med Biol Eng Comput.* 2014 Feb;52(2):141-7. doi: 10.1007/s11517-013-1125-7.  
Epub 2013 Oct 30.
54. Postma IL, Beenen LF, Bijlsma TS, Berger FH, Heetveld MJ, Bloemers FW, Goslings JC.  
Radiological work-up after mass casualty incidents: are ATLS guidelines applicable?  
*Eur Radiol.* 2014 Mar;24(3):785-91. doi: 10.1007/s00330-013-3072-y. Epub 2013 Dec 4.
55. Sierink JC, Saltzherr TP, Beenen LF, Russchen MJ, Luitse JS, Dijkgraaf MG, Goslings JC.  
A case-matched series of immediate total-body CT scanning versus the standard radiological work-up in trauma patients.  
*World J Surg.* 2014 Apr;38(4):795-802. doi: 10.1007/s00268-013-2310-4.
56. Sierink JC, Saltzherr TP, Russchen MJ, de Castro SM, Beenen LF, Schep NW, Goslings JC.  
Incidental findings on total-body CT scans in trauma patients.  
*Injury.* 2014 May;45(5):840-4. doi: 10.1016/j.injury.2013.10.009. Epub 2013 Oct 30.
57. Fahmi F, Marquering HA, Borst J, Streekstra GJ, Beenen LF, Niesten JM, Velthuis BK, Majoie CB, vanBavel E; DUST study.  
3D movement correction of CT brain perfusion image data of patients with acute ischemic stroke.  
*Neuroradiology.* 2014 Jun;56(6):445-52. doi: 10.1007/s00234-014-1358-7. Epub 2014 Apr 9.



58. Unlü C, Beenen LF, Fauquenot JM, Jensch S, Bemelman WA, Dijkgraaf MG, Vrouwenraets BC, Boermeester MA, Stoker J.  
Inter-observer reliability of computed tomographic classifications of diverticulitis.  
*Colorectal Dis.* 2014 Jun;16(6):O212-9. doi: 10.1111/codi.12533.
59. Santos EM, Marquering HA, Berkhemer OA, van Zwam WH, van der Lugt A, Majoie CB, Niessen WJ; MR CLEAN investigators.  
Development and validation of intracranial thrombus segmentation on CT angiography in patients with acute ischemic stroke.  
*PLoS One.* 2014 Jul 17;9(7):e101985. doi: 10.1371/journal.pone.0101985.  
eCollection 2014.
60. Fransen PS, Beumer D, Berkhemer OA, van den Berg LA, Lingsma H, van der Lugt A, van Zwam WH, van Oostenbrugge RJ, Roos YB, Majoie CB, Dippel DW; MR CLEAN Investigators.  
MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial.  
*Trials.* 2014 Sep 1;15:343. doi: 10.1186/1745-6215-15-343.
61. Zinkstok SM, Beenen LF, Majoie CB, Marquering HA, de Haan RJ, Roos YB.  
Early deterioration after thrombolysis plus aspirin in acute stroke: a post hoc analysis of the Antiplatelet Therapy in Combination with Recombinant t-PA Thrombolysis in Ischemic Stroke trial.  
*Stroke.* 2014 Oct;45(10):3080-2. doi: 10.1161/STROKEAHA.114.006268. Epub 2014 Aug 19.
62. Beenen LFM.  
Current controversies in emergency room CT: could trauma total-body CT scanning improve clinical outcome.  
*Clin Practice* 2014 Nov;11(6):591-603 doi:10.2217/cpr.14.59

## 2015

63. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW; MR CLEAN Investigators.  
A randomized trial of intraarterial treatment for acute ischemic stroke.  
N Engl J Med. 2015 Jan 1;372(1):11-20. doi: 10.1056/NEJMoa1411587. Epub 2014 Dec 17.
64. Büller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI; FXI-ASO TKA Investigators.  
Factor XI antisense oligonucleotide for prevention of venous thrombosis.  
N Engl J Med. 2015 Jan 15;372(3):232-40. doi: 10.1056/NEJMoa1405760. Epub 2014 Dec 7.
65. Sieswerda-Hoogendoorn T, Beenen LF, van Rijn RR.  
Normal cranial postmortem CT findings in children.  
Forensic Sci Int. 2015 Jan;246:43-9. doi: 10.1016/j.forsciint.2014.10.036. Epub 2014 Oct 31.
66. Stoel BC, Marquering HA, Staring M, Beenen LF, Slump CH, Roos YB, Majoie CB.  
Automated brain computed tomographic densitometry of early ischemic changes in acute stroke.  
J Med Imaging (Bellingham). 2015 Jan;2(1):014004. doi: 10.1117/1.JMI.2.1.014004. Epub 2015 Mar 24.
67. Borst J, Marquering HA, Beenen LF, Berkhemer OA, Dankbaar JW, Riordan AJ, Majoie CB; MR CLEAN investigators.  
Effect of extended CT perfusion acquisition time on ischemic core and penumbra volume estimation in patients with acute ischemic stroke due to a large vessel occlusion.  
PLoS One. 2015 Mar 19;10(3):e0119409. doi: 10.1371/journal.pone.0119409. eCollection 2015.

68. Beenen LF, Goslings JC.  
Re: Diagnostic error: Missed fractures in emergency medicine.  
Emerg Med Australas. 2015 Jun;27(3):277-8. doi: 10.1111/1742-6723.12386. Epub 2015 Mar 26.
69. Beenen LF, Sierink JC, Kolkman S, Nio CY, Saltzherr TP, Dijkgraaf MG, Goslings JC.  
Split bolus technique in polytrauma: a prospective study on scan protocols for trauma analysis.  
Acta Radiol. 2015 Jul;56(7):873-80. doi: 10.1177/0284185114539319. Epub 2014 Jul 17.
70. den Exter PL, van Es J, Kroft LJ, Erkens PM, Douma RA, Mos IC, Jonkers G, Hovens MM, Durian MF, ten Cate H, Beenen LF, Kamphuisen PW, Huisman MV; Prometheus Follow-Up Investigators.  
Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism.  
Thromb Haemost. 2015 Jul;114(1):26-34. doi: 10.1160/TH14-10-0842. Epub 2015 May 28.
71. van Es J, Beenen LF, Douma RA, den Exter PL, Mos IC, Kaasjager HA, Huisman MV, Kamphuisen PW, Middeldorp S, Bossuyt PM.  
A simple decision rule including D-dimer to reduce the need for computed tomography scanning in patients with suspected pulmonary embolism.  
J Thromb Haemost. 2015 Aug;13(8):1428-35. doi: 10.1111/jth.13011. Epub 2015 Jun 19.
72. Biljardt S, Brummel A, Tjihuis, R, Sieswerda-Hoogendoorn T, Beenen LF, van Rijn RR.  
Post-mortem fluid stasis in the sinus, trachea and mainstem bronchi; a computed tomography study in adults and children  
J Forensic Radiology Imaging. 2015 Sep; 3(3): 162-6.
73. Scheerder MJ, Beenen LFM.  
Verdenking urolithiasis op de SEH – Röntgenstralen of geluid?  
Imago 2015 Sep; 1(1); 54.
74. Atema JJ, Gans SL, Beenen LF, Toorenvliet BR, Laurell H, Stoker J, Boormeester MA.  
Accuracy of White Blood Cell Count and C-reactive Protein Levels Related to Duration of Symptoms in Patients Suspected of Acute Appendicitis.  
Acad Emerg Med. 2015 Sep;22(9):1015-24. doi: 10.1111/acem.12746. Epub 2015 Aug 20.

75. Tjong FV, Stam OC, van der Wal AC, Beenen LF, Bouma BJ, de Groot JR, Wilde AA, Knops RE.  
Postmortem Histopathological Examination of a Leadless Pacemaker Shows Partial Encapsulation After 19 Months.  
*Circ Arrhythm Electrophysiol.* 2015 Oct;8(5):1293-5. doi: 10.1161/CIRCEP.115.003101.
76. Slaar A, Karsten IH, Beenen LF, Maas M, Bakx R, van Rijn RR, Schep NW.  
Plain radiography in children with spoke wheel injury: A retrospective cohort study.  
*Eur J Radiol.* 2015 Nov;84(11):2296-300. doi: 10.1016/j.ejrad.2015.07.013. Epub 2015 Jul 28.
77. Dubois L, Jansen J, Schreurs R, Saeed P, Beenen L, Maal TJ, Gooris PJ, Becking AG.  
Predictability in orbital reconstruction: A human cadaver study. Part I: Endoscopic-assisted orbital reconstruction.  
*J Craniomaxillofac Surg.* 2015 Dec;43(10):2034-41. doi: 10.1016/j.jcms.2015.07.019. Epub 2015 Jul 29.
78. Borst J, Berkhemer OA, Roos YB, van Bavel E, van Zwam WH, van Oostenbrugge RJ, van Walderveen MA, Lingsma HF, van der Lugt A, Dippel DW, Yoo AJ, Marquering HA, Majoie CB; MR CLEAN investigators.  
Value of Computed Tomographic Perfusion-Based Patient Selection for Intra-Arterial Acute Ischemic Stroke Treatment.  
*Stroke.* 2015 Dec;46(12):3375-82. doi: 10.1161/STROKEAHA.115.010564. Epub 2015 Nov 5.
79. Beenen LF, Goslings JC.  
Response to “Single-pass split-bolus CT protocol in polytrauma: reproducibility and diagnostic efficacy”.  
*Acta Radiol.* 2015 Dec;56(12):NP49-50. doi: 10.1177/0284185115613899.

