

# The role of primary and secondary care in the management of pulmonary embolism: A shifting paradigm? Developments in diagnosis and treatment

Citation for published version (APA):

Erkens, P. M. G. (2013). *The role of primary and secondary care in the management of pulmonary embolism: A shifting paradigm? Developments in diagnosis and treatment*. [Doctoral Thesis, Maastricht University]. Universitaire Press. <https://doi.org/10.26481/dis.20130220pe>

## Document status and date:

Published: 01/01/2013

## DOI:

[10.26481/dis.20130220pe](https://doi.org/10.26481/dis.20130220pe)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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# The role of primary and secondary care in the management of pulmonary embolism

*A shifting paradigm?*

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ISBN: 978-94-6159-129-6

Production: Datawysse | Universitaire Pers Maastricht

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# The role of primary and secondary care in the management of pulmonary embolism

*A shifting paradigm?*

Developments in diagnosis and treatment

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,  
op gezag van de Rector Magnificus, Prof. dr. L.L.G. Soete,  
volgens het besluit van het College van Decanen,  
in het openbaar te verdedigen  
op woensdag 20 februari 2013 om 14.00 uur

door

**Petra Mathilda Gerardus Erkens**  
geboren te Sittard



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# Chapter 1

**General introduction and outline of the thesis**





## Introduction and outline of the thesis

### General introduction

In countries with highly developed systems of primary care, such as in the Netherlands, more and more procedures are being transferred from hospital to community settings. Such development is also occurring in the management of pulmonary embolism (PE). Whereas the diagnosis and treatment of PE is mainly a secondary care problem nowadays, it seems likely that in the future PE will be increasingly managed in primary care. A careful and evidence based approach to this development is necessary since PE is a potential life-threatening disease if diagnosed and treated inadequately. This thesis concerns the management of PE at the interface of community and hospital based health care, i.e. primary and secondary care, and discusses advances in PE diagnosis and treatment.

### Definition and epidemiology of pulmonary embolism

#### *Definition*

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) and is characterized by the formation of a blood clot, also called thrombus, that blocks or partially blocks a blood vessel. Venous thrombi, composed predominantly of red blood cells but also platelets and leukocytes all bound together by fibrin, form in sites of vessel damage and areas of stagnant blood flow such as the valve pockets of the deep veins of the calf or thigh. Thrombi either remain in the peripheral veins, where they eventually undergo endogenous fibrinolysis and recanalization, or they embolize to the pulmonary arteries and cause PE. PE is defined as a thrombus that blocks the main artery of the lung or one of its branches. This thesis will focus on PE.

#### *Epidemiology*

PE is the third most common cause of death from cardiovascular disease after heart attack and stroke.<sup>1</sup> Although the exact incidence of PE is unknown, cohort studies among western populations show consistency in incidence estimates. It is believed that the annual incidence of VTE is 1.50 per 1000 inhabitants and that approximately one third of these patients have PE.<sup>2,3</sup> PE results from a combination of hereditary and acquired risk factors. (Table 1.1)

Table 1.1 Risk factors for PE.<sup>2</sup>

Risk factors for PE	
Environmental	Long-haul air travel, obesity, cigarette smoking, hypertension, immobility
Natural	Increasing age
Women's health	Oral contraceptives, pregnancy, hormone replacement therapy
Medical illness	Previous PE or DVT, cancer, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, acute and chronic inflammatory diseases, antipsychotic drug use, chronic in-dwelling central venous catheter, permanent pacemaker, internal cardiac defibrillator, stroke with limb paresis, nursing-home confinement or current or repeated hospital admission, varicose veins
Surgical	Trauma, orthopaedic surgery, especially total hip replacement, total knee replacement, hip fracture surgery, knee arthroscopy, general surgery, gynaecological and urological surgery, neurosurgery
Thrombophilia	Factor V Leiden mutation, prothrombin gene mutation, hyperhomocysteinaemia, antiphospholipid antibody syndrome, deficiency of antithrombin III, deficiency of protein C, deficiency of protein S, high concentrations of factor VIII or XI
Non-thrombotic	Particulate matter / air pollution, foreign particles, amniotic fluid, bone fragments, bone marrow, fat, cement

PE= pulmonary embolism; DVT= deep vein thrombosis.