## 2016

80. Slaar A, Fockens MM, van Rijn RR, Maas M, Goslings JC, Bakx R, Streekstra GJ, Beenen LFM, Schep NWL.  
Adherence to the guidelines of paediatric cervical spine clearance in a level I trauma centre: A single centre experience.  
*Eur J Radiol.* 2016 Jan;85(1):55-60. doi: 10.1016/j.ejrad.2015.11.005. Epub 2015 Nov 4.

81. Santos EM, Niessen WJ, Yoo AJ, Berkhemer OA, Beenen LF, Majoie CB, Marquering HA; MR CLEAN investigators.  
Automated Entire Thrombus Density Measurements for Robust and Comprehensive Thrombus Characterization in Patients with Acute Ischemic Stroke.  
PLoS One. 2016 Jan 14;11(1):e0145641. doi: 10.1371/journal.pone.0145641.  
eCollection 2016.
82. Santos EM, Yoo AJ, Beenen LF, Berkhemer OA, den Blanken MD, Wismans C, Niessen WJ, Majoie CB, Marquering HA; MR CLEAN investigators.  
Observer variability of absolute and relative thrombus density measurements in patients with acute ischemic stroke.  
Neuroradiology. 2016 Feb;58(2):133-9. doi: 10.1007/s00234-015-1607-4. Epub 2015 Oct 22.
83. Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama À Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van Oostenbrugge RJ, Majoie CB, van der Lugt A, Dippel DW; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands Investigators.  
Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial.  
JAMA Neurol. 2016 Feb;73(2):190-6. doi: 10.1001/jamaneurol.2015.3886.
84. Berger FH, Körner M, Bernstein MP, Sodickson AD, Beenen LF, McLaughlin PD, Kool DR, Bilow RM.  
Emergency imaging after a mass casualty incident: role of the radiology department during training for and activation of a disaster management plan.  
Br J Radiol. 2016;89(1061):20150984. doi: 10.1259/bjr.20150984. Epub 2016 Feb 8.

85. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, Lingsma HF, Sprengers ME, Jenniskens SF, Lycklama À Nijeholt GJ, van Walderveen MA, van den Berg R, Bot JC, Beenen LF, Boers AM, Slump CH, Roos YB, van Oostenbrugge RJ, Dippel DW, van der Lugt A, van Zwam WH, Marquering HA, Majoie CB; MR CLEAN Investigators.  
Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke.  
*Stroke*. 2016 Mar;47(3):768-76. doi: 10.1161/STROKEAHA.115.011788. Epub 2016 Jan 28.
86. Santos EM, Marquering HA, den Blanken MD, Berkhemer OA, Boers AM, Yoo AJ, Beenen LF, Treurniet KM, Wismans C, van Noort K, Lingsma HF, Dippel DW, van der Lugt A, van Zwam WH, Roos YB, van Oostenbrugge RJ, Niessen WJ, Majoie CB; MR CLEAN Investigators.  
Thrombus Permeability Is Associated With Improved Functional Outcome and Recanalization in Patients With Ischemic Stroke.  
*Stroke*. 2016 Mar;47(3):732-41. doi: 10.1161/STROKEAHA.115.011187. Epub 2016 Feb 4.
87. Crijnen YS, Nouwens F, de Lau LM, Visch-Brink EG, van de Sandt-Koenderman MW, Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Roos YB, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Majoie CB, Dippel DW; MR CLEAN investigators.  
Early effect of intra-arterial treatment in ischemic stroke on aphasia recovery in MR CLEAN.  
*Neurology*. 2016 May 31;86(22):2049-55. doi: 10.1212/WNL.0000000000002724. Epub 2016 May 11.
88. Yoo AJ, Berkhemer OA, Fransen PSS, van den Berg LA, Beumer D, Lingsma HF, Schonewille WJ, Sprengers MES, van den Berg R, van Walderveen MAA, Beenen LFM, Wermer MJH, Nijeholt GJLÀ, Boiten J, Jenniskens SFM, Bot JCJ, Boers AMM, Marquering HA, Roos YBWEM, van Oostenbrugge RJ, Dippel DWJ, van der Lugt A, van Zwam WH, Majoie CBLM; MR CLEAN investigators.  
Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN).  
*Lancet Neurol*. 2016 Jun;15(7):685-694. doi: 10.1016/S1474-4422(16)00124-1. Epub 2016 May 9.

89. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB; PATCH Investigators.  
Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial.  
Lancet. 2016 Jun 25;387(10038):2605-2613. doi: 10.1016/S0140-6736(16)30392-0. Epub 2016 May 10.
90. Beenen LFM, Scheerder MJ.  
Echo voor zwangeren na abdominaal trauma?  
Imago 2016 Jun; 2(2); 59.
91. Sierink JC, Treskes K, Edwards MJ, Beuker BJ, den Hartog D, Hohmann J, Dijkgraaf MG, Luitse JS, Beenen LF, Hollmann MW, Goslings JC; REACT-2 study group.  
Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial.  
Lancet. 2016 Aug 13;388(10045):673-83. doi: 10.1016/S0140-6736(16)30932-1. Epub 2016 Jun 28.
92. Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF, Schonewille WJ, van den Berg R, Wermer MJ, Boiten J, Lycklama À Nijeholt GJ, Nederkoorn PJ, Hollmann MW, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW, Roos YB; MR CLEAN investigators.  
The effect of anesthetic management during intra-arterial therapy for acute stroke in MR CLEAN.  
Neurology. 2016 Aug 16;87(7):656-64. doi: 10.1212/WNL.0000000000002976. Epub 2016 Jul 15.
93. Iordens GI, Mahabier KC, Buisman FE, Schep NW, Muradin GS, Beenen LF, Patka P, Van Lieshout EM, Den Hartog D.  
The reliability and reproducibility of the Hertel classification for comminuted proximal humeral fractures compared with the Neer classification.  
J Orthop Sci. 2016 Sep;21(5):596-602. doi: 10.1016/j.jos.2016.05.011. Epub 2016 Jun 17.
94. Brekelmans MP, Ageno W, Beenen LF, Brenner B, Buller HR, Chen CZ, Cohen AT, Grosso MA, Meyer G, Raskob G, Segers A, Vanassche T, Verhamme P, Wells PS, Zhang G, Weitz JI.  
Recurrent venous thromboembolism in patients with pulmonary embolism and right ventricular dysfunction: a post-hoc analysis of the Hokusai-VTE study.  
Lancet Haematol. 2016 Sep;3(9):e437-45. doi: 10.1016/S2352-3026(16)30080-1.

95. Bleker SM, Beenen LF, Di Nisio M, van Es N, Büller HR, Kraaijpoel N, Rutten A. Incidental pulmonary embolism in cancer patients: Interobserver agreement on the diagnosis and extent with a focus on distal clots. *Thromb Res.* 2016 Nov;147:46-51. doi: 10.1016/j.thromres.2016.09.015. Epub 2016 Sep 17.
96. Zinkstok SM, Beenen LF, Luitse JS, Majoie CB, Nederkoorn PJ, Roos YB. Thrombolysis in Stroke within 30 Minutes: Results of the Acute Brain Care Intervention Study. *PLoS One.* 2016 Nov 18;11(11):e0166668. doi: 10.1371/journal.pone.0166668. eCollection 2016.
97. Treurniet KM, Yoo AJ, Berkhemer OA, Lingsma HF, Boers AM, Fransen PS, Beumer D, van den Berg LA, Sprengers ME, Jenniskens SF, Lycklama À Nijeholt GJ, van Walderveen MA, Bot JC, Beenen LF, van den Berg R, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Dippel DW, Roos YB, Marquering HA, Majoie CB; MR CLEAN Investigators. Clot Burden Score on Baseline Computerized Tomographic Angiography and Intra-Arterial Treatment Effect in Acute Ischemic Stroke. *Stroke.* 2016 Dec;47(12):2972-2978. doi: 10.1161/STROKEAHA.116.014565. Epub 2016 Nov 8.

## 2017

98. Treskes K, Saltzherr TP, Luitse JS, Beenen LF, Goslings JC. Indications for total-body computed tomography in blunt trauma patients: a systematic review. *Eur J Trauma Emerg Surg.* 2017 Feb;43(1):35-42. doi: 10.1007/s00068-016-0711-4. Epub 2016 Jul 19.
99. Giannakopoulos GF, Saltzherr TP, Beenen LF, Streekstra GJ, Reitsma JB, Bloemers FW, Goslings JC, Bakker FC; REACT study group. Radiological findings and radiation exposure during trauma workup in a cohort of 1124 level 1 trauma patients. *Langenbecks Arch Surg.* 2017 Feb;402(1):159-165. doi: 10.1007/s00423-016-1515-z. Epub 2016 Sep 29.
100. van den Berg LA, Dijkgraaf MG, Berkhemer OA, Fransen PS, Beumer D, Lingsma HF, Majoie CB, Dippel DW, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Roos YB; MR CLEAN Investigators. Two-Year Outcome after Endovascular Treatment for Acute Ischemic Stroke. *N Engl J Med.* 2017 Apr 6;376(14):1341-1349. doi: 10.1056/NEJMoa1612136.



101. Boers AM, Berkhemer OA, Slump CH, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Yoo AJ, Dippel DW, Marquering HA, Majoie CB; MR CLEAN trial investigators.  
Topographic distribution of cerebral infarct probability in patients with acute ischemic stroke: mapping of intra-arterial treatment effect.  
J Neurointerv Surg. 2017 May;9(5):431-436. doi: 10.1136/neurintsurg-2016-012387. Epub 2016 Apr 25.
102. Treskes K, Bos SA, Beenen LFM, Sierink JC, Edwards MJR, Beuker BJA, Muradin GSR, Hohmann J, Luitse JSK, Hollmann MW, Dijkgraaf MGW, Goslings JC; REACT-2 study group.  
High rates of clinically relevant incidental findings by total-body CT scanning in trauma patients; results of the REACT-2 trial.  
Eur Radiol. 2017 Jun;27(6):2451-2462. doi: 10.1007/s00330-016-4598-6. Epub 2016 Oct 5.
103. Treskes K, Bos SA, Beenen LFM, Sierink JC, Edwards MJR, Beuker BJA, Muradin GSR, Hohmann J, Luitse JSK, Hollmann MW, Dijkgraaf MGW, Goslings JC; REACT-2 study group.  
Erratum to: High rates of clinically relevant incidental findings by total-body CT scanning in trauma patients: Results of the REACT-2 trial.  
Eur Radiol. 2017 Jun;27(6):2463. doi: 10.1007/s00330-016-4652-4.
104. Mulder MJHL, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lycklama À Nijeholt G, Emmer BJ, van der Worp HB, Nederkoorn PJ, Roos YBWEM, van Oostenbrugge RJ, van Zwam WH, Majoie CBLM, van der Lugt A, Dippel DWJ; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) Investigators.  
Baseline Blood Pressure Effect on the Benefit and Safety of Intra-Arterial Treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands).  
Stroke. 2017 Jul;48(7):1869-1876. doi: 10.1161/STROKEAHA.116.016225. Epub 2017 Apr 21.

105. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bommel T, van Es J, Faber LM, Hazelaar GM, Heringhaus C, Hofstee H, Hovens MMC, Kaasjager KAH, van Klink RCJ, Kruij MJHA, Loeffen RF, Mairuhu ATA, Middeldorp S, Nijkeuter M, van der Pol LM, Schol-Gelok S, Ten Wolde M, Klok FA, Huisman MV; YEARS study group.  
Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study.  
*Lancet*. 2017 Jul 15;390(10091):289-297. doi: 10.1016/S0140-6736(17)30885-1. Epub 2017 May 23.
106. Scheres LJJ, Brekelmans MPA, Beenen LFM, Büller HR, Cannegieter SC, Middeldorp S.  
Sex-specific differences in the presenting location of a first venous thromboembolism.  
*J Thromb Haemost*. 2017 Jul;15(7):1344-1350. doi: 10.1111/jth.13712. Epub 2017 May 28.
107. de Muinck Keizer RJO, Beerekamp MSH, Ubbink DT, Beenen LFM, Schepers T, Goslings JC.  
Systematic CT evaluation of reduction and hardware positioning of surgically treated calcaneal fractures: a reliability analysis.  
*Arch Orthop Trauma Surg*. 2017 Sep;137(9):1261-1267. doi: 10.1007/s00402-017-2744-5. Epub 2017 Jul 26.
108. Koster RW, Beenen LF, van der Boom EB, Spijkerboer AM, Tepaske R, van der Wal AC, Beesems SG, Tijssen JG.  
Safety of mechanical chest compression devices AutoPulse and LUCAS in cardiac arrest: a randomized clinical trial for non-inferiority.  
*Eur Heart J*. 2017 Oct 21;38(40):3006-3013. doi: 10.1093/eurheartj/ehx318.
109. Ho JPTF, Schreurs R, Aydi S, Rezai R, Maal TJJ, van Wijk AJ, Beenen LFM, Dubois L, Milstein DMJ, Becking AG.  
Natural variation of the zygomaticomaxillary complex symmetry in normal individuals.  
*J Craniomaxillofac Surg*. 2017 Dec;45(12):1927-1933. doi: 10.1016/j.jcms.2017.09.017. Epub 2017 Sep 23.
110. Beenen LFM.  
Diagnostiek van acute longembolieën  
*Imago* 2017 Dec; 3(4); 20-30.

**2018**

111. Campbell BCV, van Zwam WH, Goyal M, Menon BK, Dippel DWJ, Demchuk AM, Bracard S, White P, Dávalos A, Majoie CBLM, van der Lugt A, Ford GA, de la Ossa NP, Kelly M, Bourcier R, Donnan GA, Roos YBWEM, Bang OY, Nogueira RG, Devlin TG, van den Berg LA, Clarençon F, Burns P, Carpenter J, Berkhemer OA, Yavagal DR, Pereira VM, Ducrocq X, Dixit A, Quesada H, Epstein J, Davis SM, Jansen O, Rubiera M, Urra X, Micard E, Lingsma HF, Naggara O, Brown S, Guillemin F, Muir KW, van Oostenbrugge RJ, Saver JL, Jovin TG, Hill MD, Mitchell PJ; HERMES collaborators.  
Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data.  
Lancet Neurol. 2018 Jan;17(1):47-53. doi: 10.1016/S1474-4422(17)30407-6. Epub 2017 Dec 16.
112. Treurniet KM, Berkhemer OA, Immink RV, Lingsma HF, Ward-van der Stam VMC, Hollmann MW, Vuyk J, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Dippel DWJ, Coutinho JM, Roos YBWEM, Marquering HA, Majoie CBLM; MR CLEAN investigators.  
A decrease in blood pressure is associated with unfavorable outcome in patients undergoing thrombectomy under general anesthesia.  
J Neurointerv Surg. 2018 Feb;10(2):107-111. doi: 10.1136/neurintsurg-2017-012988. Epub 2017 Apr 12.
113. Jansen J, Dubois L, Schreurs R, Gooris PJJ, Maal TJJ, Beenen LF, Becking AG. Should Virtual Mirroring Be Used in the Preoperative Planning of an Orbital Reconstruction?  
J Oral Maxillofac Surg. 2018 Feb;76(2):380-387. doi: 10.1016/j.joms.2017.09.018. Epub 2017 Oct 9.
114. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Büller HR; Hokusai VTE Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism.  
N Engl J Med. 2018 Feb 15;378(7):615-624. doi: 10.1056/NEJMoa1711948. Epub 2017 Dec 12.
115. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry).  
BMJ. 2018 Mar 9;360:k949. doi: 10.1136/bmj.k949.

116. Kimberly WT, Dutra BG, Boers AMM, Alves HCBR, Berkhemer OA, van den Berg L, Sheth KN, Roos YBWEM, van der Lugt A, Beenen LFM, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ, Lingsma HF, Marquering H, Majoie CBLM; MR CLEAN Investigators.  
Association of Reperfusion With Brain Edema in Patients With Acute Ischemic Stroke: A Secondary Analysis of the MR CLEAN Trial.  
JAMA Neurol. 2018 Apr 1;75(4):453-461. doi: 10.1001/jamaneurol.2017.5162.
117. de Roo MGA, Dobbe JGG, Ridderikhof ML, Goslings JC, van der Horst CMAM, Beenen LFM, Streekstra GJ, Strackee SD.  
Analysis of instability patterns in acute scaphoid fractures by 4-dimensional computed tomographic imaging - A prospective cohort pilot study protocol.  
Int J Surg Protoc. 2018 Apr 20;9:1-5. doi: 10.1016/j.isjp.2018.04.003. eCollection 2018.
118. Wellenberg RHH, Donders JCE, Kloen P, Beenen LFM, Kleipool RP, Maas M, Streekstra GJ.  
Exploring metal artifact reduction using dual-energy CT with pre-metal and post-metal implant cadaver comparison: are implant specific protocols needed?  
Skeletal Radiol. 2018 Jun;47(6):839-845. doi: 10.1007/s00256-017-2750-2. Epub 2017 Aug 25.
119. Boers AMM, Sales Barros R, Jansen IGH, Berkhemer OA, Beenen LFM, Menon BK, Dippel DWJ, van der Lugt A, van Zwam WH, Roos YBWEM, van Oostenbrugge RJ, Slump CH, Majoie CBLM, Marquering HA; MR CLEAN investigators.  
Value of Quantitative Collateral Scoring on CT Angiography in Patients with Acute Ischemic Stroke.  
AJNR Am J Neuroradiol. 2018 Jun;39(6):1074-1082. doi: 10.3174/ajnr.A5623. Epub 2018 Apr 19.
120. Autar ASA, Hund HM, Ramlal SA, Hansen D, Lycklama À Nijeholt GJ, Emmer BJ, de Maat MPM, Dippel DWJ, van der Lugt A, van Es ACGM, van Beusekom HMM; MR CLEAN Registry Investigators.  
High-Resolution Imaging of Interaction Between Thrombus and Stent-Retriever in Patients With Acute Ischemic Stroke.  
J Am Heart Assoc. 2018 Jun 22;7(13):e008563. doi: 10.1161/JAHA.118.008563.