The overall 3-month mortality rate in patients with PE is approximately 17%.<sup>4</sup> Many of these patients die from underlying comorbid disorders, especially cancer and cardiorespiratory diseases.<sup>5</sup> Adequate diagnostics and therapy are crucial in reducing the mortality rate. Without treatment PE is fatal in approximately 30%, whereas the mortality rate for PE is only 2% to 8% with adequate therapy.<sup>6</sup>

In addition, 2% to 4% of all PE patients develop chronic thromboembolic hypertension (CTEPH) within the second year following their event.<sup>7</sup> CTEPH is defined as a mean pulmonary-artery pressure greater than 25 mmHg that persists 6 months after PE is diagnosed.<sup>7</sup> It often presents with exercise intolerance, fatigue and dyspnoea and has a major impact on the quality of life of patients.

### Diagnosing pulmonary embolism in primary care

Diagnosis of PE is a major challenge because patients often present with non-specific symptoms such as sudden unexplained dyspnoea, pain on inspiration and unexplained cough. With increasing age, PE tends to masquerade as other illnesses such as acute coronary syndrome or exacerbation of chronic obstructive pulmonary disease.<sup>2</sup> Additionally, accurate diagnosis of PE is particularly difficult when patients present with concurrent illnesses, such as pneumonia or congestive heart failure.<sup>2</sup>

Catheter guided pulmonary angiography has been the gold standard reference test for PE for many years. However, this technique is invasive, expensive, not readily available and labor intensive. Consequently, non-invasive ventilation-perfusion

scanning was performed first in patients with suspected PE. A major problem, however, was that in 28% to 46% of all patients with suspected PE the test results were inconclusive. Nowadays, computed tomography pulmonary angiography (CTPA) is the first-line imaging test in patients suspected for PE. CTPA has a high sensitivity (96% to 100%) and specificity (97% to 98%).<sup>8</sup> Nevertheless, since there are some concerns regarding the risk of cancer following radiation exposure with CTPA scanning, a potential harmful CTPA scan should be avoided in patients with a low probability of PE.<sup>9,10</sup> Clinical decision rules can help in discriminating between patients who have a high probability of PE and patients with a low probability. The most widely used and validated clinical decision rule for PE is the Wells rule.<sup>11</sup> The Wells rule is a seven-item bedside assessment that classifies patients as 'PE likely' or 'PE unlikely'. (Table 1.2)

Table 1.2 Wells clinical decision rule for pulmonary embolism.

Variable	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
PE more likely than an alternative diagnosis	3.0
Heart rate >100/min	1.5
Immobilization (>3days) or surgery in the previous 4 weeks	1.5
Previous PE or DVT	1.5
Haemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0

Wells score >4, PE likely; Wells score ≤4, PE unlikely. DVT= deep vein thrombosis; PE= pulmonary embolism.

For optimum diagnostic accuracy the Wells clinical decision rule should be combined with D-dimer testing.<sup>11</sup> Plasma D-dimers are cross-linked fibrin derivatives produced when fibrin is degraded by plasmin.<sup>12</sup> Large diagnostic management studies in secondary care showed that a negative laboratory based quantitative D-dimer test in patients with a Wells-score ≤4 safely excluded PE without the need for additional work-up by imaging and resulted in the following diagnostic algorithm for suspected PE.<sup>13,14</sup> (Figure 1.1)

The diagnostic strategy of assessing the probability of PE by using the Wells rule and D-dimer testing seems also ideal for primary care to decide which patients need to be referred to secondary care for further diagnostic work-up, in particular since easy-to-use point-of-care D-dimer tests are available for use at the office or in the patient's home. Use of the Wells rule for PE combined with point-of-care D-dimer testing might be a simple, safe, efficient and inexpensive diagnostic strategy to exclude PE in primary care. However, due to differences in disease spectrum, symptomatology and physician experience, results from secondary care cannot be translated to primary care without thorough research. Before implementing such a diagnostic strategy it must be validated in the proper setting, i.e. primary care.