121. van de Graaf RA, Samuels N, Mulder MJHL, Eralp I, van Es ACGM, Dippel DWJ, van der Lugt A, Emmer BJ; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry Investigators.  
Conscious sedation or local anesthesia during endovascular treatment for acute ischemic stroke.  
*Neurology*. 2018 Jul 3;91(1):e19-e25. doi: 10.1212/WNL.0000000000005732. Epub 2018 Jun 1.
122. Beenen LFM, Bossuyt PMM, Stoker J, Middeldorp S.  
Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism.  
*Eur Respir J*. 2018 Jul 4;52(1):1702611. doi: 10.1183/13993003.02611-2017. Print 2018 Jul.
123. Jeavons C, Hacking C, Beenen LF, Gunn ML.  
A review of split-bolus single-pass CT in the assessment of trauma patients.  
*Emerg Radiol*. 2018 Aug;25(4):367-374. doi: 10.1007/s10140-018-1591-1. Epub 2018 Feb 24.
124. Kröner A, Beenen L, du Raan M, Meijer P, Spronk PE, Stoker J, Hollmann MW, Schultz MJ.  
The clinical value of routinely obtained postoperative chest radiographs in post-anaesthesia care unit patients seems poor-a prospective observational study.  
*Ann Transl Med*. 2018 Sep;6(18):360. doi: 10.21037/atm.2018.08.33.
125. Román LS, Menon BK, Blasco J, Hernández-Pérez M, Dávalos A, Majoie CBLM, Campbell BCV, Guillemin F, Lingsma H, Anxionnat R, Epstein J, Saver JL, Marquering H, Wong JH, Lopes D, Reimann G, Desal H, Dippel DWJ, Coutts S, du Mesnil de Rochemont R, Yavagal D, Ferre JC, Roos YBWEM, Liebeskind DS, Lenthall R, Molina C, Al Ajlan FS, Reddy V, Dowlatshahi D, Sourour NA, Oppenheim C, Mitha AP, Davis SM, Weimar C, van Oostenbrugge RJ, Cobo E, Kleinig TJ, Donnan GA, van der Lugt A, Demchuk AM, Berkhemer OA, Boers AMM, Ford GA, Muir KW, Brown BS, Jovin T, van Zwam WH, Mitchell PJ, Hill MD, White P, Bracard S, Goyal M; HERMES collaborators.  
Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data.  
*Lancet Neurol*. 2018 Oct;17(10):895-904. doi: 10.1016/S1474-4422(18)30242-4. Epub 2018 Sep 18.

126. van der Pol LM, Bistervels IM, van Mens TE, van der Hulle T, Beenen LFM, den Exter PL, Kroft LJM, Mairuhu ATA, Middeldorp S, van Werkhoven JM, Ten Wolde M, Huisman MV, Klok FA.  
Lower prevalence of subsegmental pulmonary embolism after application of the YEARS diagnostic algorithm.  
Br J Haematol. 2018 Nov;183(4):629-635. doi: 10.1111/bjh.15556. Epub 2018 Sep 10.
127. Boers AMM, Jansen IGH, Beenen LFM, Devlin TG, San Roman L, Heo JH, Ribó M, Brown S, Almekhlafi MA, Liebeskind DS, Teitelbaum J, Lingsma HF, van Zwam WH, Cuadras P, du Mesnil de Rochemont R, Beaumont M, Brown MM, Yoo AJ, van Oostenbrugge RJ, Menon BK, Donnan GA, Mas JL, Roos YBWEM, Oppenheim C, van der Lugt A, Dowling RJ, Hill MD, Davalos A, Moulin T, Agrinier N, Demchuk AM, Lopes DK, Aja Rodríguez L, Dippel DWJ, Campbell BCV, Mitchell PJ, Al-Ajlan FS, Jovin TG, Madigan J, Albers GW, Soize S, Guillemin F, Reddy VK, Bracard S, Blasco J, Muir KW, Nogueira RG, White PM, Goyal M, Davis SM, Marquering HA, Majoie CBLM.  
Association of follow-up infarct volume with functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials.  
J Neurointerv Surg. 2018 Dec;10(12):1137-1142. doi: 10.1136/neurintsurg-2017-013724. Epub 2018 Apr 7.

## 2019

128. Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, van Zwam WH, van Oostenbrugge RJ, Demchuk AM, Guillemin F, White P, Dávalos A, van der Lugt A, Butcher KS, Cherifi A, Marquering HA, Cloud G, Macho Fernández JM, Madigan J, Oppenheim C, Donnan GA, Roos YBWEM, Shankar J, Lingsma H, Bonafé A, Raoult H, Hernández-Pérez M, Bharatha A, Jahan R, Jansen O, Richard S, Levy EI, Berkhemer OA, Soudant M, Aja L, Davis SM, Krings T, Tisserand M, San Román L, Tomasello A, Beumer D, Brown S, Liebeskind DS, Bracard S, Muir KW, Dippel DWJ, Goyal M, Saver JL, Jovin TG, Hill MD, Mitchell PJ; HERMES collaborators.  
Penumbra imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data.  
Lancet Neurol. 2019 Jan;18(1):46-55. doi: 10.1016/S1474-4422(18)30314-4. Epub 2018 Nov 6.

129. Compagne KCJ, Boers AMM, Marquering HA, Berkhemer OA, Yoo AJ, Beenen LFM, van Oostenbrugge RJ, van Zwam WH, Roos YBWEM, Majoie CB, van Es ACGM, van der Lugt A, Dippel DWJ, Lingsma H; MR CLEAN Investigators. Follow-up infarct volume as a mediator of endovascular treatment effect on functional outcome in ischaemic stroke. *Eur Radiol.* 2019 Feb;29(2):736-744. doi: 10.1007/s00330-018-5578-9. Epub 2018 Jul 9.
130. Compagne KCJ, van der Sluijs PM, van den Wijngaard IR, Roozenbeek B, Mulder MJHL, van Zwam WH, Emmer BJ, Majoie CBLM, Yoo AJ, Lycklama À Nijeholt GJ, Lingsma HF, Dippel DWJ, van der Lugt A, van Es ACGM; MR CLEAN Registry Investigators. Endovascular Treatment: The Role of Dominant Caliber M2 Segment Occlusion in Ischemic Stroke. *Stroke.* 2019 Feb;50(2):419-427. doi: 10.1161/STROKEAHA.118.023117. Epub 2019 Jan 21.
131. Treskes K, Saltzherr TP, Edwards MJR, Beuker BJA, Den Hartog D, Hohmann J, Luitse JS, Beenen LFM, Hollmann MW, Dijkgraaf MGW, Goslings JC; REACT-2 study group. Emergency Bleeding Control Interventions After Immediate Total-Body CT Scans in Trauma Patients. *World J Surg.* 2019 Feb;43(2):490-496. doi: 10.1007/s00268-018-4818-0.
132. Boers AMM, Jansen IGH, Brown S, Lingsma HF, Beenen LFM, Devlin TG, Román LS, Heo JH, Ribó M, Almekhlafi MA, Liebeskind DS, Teitelbaum J, Cuadras P, du Mesnil de Rochemont R, Beaumont M, Brown MM, Yoo AJ, Donnan GA, Mas JL, Oppenheim C, Dowling RJ, Moulin T, Agrinier N, Lopes DK, Aja Rodríguez L, Compagne KCJ, Al-Ajlan FS, Madigan J, Albers GW, Soize S, Blasco J, Davis SM, Nogueira RG, Dávalos A, Menon BK, van der Lugt A, Muir KW, Roos YBWEM, White P, Mitchell PJ, Demchuk AM, van Zwam WH, Jovin TG, van Oostenbrugge RJ, Dippel DWJ, Campbell BCV, Guillemin F, Bracard S, Hill MD, Goyal M, Marquering HA, Majoie CBLM. Mediation of the Relationship Between Endovascular Therapy and Functional Outcome by Follow-up Infarct Volume in Patients With Acute Ischemic Stroke. *JAMA Neurol.* 2019 Feb 1;76(2):194-202. doi: 10.1001/jamaneurol.2018.3661.

133. Beerekamp MSH, de Muinck Keizer RJO, Schepers T, Beenen LFM, Luitse JSK, Schep NW, Ubbink DT, Goslings JC; EF3X-studygroup.  
The correlation between intra-operative 2D- and 3D fluoroscopy with postoperative CT-scans in the treatment of calcaneal fractures.  
Eur J Radiol. 2019 Mar;112:222-228. doi: 10.1016/j.ejrad.2019.01.013. Epub 2019 Jan 18.
134. van der Pol LM, Tromeur C, Bistervels IM, Ni Ainle F, van Bommel T, Bertoletti L, Couturaud F, van Dooren YPA, Elias A, Faber LM, Hofstee HMA, van der Hulle T, Kruijpmans MJHA, Maignan M, Mairuhu ATA, Middeldorp S, Nijkeuter M, Roy PM, Sanchez O, Schmidt J, Ten Wolde M, Klok FA, Huisman MV; Artemis Study Investigators.  
Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism.  
N Engl J Med. 2019 Mar 21;380(12):1139-1149. doi: 10.1056/NEJMoa1813865
135. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CB, Mitchell PJ, van der Lugt A, Menon BK, San Román L, Campbell BC, Muir KW, Hill MD, Dippel DW, Saver JL, Demchuk AM, Dávalos A, White P, Brown S, Goyal M; HERMES Collaborators.  
eTICI reperfusion: defining success in endovascular stroke therapy.  
J Neurointerv Surg. 2019 May;11(5):433-438. doi: 10.1136/neurintsurg-2018-014127. Epub 2018 Sep 7.
136. Schokker S, van der Woude SO, van Kleef JJ, van Zoen DJ, van Oijen MGH, Mearadji B, Beenen LFM, Stroes CI, Waasdorp C, Jibodh RA, Creemers A, Meijer SL, Hooijer GKJ, Punt CJA, Bijlsma MF, van Laarhoven HWM.  
Phase I Dose Escalation Study with Expansion Cohort of the Addition of Nab-Paclitaxel to Capecitabine and Oxaliplatin (CapOx) as First-Line Treatment of Metastatic Esophagogastric Adenocarcinoma (ACTION Study) Cancers (Basel).  
2019 Jun 14;11(6):827. doi: 10.3390/cancers11060827.
137. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, Beenen LFM, Boon GJAM, Middeldorp S, Nossent EJ, Symersky P, Huisman MV, Bogaard HJ, Vonk Noordegraaf A, Klok FA.  
Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study.  
J Heart Lung Transplant. 2019 Jul;38(7):731-738. doi: 10.1016/j.healun.2019.03.003. Epub 2019 Mar 15.



138. Kraaijpoel N, Bleker SM, Meyer G, Mahé I, Muñoz A, Bertoletti L, Bartels-Rutten A, Beyer-Westendorf J, Porreca E, Boulon C, van Es N, Iosub DI, Couturaud F, Biosca M, Lerede T, Lacroix P, Maraveyas A, Aggarwal A, Girard P, Büller HR, Di Nisio M; UPE investigators.  
Treatment and Long-Term Clinical Outcomes of Incidental Pulmonary Embolism in Patients With Cancer: An International Prospective Cohort Study.  
*J Clin Oncol.* 2019 Jul 10;37(20):1713-1720. doi: 10.1200/JCO.18.01977. Epub 2019 May 22.
139. van de Graaf RA, Chalos V, van Es ACGM, Emmer BJ, Lycklama À Nijeholt GJ, van der Worp HB, Schonewille WJ, van der Lugt A, Dippel DWJ, Lingsma HF, Roozenbeek B; Coinvestigators MR CLEAN Registry.  
Periprocedural Intravenous Heparin During Endovascular Treatment for Ischemic Stroke: Results From the MR CLEAN Registry.  
*Stroke.* 2019 Aug;50(8):2147-2155. doi: 10.1161/STROKEAHA.119.025329. Epub 2019 Jul 9.
140. Hinsenveld WH, de Ridder IR, van Oostenbrugge RJ, Vos JA, Groot AE, Coutinho JM, Lycklama À Nijeholt GJ, Boiten J, Schonewille WJ; MR CLEAN Registry Investigators.  
Workflow Intervals of Endovascular Acute Stroke Therapy During On- Versus Off-Hours: The MR CLEAN Registry.  
*Stroke.* 2019 Oct;50(10):2842-2850. doi: 10.1161/STROKEAHA.119.025381. Epub 2019 Aug 7.
141. Koopman MS, Berkhemer OA, Geuskens RREG, Emmer BJ, van Walderveen MAA, Jenniskens SFM, van Zwam WH, van Oostenbrugge RJ, van der Lugt A, Dippel DWJ, Beenen LF, Roos YBWEM, Marquering HA, Majoie CBLM; MR CLEAN Trial Investigators.  
Comparison of three commonly used CT perfusion software packages in patients with acute ischemic stroke.  
*J Neurointerv Surg.* 2019 Dec;11(12):1249-1256. doi: 10.1136/neurintsurg-2019-014822. Epub 2019 Jun 15.

142. Guglielmi V, LeCouffe NE, Zinkstok SM, Compagne KCJ, Eker R, Treurniet KM, Tolhuisen ML, van der Worp HB, Jansen IGH, van Oostenbrugge RJ, Marquering HA, Dippel DWJ, Emmer BJ, Majoie CBLM, Roos YBWEM, Coutinho JM; MR-CLEAN Registry Investigators.  
Collateral Circulation and Outcome in Atherosclerotic Versus Cardioembolic Cerebral Large Vessel Occlusion.  
Stroke. 2019 Dec;50(12):3360-3368. doi: 10.1161/STROKEAHA.119.026299. Epub 2019 Oct 29.

## 2020

143. Treskes K, Russchen MJAM, Beenen LFM, de Jong VM, Kolkman S, de Bruin IGJM, Dijkgraaf MGW, Van Lieshout EMM, Saltzherr TP, Goslings JC.  
Early detection of severe injuries after major trauma by immediate total-body CT scouts.  
Injury. 2020 Jan;51(1):15-19. doi: 10.1016/j.injury.2019.08.040. Epub 2019 Aug 28.
144. Chalos V, van der Ende NAM, Lingsma HF, Mulder MJHL, Venema E, Dijkland SA, Berkhemer OA, Yoo AJ, Broderick JP, Palesch YY, Yeatts SD, Roos YBWEM, van Oostenbrugge RJ, van Zwam WH, Majoie CBLM, van der Lugt A, Roozenbeek B, Dippel DWJ; MR CLEAN Investigators.  
National Institutes of Health Stroke Scale: An Alternative Primary Outcome Measure for Trials of Acute Treatment for Ischemic Stroke.  
Stroke. 2020 Jan;51(1):282-290. doi: 10.1161/STROKEAHA.119.026791. Epub 2019 Dec 4.
145. Goldhoorn RB, Bernsen MLE, Hofmeijer J, Martens JM, Lingsma HF, Dippel DWJ, van der Lugt A, Buhre WFFA, Roos YBWEM, Majoie CBLM, Vos JA, Boiten J, Emmer B, van Oostenbrugge RJ, van Zwam WH; MR CLEAN Registry Investigators.  
Anesthetic management during endovascular treatment of acute ischemic stroke in the MR CLEAN Registry.  
Neurology. 2020 Jan 7;94(1):e97-e106. doi: 10.1212/WNL.0000000000008674. Epub 2019 Dec 5.
146. Beenen LFM, Scheres LJJ, Stoker J, Middeldorp S.  
Prognostic characteristics and body mass index in patients with pulmonary embolism: does size matter?  
ERJ Open Res. 2020 Jan 10;6(1):00163-2019. doi: 10.1183/23120541.00163-2019. eCollection 2020 Jan.

147. Mulder FI, Di Nisio M, Ay C, Carrier M, Bosch FTM, Segers A, Kraaijpoel N, Grosso MA, Zhang G, Verhamme P, Wang TF, Weitz JI, Middeldorp S, Raskob G, Beenen LFM, Büller HR, van Es N.  
Clinical implications of incidental venous thromboembolism in cancer patients.  
*Eur Respir J.* 2020 Feb 6;55(2):1901697. doi: 10.1183/13993003.01697-2019. Print 2020 Feb.
148. Otten M, Beenen LFM, Dirven PJ, Haerkens M.  
Rol van radiologie bij explosieletsels.  
*Imago.* 2020 Maart: 18-24.
149. Baharoglu MI, Al-Shahi Salman R, Cordonnier C, Koopman MM, Manson L, Susen S, Marquering HA, Beenen LF, Majoie CB, Roos YB.  
PATCH trial: explanatory analyses.  
*Blood.* 2020 Apr 16;135(16):1406-1409. doi: 10.1182/blood.2019003298.
150. de Wit PAM, Tielbeek JAW, van Diepen PR, Oulad Abdennabi I, Beenen LFM, Bipat S.  
A prospective study comparing water only with positive oral contrast in patients undergoing abdominal CT scan.  
*Sci Rep.* 2020 Apr 22;10(1):6813. doi: 10.1038/s41598-020-63838-3.
151. Schreurs R, Dubois L, Ho JPTF, Klop C, Beenen LFM, Habets PEMH, Becking AG, Maal TJJ.  
Implant-oriented navigation in orbital reconstruction part II: preclinical cadaver study.  
*Int J Oral Maxillofac Surg.* 2020 May;49(5):678-685. doi: 10.1016/j.ijom.2019.09.009. Epub 2019 Oct 3.
152. Treskes K, Saltzherr TP, Edwards MJR, Beuker BJA, Van Lieshout EMM, Hohmann J, Luitse JSK, Beenen LFM, Hollmann MW, Dijkgraaf MGW, Goslings JC; REACT-2 study group.  
Refining the criteria for immediate total-body CT after severe trauma.  
*Eur Radiol.* 2020 May;30(5):2955-2963. doi: 10.1007/s00330-019-06503-2. Epub 2020 Jan 23.