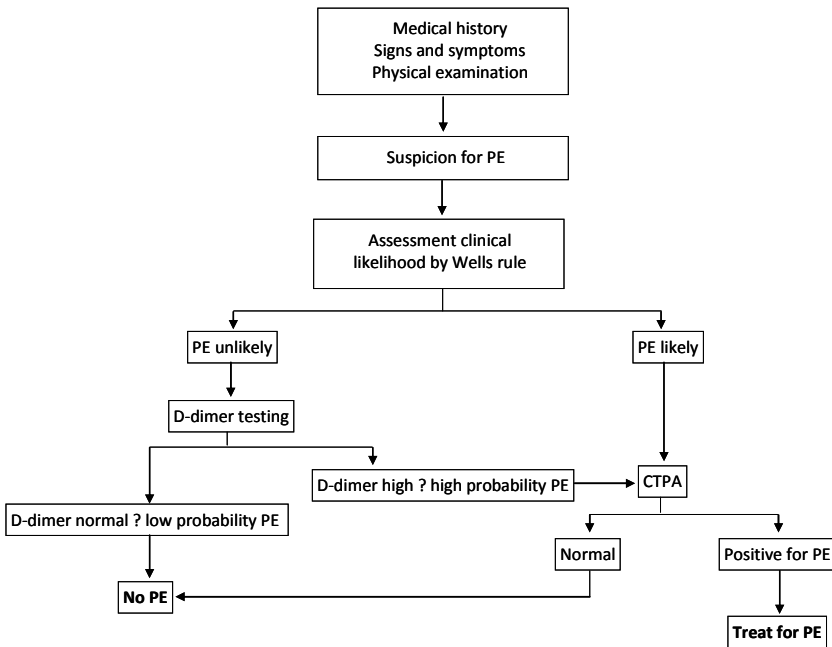


Figure 1.1 Diagnostic algorithm for suspected PE.  
PE= pulmonary embolism; CTPA= computed tomography pulmonary angiography.

*Rationale and aim of part I: ‘Diagnosing pulmonary embolism in primary care’*

In the Netherlands, the primary care physician is commonly the first to encounter outpatients suspected of PE. It is the primary care physician’s task to triage these patients: i.e. to discriminate between those who probably have PE and need to be referred to secondary care and those who can safely be kept under the surveillance of the primary care physician without further diagnostic work-up. To increase the safety and efficiency in the management of patients suspected of PE, primary care physician’s require an accurate diagnostic tool. The aim of the Amsterdam Maastricht Utrecht Study on thromboembolism (AMUSE-2) was to assess the accuracy and safety of the Wells clinical decision rule combined with point-of-care D-dimer testing for excluding PE in the primary care setting.

Treatment of pulmonary embolism in secondary care

Nowadays PE is primarily treated by anticoagulation, but anticoagulants did not appear until 1940. Up till then surgical procedures focused on the removal of the

embolus were performed for the management of PE.<sup>15</sup> Although the utility of heparin in the management of VTE was confirmed in the thirties of the 20<sup>th</sup> century, the evidence that a regimen of intravenous unfractionated heparin plus vitamin K antagonists (VKA) is more effective in preventing recurrence than VKA alone came from a randomized control trial in 1992.<sup>15,16</sup> In the same decade a number of low molecular weight heparins (LMWH) were developed for clinical use. Compared with unfractionated heparin, LMWH preparations have less inter-individual variability in anticoagulant response and as a result of their pharmacokinetic properties, a stable and sustained anticoagulant effect is achieved without laboratory monitoring and dose adjustments when LMWH is administered subcutaneously once or twice daily,<sup>17,18</sup> Due to the subcutaneous administration and no need for laboratory monitoring LWMH can be administered at home and thus enables outpatient treatment of PE. Outpatient treatment in patients with PE may be important to reduce hospitalizations and medical costs and hence save health care resources. A prognostic model, such as the PE severity index, that accurately predicts short-term adverse outcomes may help in the identification of patients appropriate for outpatient treatment. (Table 1.3)

Table 1.3 Pulmonary embolism severity index.

Predictors	Original score*	Simplified score <sup>¶</sup>
<i>Demographic characteristics</i>		
Age >80 years	Age, in years	1
Male sex	+10	
<i>Comorbid illnesses</i>		
Cancer <sup>†</sup>	+30	1
Heart failure	+10	] 1**
Chronic lung disease	+10	
<i>Clinical findings</i>		
Pulse ≥110/min	+20	1
Systolic blood pressure <100 mmHg	+30	1
Respiratory rate ≥30/min	+20	
Temperature <36°C	+20	
Altered mental status <sup>‡</sup>	+60	
Arterial oxygen saturation <90% <sup>§</sup>	+20	1

\* A total point score for a given patient is obtained by summing the patient's age in years and the points for each predictor when present. The score corresponds with the following risk classes: <65, class I; 66–85, class II; 86–105, class III; 106–125, class IV; and ≥125, class V. Patients in risk class I and II are defined as being at low risk. <sup>†</sup> Cancer defined as a history of cancer or active cancer; <sup>‡</sup> Defined as disorientation, lethargy, stupor or coma; <sup>§</sup> With and without the administration of supplemental oxygen. <sup>¶</sup> A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥1, high risk. Empty cells indicate that the variable was not included. \*\* The variables were combined into a single category of chronic cardiopulmonary disease.

As mentioned earlier anticoagulant therapy is the treatment of choice for most patients with PE. Patients are usually treated with LMWH for 5 to 10 days simultaneously with VKA. LMWH is discontinued if the International Normalized Ratio (INR) is above 2.0 on two consecutive readings.<sup>19</sup> The guidelines of the American College of Chest Physicians recommend to treat patients with a first provoked PE for 3 months, patients with a first episode of idiopathic PE at least 6 to 12 months and patients with two or more objectively documented PE indefinitely.<sup>19</sup>

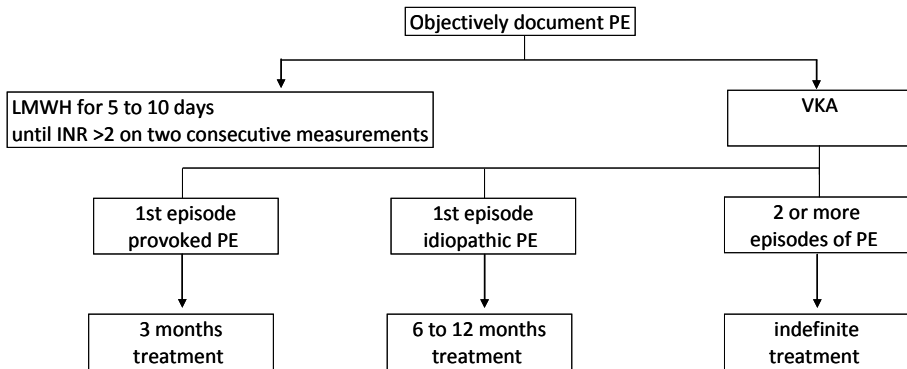


Figure 1.2 Treatment of pulmonary embolism.

PE= pulmonary embolism; LMWH= low molecular weight heparin; INR= international normalized ratio; VKA= vitamin K antagonist.

Although VKA therapy is highly effective in the treatment of PE, the effect depends on many factors including variation in dose response between patients, individual variation in pharmacokinetics and pharmacodynamic response, multiple interactions with food, co-medication and finally also by variation in adherence.<sup>19,20</sup> Moreover, VKA have a narrow therapeutic index, which needs to be monitored carefully in order to reduce the risk of thromboembolic events as well as bleeding complications. The International Normalized Ratio (INR) is established by the World Health Organization and the International Committee on Thrombosis and Hemostasis for monitoring the effects of VKA. A target INR range of 2.0 to 3.0 is recommended for the treatment of VTE.<sup>19</sup> The most recognized way to measure the therapeutic effectiveness of VKA over time is to measure the percentage of time in the therapeutic range (TTR). TTR has been shown to strongly correlate with the clinical outcomes of hemorrhage or thrombosis and, thus, TTR is a reliable measure of the quality of anticoagulation management.<sup>21</sup>

Recently, new direct acting anticoagulant medication, such as rivaroxaban and dabigatran, with a similar efficacy as VKA has been developed and approved in many countries worldwide.<sup>22-26</sup> The main advantage of these novel drugs is that there is no

need for laboratory monitoring and dose adjustments anymore due to a more stable pharmacokinetics. In the future, as the novel anticoagulants become the standard treatment of DVT and PE, the role of primary care physicians in the management of PE may increase. However, first the effectiveness of the novel drugs in daily clinical practice needs to be investigated.