153. Wiegers EJA, Mulder MJHL, Jansen IGH, Venema E, Compagne KCJ, Berkhemer OA, Emmer BJ, Marquering HA, van Es ACGM, Sprengers ME, van Zwam WH, van Oostenbrugge RJ, Roos YBWEM, Majoie CBLM, Roozenbeek B, Lingsma HF, Dippel DWJ, van der Lugt A; MR CLEAN Trial and MR CLEAN Registry Investigators.  
Clinical and Imaging Determinants of Collateral Status in Patients With Acute Ischemic Stroke in MR CLEAN Trial and Registry.  
*Stroke*. 2020 May;51(5):1493-1502. doi: 10.1161/STROKEAHA.119.027483. Epub 2020 Apr 13.
154. Goldhoorn RB, van de Graaf RA, van Rees JM, Lingsma HF, Dippel DWJ, Hinsenveld WH, Postma A, van den Wijngaard I, van Zwam WH, van Oostenbrugge RJ, Roozenbeek B; MR CLEAN Registry Investigators—Group Authors.  
Endovascular Treatment for Acute Ischemic Stroke in Patients on Oral Anticoagulants: Results From the MR CLEAN Registry.  
*Stroke*. 2020 Jun;51(6):1781-1789. doi: 10.1161/STROKEAHA.119.028675. Epub 2020 May 11.
155. Boodt N, Compagne KCJ, Dutra BG, Samuels N, Tolhuisen ML, Alves HCBR, Kappelhof M, Lycklama À Nijeholt GJ, Marquering HA, Majoie CBLM, Lingsma HF, Dippel DWJ, van der Lugt A; Coinvestigators MR CLEAN Registry.  
Stroke Etiology and Thrombus Computed Tomography Characteristics in Patients With Acute Ischemic Stroke: A MR CLEAN Registry Substudy.  
*Stroke*. 2020 Jun;51(6):1727-1735. doi: 10.1161/STROKEAHA.119.027749. Epub 2020 May 14.
156. Vester MEM, van Rijn RR, Duijst WLJM, Beenen LFM, Clercx M, Oostra RJ  
Added value of post-mortem computed tomography (PMCT) to clinical findings for cause of death determination in adult “natural deaths”.  
*Int J Legal Med*. 2020 Jul;134(4):1457-1463. doi: 10.1007/s00414-019-02219-6. Epub 2019 Dec 18.
157. van Meenen LCC, Groot AE, Venema E, Emmer BJ, Smeekes MD, Kommer GJ, Majoie CBLM, Roos YBWEM, Schonewille WJ, Roozenbeek B, Coutinho JM; MR CLEAN Registry Investigators.  
Interhospital transfer vs. direct presentation of patients with a large vessel occlusion not eligible for IV thrombolysis.  
*J Neurol*. 2020 Jul;267(7):2142-2150. doi: 10.1007/s00415-020-09812-5. Epub 2020 Apr 7.

158. Groot AE, Treurniet KM, Jansen IGH, Lingsma HF, Hinsenveld W, van de Graaf RA, Roozenbeek B, Willems HC, Schonewille WJ, Marquering HA, van den Berg R, Dippel DWJ, Majoie CBLM, Roos YBWEM, Coutinho JM; MR CLEAN Registry Investigators.  
Endovascular treatment in older adults with acute ischemic stroke in the MR CLEAN Registry.  
*Neurology*. 2020 Jul 14;95(2):e131-e139. doi: 10.1212/WNL.0000000000009764. Epub 2020 Jun 11.
159. Wieggers EJA, Compagne KCJ, Janssen PM, Venema E, Deckers JW, Schonewille WJ, Albert Vos J, Lycklama À Nijeholt GJ, Roozenbeek B, Martens JM, Hofmeijer J, van Oostenbrugge RJ, van Zwam WH, Majoie CBLM, van der Lugt A, Lingsma HF, Roos YBWEM, Dippel DWJ; MR CLEAN Registry Collaborators.  
Path From Clinical Research to Implementation: Endovascular Treatment of Ischemic Stroke in the Netherlands.  
*Stroke*. 2020 Jul;51(7):1941-1950. doi: 10.1161/STROKEAHA.119.026731. Epub 2020 Jun 17.
160. Chalos V, A van de Graaf R, Roozenbeek B, C G M van Es A, M den Hertog H, Staals J, van Dijk L, F M Jenniskens S, J van Oostenbrugge R, H van Zwam W, B W E M Roos Y, B L M Majoie C, F Lingsma H, van der Lugt A, W J Dippel D; MR CLEAN-MED investigators.  
Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both, or neither (MR CLEAN-MED). Rationale and study design.  
*Trials*. 2020 Jul 14;21(1):644. doi: 10.1186/s13063-020-04514-9.
161. van Engelen TSR, Kanglie MMNP, van den Berk IAH, Bouwman MLJ, Suhooli HJM, Heckert SL, Stoker J, Bossuyt PMM, Prins JM; OPTIMACT Study Group.  
Classifying the diagnosis of study participants in clinical trials: a structured and efficient approach.  
*Eur Radiol Exp*. 2020 Jul 17;4(1):44. doi: 10.1186/s41747-020-00169-y.
162. Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society.  
CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation.  
*Radiology*. 2020 Aug;296(2):E97-E104. doi: 10.1148/radiol.2020201473. Epub 2020 Apr 27.

163. Halm JA, Beerekamp MSH, de Muinck-Keijzer RJ, Beenen LFM, Maas M, Goslings JC, Schepers T.  
Intraoperative Effect of 2D vs 3D Fluoroscopy on Quality of Reduction and Patient-Related Outcome in Calcaneal Fracture Surgery.  
Foot Ankle Int. 2020 Aug;41(8):954-963. doi: 10.1177/1071100720926111. Epub 2020 Jun 9.
164. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N.  
Incidence of venous thromboembolism in hospitalized patients with COVID-19.  
J Thromb Haemost. 2020 Aug;18(8):1995-2002. doi: 10.1111/jth.14888. Epub 2020 Jul 27.
165. Korevaar DA, Kootte RS, Smits LP, van den Aardweg JG, Bonta PI, Schinkel J, Vigeveno RM, van den Berk IAH, Scheerder MJ, Lemkes BA, Goorhuis A, Beenen LFM, Annema JT; Amsterdam UMC location AMC COVID-19 group.  
Added value of chest computed tomography in suspected COVID-19: an analysis of 239 patients.  
Eur Respir J. 2020 Aug 20;56(2):2001377. doi: 10.1183/13993003.01377-2020. Print 2020 Aug.
166. Bos LDJ, Paulus F, Vlaar APJ, Beenen LFM, Schultz MJ.  
Subphenotyping Acute Respiratory Distress Syndrome in Patients with COVID-19: Consequences for Ventilator Management.  
Ann Am Thorac Soc. 2020 Sep;17(9):1161-1163. doi: 10.1513/AnnalsATS.202004-376RL.

167. den Exter PL, Kroft LJM, Gonsalves C, Le Gal G, Schaefer-Prokop CM, Carrier M, Huisman MV, Klok FA, Meijboom L, Beenen LF, de Roos A, Hartmann I, Dennie C, Revel MP, Haramati L, van Beek E, Screatton N, Ferretti G, Ghaye B, Das M, White C, Pena Fernandez E, Paul N, Vlahos I, Renapurkar RD, Ravenel J, Kanne J, Abbara S, Rémy-Jardin M, Geurts B, Frauenfelder T, Sverzellati N, Prosch H, Goo JM, Vogel-Claussen J, MacMahon PJ, Bhalla S, Kahn S, Shivakumar S, Wells P, Rodger M, Castellucci L, Duffett L, Delluc A, Siegal D, Lazo-Langner A, Wu C, Lee A, Garcia D, Zwicker J, Aujesky D, Jimenez D, Righini M, Blondon M, Ay C, Barco S, Kamphuisen PW, Ferreira M, Sanchez O, Moores LK, Tromeur C, Ageno W, Hunt B, Prandoni P, Monreal M, Crowther M, Roy PM, Pabinger I, Donadini MP, Moustafa F, Jara-Palomares L, Pedroc R, Bertolotti L, Verhamme P, Eikenboom H, van der Meer F, Büller HR, van Es N.  
Establishing diagnostic criteria and treatment of subsegmental pulmonary embolism: A Delphi analysis of experts.  
*Res Pract Thromb Haemost.* 2020 Oct 1;4(8):1251-1261. doi: 10.1002/rth2.12422. eCollection 2020 Nov.
168. Arrarte Terreros N, Tolhuisen ML, Bennink E, de Jong HWAM, Beenen LFM, Majoie CBLM, van Bavel E, Marquering HA.  
From perviousness to permeability, modelling and measuring intra-thrombus flow in acute ischemic stroke.  
*J Biomech.* 2020 Oct 9;111:110001. doi: 10.1016/j.jbiomech.2020.110001. Epub 2020 Aug 21.
169. Amini M, van Leeuwen N, Eijkenaar F, Mulder MJHL, Schonewille W, Lycklama À Nijeholt G, Hinsenveld WH, Goldhoorn RB, van Doormaal PJ, Jenniskens S, Hazelzet J, Dippel DWJ, Roozenbeek B, Lingsma HF; MR CLEAN Registry Investigators.  
Improving quality of stroke care through benchmarking center performance: why focusing on outcomes is not enough.  
*BMC Health Serv Res.* 2020 Oct 31;20(1):998. doi: 10.1186/s12913-020-05841-y.
170. van den Berg SA, Uniken Venema SM, Mulder MJHL, Treurniet KM, Samuels N, Lingsma HF, Goldhoorn RB, Jansen IGH, Coutinho JM, Roozenbeek B, Dippel DWJ, Roos YBWEM, van der Worp HB, Nederkoorn PJ; MR CLEAN Registry Investigators†.  
Admission Blood Pressure in Relation to Clinical Outcomes and Successful Reperfusion After Endovascular Stroke Treatment.  
*Stroke.* 2020 Nov;51(11):3205-3214. doi: 10.1161/STROKEAHA.120.029907. Epub 2020 Oct 12.