*Rationale and aim of the second part 'Treatment of pulmonary embolism in secondary care'*

Patients with DVT can be safely managed and treated as outpatients using subcutaneous LMWH. The role of outpatient therapy in patients with PE, however, is unclear and has been a matter of debate in literature. Physicians are reluctant to treat patients with PE at home due to uncertainty on how to safely identify patients who are at low risk for short-term adverse events, irrespective of whether the adverse events could be averted by hospitalization. We aimed to investigate whether patients with hemodynamically stable PE could be safely treated out of the hospital and whether the pulmonary embolism severity index, a prognostic model for prediction of short-term adverse outcomes, could help in the identification of appropriate patients for outpatient management.

Outpatient treatment may become more convenient if novel drugs, such as rivaroxaban and dabigatran, which do not need laboratory monitoring, become the standard treatment. Several recent large randomized controlled trials have shown non-inferiority in effectiveness and safety of the new anticoagulants compared to VKA treatment. However, the percentage of time within therapeutic range in the VKA-group, representing the quality of the control group, appears to vary considerably among these studies. In order to adequately compare all treatment options, including novel anticoagulants and VKA, and to interpret the relative efficacy, effectiveness and safety of these novel anticoagulants, it is important to properly assess the quality of anticoagulant control, i.e. time in therapeutic range (TTR), in the VKA group. We performed a systematic review and meta-analysis to provide a benchmark of TTR in patients with VTE receiving VKA and discuss the pros and cons of various ways to calculate TTR.

## Outline of the thesis

This thesis consists of two parts. The first part focuses on the diagnosis of PE. *Chapter 2* describes the Amsterdam Maastricht Utrecht study on thromboembolism (AMUSE-2) in which we investigated the safety of using the Wells clinical decision rule for PE combined with point-of-care D-dimer testing to exclude PE in primary care. The Wells rule for PE includes the attending physician's judgement of whether an alternative diagnosis is less or more likely than PE. In order to estimate the probability of PE primary care physicians need information on the alternative diagnoses of PE as



seen in primary care in patients suspected for PE. The final alternative diagnoses in patients in whom PE was excluded are shown in *chapter 3*.

A frame of reference is needed to interpret the results of the AMUSE-2 study. To see whether the Wells rule for PE in primary care has a similar accuracy as clinical decision rules in secondary care an overview of clinical decision rules used in secondary care is presented in *chapter 4*.

The second part of this thesis focuses on the treatment of PE. In *chapter 5* the literature is reviewed to determine the effect of LMWH compared with unfractionated heparin for the initial treatment of VTE. The use of subcutaneous LMWH enables outpatient treatment of PE. In *chapter 6* the safety of outpatient treatment in hemodynamically stable patients with acute PE is investigated. Since physicians are reluctant to treat patients with PE at home due to uncertainty on how to safely identify patients who are at low risk of short-term adverse events, we study in *chapter 7* whether the pulmonary embolism severity index can help in identifying low risk patients. In *chapter 8* a benchmark for TTR in VKA treatment of VTE is presented. The introduction of novel oral anticoagulants will cause major changes in the management of thrombosis in the near future. In order to adequately compare all treatment options it is important to properly assess the quality of anticoagulant control in VKA.

The thesis ends with *chapter 9*. This chapter discusses the overall methodological considerations of the presented studies and addresses possible implications for clinical practice and future research.

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# Part I

## Diagnostics of Pulmonary Embolism in Primary Care



# Chapter 2

## Safe exclusion of pulmonary embolism using the Wells rule and D-dimer testing in primary care: a diagnostic validation study

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\* These three authors contributed equally

*British Medical Journal 2012; 345: e6564*

## Abstract

### Background

For the primary care setting no clinical decision rule for the diagnosis pulmonary embolism (PE) is available. To validate the Wells PE-rule combined with D-dimer testing with the aim to safely exclude PE in primary care.

### Methods

A prospective multicenter diagnostic validation study in primary care. We included 598 adult patients with suspected PE. After medical history and physical examination, primary care physicians scored the seven variables of the Wells PE-rule, and performed a point-of-care D-dimer test. All patients were referred to secondary care and diagnosed according to local protocols. PE was confirmed or refuted based on a composite reference standard, including spiral CT and 3 months of follow-up. The proportion of 'low-risk' patients (efficiency) and the number of missed PE cases in the low-risk category (failure rate) were calculated.

### Results

PE was present in 73 patients (prevalence 12%). Using a threshold score  $\leq 4$  on the Wells PE rule and a negative point-of-care D-dimer test, 272 of these patients were classified as 'low-risk' (efficiency 45%). In these patients 4 PE cases were observed (false negative rate 1.5%, 95% CI 0.4 to 3.7). The sensitivity and specificity of this diagnostic approach were 94.5% (95% CI 86.6 to 98.5) and 51.0% (95% CI 46.7 to 55.4).

### Conclusions

Excluding PE using a Wells score  $\leq 4$  combined with a negative qualitative or quantitative D-dimer test is safe and efficient when used in primary care.

## Introduction

For many physicians, patients with unexplained shortness of breath or pleuritic chest pain pose a diagnostic dilemma. In particular primary care physicians (PCPs) – who in many countries are the physicians whom patients consult first with these symptoms – have to differentiate between the frequently occurring self-limiting diseases (e.g. myalgia or respiratory infections) and the more rare possibility of a life threatening disease such as pulmonary embolism (PE). As symptoms can be relatively mild, PE is an easily missed diagnosis.<sup>1,2</sup> When a PE diagnosis is initially missed, physicians do not always get a second chance due to its high mortality rate if left untreated.<sup>3</sup> As a consequence, most physicians working in primary care have a low threshold for referral for further work-up of patients suspected of having PE. Consequently, PE is actually diagnosed in only 10-15% of referred patients.<sup>4</sup>

To stratify patients with suspected PE between “high probability” (need for referral) versus “low probability” of having PE clinical decision rules (CDRs) – combining different patient and disease characteristics into a score – have been developed. The CDR developed by Wells and colleagues is the most widely known, validated and implemented CDR for PE in secondary care (the ‘Wells PE rule’; Table 2.1). This rule combines seven items into a score ranging from 0 to 12·5. Based on many previous studies in secondary care, a threshold was introduced at either <2 or ≤4.<sup>5</sup> Below these respective levels, patients are classified as being at ‘very low-risk’ or ‘low-risk’ of having PE, respectively. A large diagnostic management study in secondary care concluded that a negative laboratory based quantitative D-dimer (degradation product of fibrin) test in patients with a Wells-score ≤4 safely excluded PE without the need for additional work-up by imaging.<sup>6</sup>

Table 2.1 Items of the Wells PE Rule.

Variable	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
PE more likely than an alternative diagnosis	3.0
Heart rate > 100/min	1.5
Immobilization (>3days) or surgery in the previous 4 weeks	1.5
Previous PE or DVT	1.5
Haemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0

DVT= deep vein thrombosis; PE= pulmonary embolism.

Such a diagnostic strategy seems ideal for primary care for decide on referral to secondary care, in particular since easy-to-use point-of-care D-dimer tests – providing results within minutes – are available for use at the office or in the patient’s home.<sup>7</sup> Yet, before implementing such a diagnostic strategy it must be validated in the proper



setting, i.e. primary care.<sup>8,9</sup> Due to differences in disease spectrum, symptomatology and physician experience, encouraging results from those in referral centers may not readily be applicable in primary care.<sup>10,11</sup>

Therefore, we performed a formal external validation study of the Wells PE rule combined with a point-of-care D-Dimer test, in primary care. The aim of this study was to evaluate the safety of excluding PE with the Wells PE rule (using both available thresholds;  $\leq 4$  or  $< 2$ ), combined with a negative point-of-care D-dimer test. Also, we assessed the efficiency of such a PE rule-out strategy, in primary care.

## Methods

### Study design and participants

AMUSE-2 (the Amsterdam Maastricht Utrecht Study on thrombo-Embolism) was a prospective cohort study in primary care, evaluating a diagnostic strategy consisting of the Wells PE rule (see Table 2.1) and a point-of-care D-dimer test (Clearview Simplify, Inverness Medical, Bedford, UK). Patients were included during and outside of office hours by more than 300 primary care physicians across three different regions of the Netherlands (Amsterdam, Maastricht, and Utrecht).