171. Beenen LFM, Bos LD, Scheerder MJ, Lobé NHJ, Muller MCA, Schultz MJ, van den Aardweg JG, Goorhuis A, Bonta PI, Middeldorp S, Vlaar AP.  
Extensive pulmonary perfusion defects compatible with microthrombosis and thromboembolic disease in severe Covid-19 pneumonia.  
Thromb Res. 2020 Dec;196:135-137. doi: 10.1016/j.thromres.2020.08.026. Epub 2020 Aug 22.
172. Bavalia R, Abdoellakhan R, Beenen LF, Brekelmans MPA, Olie RH, Ten Cate H, Huisman MV, Kruij M, Middeldorp S, Meijer K, Hutten BA, Coppens M.  
Outcome of intracranial bleeding managed with prothrombin complex concentrate in patients on direct factor Xa inhibitors or vitamin K antagonists.  
Thromb Res. 2020 Dec;196:404-409. doi: 10.1016/j.thromres.2020.09.028. Epub 2020 Sep 21.
173. Ospel J, Kappelhof M, Groot AE, LeCouffe NE, Coutinho JM, Yoo AJ, Yo LSF, Beenen LFM, van Zwam WH, van der Lugt A, Postma AA, Roos YBWEM, Goyal M, Majoie CBLM; MR CLEAN Registry Investigators†.  
Combined Effect of Age and Baseline Alberta Stroke Program Early Computed Tomography Score on Post-Thrombectomy Clinical Outcomes in the MR CLEAN Registry.  
Stroke. 2020 Dec;51(12):3742-3745. doi: 10.1161/STROKEAHA.120.031773. Epub 2020 Oct 23.
174. van der Hoeven S, Ball L, Constantino F, van Meenen DM, Pelosi P, Beenen LF, Schultz MJ, Paulus F; NEBULAE-investigators.  
Effect of routine vs on-demand nebulization of acetylcysteine with salbutamol on accumulation of airway secretions in endotracheal tubes: substudy of a randomized clinical trial.  
Intensive Care Med Exp. 2020 Dec 18;8(Suppl 1):71. doi: 10.1186/s40635-020-00351-x.
175. Leader A, Hamulyák EN, Carney BJ, Avrahami M, Knip JJ, Rozenblatt S, Beenen LFM, Yust-Katz S, Icht O, Coppens M, Raanani P, Middeldorp S, Büller HR, Zwicker JJ, Spectre G.  
Intracranial hemorrhage with direct oral anticoagulants in patients with brain metastases.  
Blood Adv. 2020 Dec 22;4(24):6291-6297. doi: 10.1182/bloodadvances.2020003238.



176. Guglielmi V, Rinkel LA, Groeneveld NS, Lobé NH, Boekholdt SM, Bouma BJ, Beenen LF, Marquering HA, Majoie CB, Roos YB, van Randen A, Planken RN, Coutinho JM.  
Mind the Heart: Electrocardiography-gated cardiac computed tomography-angiography in acute ischaemic stroke-rationale and study design.  
Eur Stroke J. 2020 Dec;5(4):441-448. doi: 10.1177/2396987320962911. Epub 2020 Oct 11.PMID: 33598563

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177. Samuels N, van de Graaf RA, van den Berg CAL, Nieboer D, Eralp I, Treurniet KM, Emmer BJ, Immink RV, Majoie CBLM, van Zwam WH, Bokkers RPH, Uyttenboogaart M, van Hasselt BAAM, Mühlring J, Burke JF, Roozenbeek B, van der Lugt A, Dippel DWJ, Lingsma HF, van Es ACGM; MR CLEAN Registry Investigators.  
Blood Pressure During Endovascular Treatment Under Conscious Sedation or Local Anesthesia.  
Neurology. 2021 Jan 12;96(2):e171-e181. doi: 10.1212/WNL.0000000000011006. Epub 2020 Oct 7.
178. Luijten SPR, Bos D, Compagne KCJ, Wolff L, Majoie CBLM, Roos YBWEM, van Zwam WH, van Oostenbrugge RJ, Dippel DWJ, van der Lugt A, van Es ACGM; MR CLEAN trial investigators.  
Association of White Matter Lesions and Outcome After Endovascular Stroke Treatment.  
Neurology. 2021 Jan 19;96(3):e333-e342. doi: 10.1212/WNL.0000000000010994. Epub 2020 Oct 12.
179. Bernsen MLE, Goldhoorn RB, Lingsma HF, van Oostenbrugge RJ, van Zwam WH, Uyttenboogaart M, Roos YBWEM, Martens JM, Hofmeijer J; MR CLEAN Registry investigators.  
Importance of Occlusion Site for Thrombectomy Technique in Stroke: Comparison Between Aspiration and Stent Retriever.  
Stroke. 2021 Jan;52(1):80-90. doi: 10.1161/STROKEAHA.120.030031. Epub 2020 Dec 22.

180. Lessmann N, Sánchez CI, Beenen L, Boulogne LH, Brink M, Calli E, Charbonnier JP, Dofferhoff T, van Everdingen WM, Gerke PK, Geurts B, Gietema HA, Groeneveld M, van Harten L, Hendrix N, Hendrix W, Huisman HJ, Išgum I, Jacobs C, Kluge R, Kok M, Krdzalic J, Lassen-Schmidt B, van Leeuwen K, Meakin J, Overkamp M, van Rees Vellinga T, van Rikxoort EM, Samperna R, Schaefer-Prokop C, Schalekamp S, Scholten ET, Sital C, Stöger JL, Teuwen J, Venkadesh KV, de Vente C, Vermaat M, Xie W, de Wilde B, Prokop M, van Ginneken B.  
Automated Assessment of COVID-19 Reporting and Data System and Chest CT Severity Scores in Patients Suspected of Having COVID-19 Using Artificial Intelligence.  
Radiology. 2021 Jan;298(1):E18-E28. doi: 10.1148/radiol.2020202439. Epub 2020 Jul 30.
181. van Voorst H, Kunz WG, van den Berg LA, Kappelhof M, Pinckaers FME, Goyal M, Hunink MGM, Emmer BJ, Mulder MJHL, Dippel DWJ, Coutinho JM, Marquering HA, Boogaarts HD, van der Lugt A, van Zwam WH, Roos YBWEM, Buskens E, Dijkgraaf MGW, Majoie CBLM; MR CLEAN Registry investigators.  
Quantified health and cost effects of faster endovascular treatment for large vessel ischemic stroke patients in the Netherlands.  
J Neurointerv Surg. 2021 Jan 21;neurintsurg-2020-017017. doi: 10.1136/neurintsurg-2020-017017.
182. Schalekamp S, Bleeker-Rovers CP, Beenen LFM, Quarles van Ufford HME, Gietema HA, Stöger JL, Harris V, Reijers MHE, Rahamat-Langendoen J, Korevaar DA, Smits LP, Korteweg C, van Rees Vellinga T, Vermaat M, Stassen PM, Scheper H, Wijnakker R, Borm FJ, Dofferhoff ASM, Prokop WM.  
Chest CT in the Emergency Department for Diagnosis of COVID-19 Pneumonia: Dutch Experience.  
Radiology. 2021 Feb;298(2):E98-E106. doi: 10.1148/radiol.2020203465. Epub 2020 Nov 17.
183. Rinkel LA, Prick JCM, Slot RER, Sombroek NMA, Burggraaff J, Groot AE, Emmer BJ, Roos YBWEM, Brouwer MC, van den Berg-Vos RM, Majoie CBLM, Beenen LFM, van de Beek D, Visser MC, van Schaik SM, Coutinho JM.  
Impact of the COVID-19 outbreak on acute stroke care.  
J Neurol. 2021 Feb;268(2):403-408. doi: 10.1007/s00415-020-10069-1. Epub 2020 Jul 20.

184. van Meenen LCC, Arrarte Terreros N, Groot AE, Kappelhof M, Beenen LFM, Marquering HA, Emmer BJ, Roos YBWEM, Majoie CBLM, Coutinho JM. Value of repeated imaging in patients with a stroke who are transferred for endovascular treatment. *J Neurointerv Surg.* 2021 Mar 8:neurintsurg-2020-017050. doi: 10.1136/neurintsurg-2020-017050.
185. den Hartog SJ, Zaidat O, Roozenbeek B, van Es ACGM, Bruggeman AAE, Emmer BJ, Majoie CBLM, van Zwam WH, van den Wijngaard IR, van Doormaal PJ, Lingsma HF, Burke JF, Dippel DWJ; MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry Investigators. Effect of First-Pass Reperfusion on Outcome After Endovascular Treatment for Ischemic Stroke. *J Am Heart Assoc.* 2021 Apr 6;10(7):e019988. doi: 10.1161/JAHA.120.019988. Epub 2021 Mar 19.
186. Treskes K, Sierink JC, Edwards MJR, Beuker BJA, Van Lieshout EMM, Hohmann J, Saltzherr TP, Hollmann MW, Van Dieren S, Goslings JC, Dijkgraaf MGW; REACT-2 study group. Cost-effectiveness of immediate total-body CT in patients with severe trauma (REACT-2 trial). *Br J Surg.* 2021 Apr 5;108(3):277-285. doi: 10.1093/bjs/znaa091.
187. Dekker L, Venema E, Pirson FAV, Majoie CBLM, Emmer BJ, Jansen IGH, Mulder MJHL, Lemmens R, Goldhoorn RB, Wermer MJH, Boiten J, Lycklama À Nijeholt GJ, Roos YBWEM, van Es ACGM, Lingsma HF, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ, van den Wijngaard IR; MR CLEAN Registry investigators. Endovascular treatment in anterior circulation stroke beyond 6.5 hours after onset or time last seen well: results from the MR CLEAN Registry. *Stroke Vasc Neurol.* 2021 Apr 7:svn-2020-000803. doi: 10.1136/svn-2020-000803.
188. Viddeleer AR, Raaphorst J, Min M, Beenen LFM, Scheerder MJ, Vlaar APJ; Amsterdam UMC COVID-19 Biobank, Beudel M, Hemke R. Intramuscular adipose tissue at level Th12 is associated with survival in COVID-19. *J Cachexia Sarcopenia Muscle.* 2021 May 3;12(3):823-7. doi: 10.1002/jcsm.12696.

189. Arrarte Terreros N, Bruggeman AAE, Swijnenburg ISJ, van Meenen LCC, Groot AE, Coutinho JM, Roos YBWEM, Emmer BJ, Beenen LFM, van Bavel E, Marquering HA, Majoie CBLM.  
Early recanalization in large-vessel occlusion stroke patients transferred for endovascular treatment.  
J Neurointerv Surg. 2021 May 13;neurintsurg-2021-017441. doi: 10.1136/neurintsurg-2021-017441.
190. Schreurs R, Baan F, Klop C, Dubois L, Beenen LFM, Habets PEMH, Becking AG, Maal TJJ.  
Virtual splint registration for electromagnetic and optical navigation in orbital and craniofacial surgery.  
Sci Rep. 2021 May 17;11(1):10406. doi: 10.1038/s41598-021-89897-8.
191. Almekhlafi MA, Goyal M, Dippel DWJ, Majoie CBLM, Campbell BCV, Muir KW, Demchuk AM, Bracard S, Guillemin F, Jovin TG, Mitchell P, White P, Hill MD, Brown S, Saver JL; HERMES Trialists Collaboration.  
Healthy Life-Year Costs of Treatment Speed From Arrival to Endovascular Thrombectomy in Patients With Ischemic Stroke: A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials.  
JAMA Neurol. 2021 Jun 1;78(6):709-717. doi: 10.1001/jamaneurol.2021.1055.
192. Braams NJ, Boon GJAM, de Man FS, van Es J, den Exter PL, Kroft LJM, Beenen LFM, Huisman MV, Nossent EJ, Boonstra A, Vonk Noordegraaf A, Ruigrok D, Klok FA, Bogaard HJ, Meijboom LJ.  
Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH.  
Eur Respir J. 2021 Jun 10;2100699. doi: 10.1183/13993003.00699-2021.
193. Korevaar DA, Aydemir I, Minnema MW, Azijli K, Beenen LF, Heijmans J, van Es N, Al Masoudi M, Meijboom LJ, Middeldorp S, Nanayakkara PW, Meijer RI, Bonta PI, van Es J.  
Routine screening for pulmonary embolism in COVID-19 patients at the emergency department: impact of D-dimer testing followed by CTPA.  
J Thromb Thrombolysis. 2021 Jun 23;1-6. doi: 10.1007/s11239-021-02508-1

194. Boon GJAM, Jairam PM, Groot GMC, van Rooden CJ, Ende-Verhaar YM, Beenen LFM, Kroft LJM, Bogaard HJ, Huisman MV, Symersky P, Vonk Noordegraaf A, Meijboom LJ, Klok FA.  
Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. *Eur J Intern Med.* 2021 Jul 19:S0953-6205(21)00243-0. doi: 10.1016/j.ejim.2021.07.001
195. Uniken Venema SM, Postma AA, van den Wijngaard IR, Vos JA, Lingsma HF, Bokkers RPH, Hofmeijer J, Dippel DWJ, Majoie CB, van der Worp HB; MR CLEAN Registry Investigators.  
White Matter Lesions and Outcomes After Endovascular Treatment for Acute Ischemic Stroke: MR CLEAN Registry Results. *Stroke.* 2021 Aug;52(9):2849-2857. doi: 10.1161/STROKEAHA.120.033334. Epub 2021 Jun 3.
196. Venema E, Roozenbeek B, Mulder MJHL, Brown S, Majoie CBLM, Steyerberg EW, Demchuk AM, Muir KW, Dávalos A, Mitchell PJ, Bracard S, Berkhemer OA, Lycklama À Nijeholt GJ, van Oostenbrugge RJ, Roos YBWEM, van Zwam WH, van der Lugt A, Hill MD, White P, Campbell BCV, Guillemin F, Saver JL, Jovin TG, Goyal M, Dippel DWJ, Lingsma HF; HERMES collaborators and MR CLEAN Registry Investigators.  
Prediction of Outcome and Endovascular Treatment Benefit: Validation and Update of the MR PREDICTS Decision Tool. *Stroke.* 2021 Aug;52(9):2764-2772. doi: 10.1161/STROKEAHA.120.032935. Epub 2021 Jul 16.
197. Smit MR, Beenen LFM, Valk CMA, de Boer MM, Scheerder MJ, Annema JT, Paulus F, Horn J, Vlaar APJ, Kooij FO, Hollmann MW, Schultz MJ, Bos LDJ.  
Assessment of Lung Reaeration at 2 Levels of Positive End-expiratory Pressure in Patients With Early and Late COVID-19-related Acute Respiratory Distress Syndrome. *J Thorac Imaging.* 2021 Sep 1;36(5):286-293. doi: 10.1097/RTI.0000000000000600.

198. Smit MR, Pisani L, de Bock EJE, van der Heijden F, Paulus F, Beenen LFM, Leopold SJ, Huson MAM, Henwood PC, Riviello ED, Walden AP, Dondorp AM, Schultz MJ, Bos LDJ; Lung Ultrasound Consortium.  
Ultrasound versus Computed Tomography Assessment of Focal Lung Aeration in Invasively Ventilated ICU Patients.  
*Ultrasound Med Biol.* 2021 Sep;47(9):2589-2597. doi: 10.1016/j.ultrasmedbio.2021.05.019. Epub 2021 Jun 23.
199. Schreurs R, Dubois L, Klop C, Beenen LFM, Habets PEMH, Maal TJJ, Becking AG.  
Surgical instrument to improve implant positioning in orbital reconstruction: a feasibility study.  
*Br J Oral Maxillofac Surg.* 2021 Sep;59(7):826-830. doi: 10.1016/j.bjoms.2021.02.023. Epub 2021 Mar 26.
200. Tolhuisen ML, Ernst M, Boers AMM, Brown S, Beenen LFM, Guillemin F, Roos YBWEM, Saver JL, van Oostenbrugge R, Demchuck AM, van Zwam W, Jovin TG, Berkhemer OA, Muir KW, Bracard S, Campbell BCV, van der Lugt A, White P, Hill MD, Dippel DWJ, Mitchell PJ, Goyal M, Caan MWA, Marquering HA, Majoie CBLM; HERMES collaborators.  
Value of infarct location in the prediction of functional outcome in patients with an anterior large vessel occlusion: results from the HERMES study.  
*Neuroradiology.* 2021 Sep 3. doi: 10.1007/s00234-021-02784-x.

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## Curriculum vitae – About the author

Ludo F.M. Beenen, was born on 23<sup>rd</sup> January 1963 in Delft. He finished his pre-university education at the W.P.-Kees Boeke School Bilthoven in 1981, after which he received his propaedeutische degree in Biology at the State University Utrecht. In 1982 he started his medical training at the State University Utrecht. In the meantime, he worked as a supervising assistant at the department of Anatomy.



Ludo received his medical degree in 1989. In 1990 / 91 he served his country as a military doctor in Utrecht. In the following years he gained broad clinical experience during his work as resident-not-in-training in medical oncology and surgery at the NKI/Antonie van Leeuwenhoekhuis Amsterdam, neurosurgery at the Free University Amsterdam, and medicine, surgery, cardiology and emergency medicine at the Beatrix Hospital Gorinchem.

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