Eligible for inclusion were consecutive adult patients ( $\geq 18$  years) with suspected PE, based on the presence of at least one of the following symptoms: unexplained (sudden) dyspnoea, deteriorating of existing dyspnoea, pain on inspiration, or unexplained cough. Patients were excluded from the study if they received anticoagulant treatment (i.e. vitamin K antagonists or heparin) at presentation, if they were pregnant, if follow-up was not possible or if patients were unwilling or unable to provide written informed consent.

Detailed instruction took place immediately before the start of the project. One of the researchers (GJG, PE, or WL) contacted all primary care physicians willing to cooperate with the study and explained the logistics, the use of study forms and the point-of-care D-dimer test.

The study was executed between July 1, 2007 and December 31, 2010. The protocol was approved of by the medical ethical committee of the University Medical Center Utrecht, the Netherlands.

### Diagnostic strategy under study

After written informed consent, the primary care physician documented information on the patient's history, physical examination and applied the Wells PE rule using a standard form.

Subsequently the point-of care Simplify D-dimer test (Clearview, Inverness Medical, Bedford, UK) was performed. The Simplify D-dimer test is a qualitative test and is performed by mixing 35 µl of capillary or venous blood with two drops of test reagent in a disposable device.<sup>7</sup> A positive test result – occurring when the D-dimer level exceeds 80 ng/ml – is indicated by a pink-purple colored line. The test can be read at 10 minutes. Before the start of the project, all primary care physicians received a written hands-on instruction on how to perform the test.

Regardless of the outcome of the Wells PE rule and the point-of-care D-dimer test, primary care physicians were asked to refer all patients to secondary care for reference testing. In addition, to avoid interference with our aim to externally validate the Wells PE rule combined with point-of-care D-dimer testing, we explicitly provided no guidance on how to use the score (which score thresholds) to guide subsequent management.<sup>8,9</sup> Hence, secondary care physicians were asked to perform the diagnostic procedures (at their own discretion based on local hospital guidelines), and independent of the results from the point-of-care D-dimer assay, or Wells PE rule as scored in primary care.

## Reference standard

In secondary care, the diagnostic strategy was based on current guidelines and routine care protocols. In the Netherlands, this mostly is a combination of probability estimation and quantitative laboratory based D-dimer testing, followed by CT-scanning if indicated. Following most diagnostic studies in this field<sup>5,6,12,13</sup> we used a composite reference standard of spiral CT-scanning, ventilation-perfusion (V/Q) scanning, pulmonary angiography, leg ultrasonography, and clinical probability assessment as done in secondary care (with or without D-dimer testing).

We retrieved medical information about the investigations done to establish or refute a diagnosis of PE, including hospital discharge letters. In addition, all patients were followed up for 3 months. During these 3 months, primary care physicians were asked to document the occurrence of any potential (recurrent) venous thromboembolic events and bleeding complications associated with anticoagulant therapy (if given). Finally, an independent adjudication committee evaluated all patients with a diagnosis of PE despite a negative Wells PE rule and a negative point-of-care D-dimer test (see Table 2.2 for a full description of our reference standard strategy).

The primary outcome of the study was the presence of symptomatic venous thromboembolism (VTE), based on our composite reference standard, including the follow-up period of 3 months.

Table 2.2 Composite reference standard used in AMUSE-2.

PE confirmed	PE refuted – no anticoagulant treatment
Spiral CT scanning demonstrating central, or (sub) segmental PE	Spiral CT scanning demonstrating no signs of PE, plus 3 months of uneventful follow-up in primary care
Ventilation-perfusion scanning findings demonstrating PE, in accordance with the PIOPED II study protocol #	Ventilation-perfusion scanning findings without signs of PE, in accordance with the PIOPED II study protocol #, plus 3 months of uneventful follow-up in primary care
Digital subtraction angiography demonstrating PE	Digital subtraction angiography without signs of PE, plus 3 months of uneventful follow-up in primary care
Compression ultrasonography demonstrating proximal deep vein thrombosis in a patient with clinical symptoms and signs of PE	If no imaging test was performed in secondary care ¥, PE was also considered refuted if uneventful follow-up of at least three months in primary care demonstrated no signs of acute venous thromboembolism §
Wells-PE rule $\leq 4$ AND negative quantitative D-dimer test, but with a VTE event during 3 months of follow-up in primary care	Wells-PE rule $\leq 4$ AND negative quantitative D-dimer test, and 3 months of uneventful follow-up in primary care

§ Patients received follow-up in primary care; follow-up was considered uneventful if a patient was not diagnosed with acute PE or deep vein thrombosis during 3 months of follow-up; ¥ For example because of a low clinical probability assessment plus a negative D-dimer test as performed in secondary care, or because after referral an alternative diagnosis was found that completely explained the symptoms of an included patient (at the discretion of the attending physician); # Sostman, H.D., et al., *Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study*. Radiology, 2008;246:941-946.

## Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences Software (PASW version 17; SPSS, IBM, Somers, NY, USA).

We quantified the safety and efficiency of ruling out PE based on a ‘low risk score’ by our diagnostic strategy. Patients at ‘low-risk’ were initially defined by a Wells PE rule score of  $\leq 4$  and a negative point-of-care D-dimer test. The ‘Failure Rate’ was defined as the proportion of patients with a missed symptomatic and proven VTE during 3 months follow-up in those patients who were initially classified by the strategy to be at ‘low-risk for PE’, including a 95% confidence interval (using Fischer’s exact test). In contrast to therapeutic or intervention studies, formal sample size calculations based on power assumptions for diagnostic (or prognostic) modeling cohort studies do not exist, and are seldom considered. However, for single dichotomous tests, such calculations can be done for the expected positive or negative predictive values or their complements (false positive or false negative proportion, respectively).<sup>14</sup> To obtain some insight a-priori what number of patients and thus physicians had to be included, we considered the original continuous Wells rule plus D-dimer test result as one overall single test and dichotomized its result. We focused clearly on the

exclusion of PE with a minimum of missed of PE cases (false negative proportion or failure rate). Based on various previous studies performed in secondary care (notably the Christopher study<sup>6</sup>), we assumed that the point estimate of this failure rate would be around 0.5%. We subsequently used this estimate to calculate the number of patients for our study<sup>14</sup>, where we selected a stringent upper limit of the confidence interval of this estimate at 2.0%, even though previous studies addressed higher upper limits (4%).<sup>5,15</sup> Accordingly, expecting a PE failure rate of 0.5% and being able to exclude a percentage of (maximally) 2.0% PE cases, and using a type I error of 0.05 (one sided, since any value below 0.5% is desired) and type 2 error of 0.2, about 335 patients with a low-risk of PE needed to be included.

Next, we calculated the efficiency of the ability to exclude PE using the Wells PE rule. Efficiency was defined as the proportion of patients at 'low-risk for PE' among all study patients. Subsequently, we similarly estimated the failure rate and efficiency, using a Wells threshold score of <2 plus a negative point-of-care D-dimer assay (i.e. the 'very low-risk' patients).

In addition to the failure rate and efficiency, we calculated the conventional diagnostic accuracy measures (sensitivity, specificity and predictive values) for the different thresholds on the Wells PE-rule, in combination with point-of-care D-dimer testing.

Missing values on items of the Wells PE rule or point-of-care Simplify D-dimer results were observed in 24 patients (4.0% for missing values on any of the Wells PE rule items or point-of-care D-dimer test; range 0.5% for heart rate >100 beats per minute to 2.7% for results of the point-of-care D-dimer test). To minimize the effect of the bias associated with selectively "ignoring" these 24 patients, we imputed these missing values using multiple imputation techniques. Imputation techniques are based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects, using all available observed data.<sup>16,17</sup>

## Role of the funding source

The Netherlands Heart Foundation funded the study (NHS-2006B237). GlaxoSmithKline and Inverness Medical co-funded the study with unrestricted research grants. All funding sources had no role in the design, conduct, analyses or reporting of the study or in the decision to submit the manuscript for publication.

## Results

### Participants

We prospectively collected data on 662 patients suspected of PE by their primary care physician (Figure 2.1). In 64 patients one or more of the pre-defined exclusion criteria

were met: 28 patients used vitamin K antagonists or low-molecular weight heparin at the time of inclusion, 15 patients were pregnant, 3 patients were below 18 years of age, and in 18 patients follow-up was not possible (due to logistic reasons). Therefore, our study population consisted of 598 patients. Mean age was 48 years, and 71% were females.

PE was diagnosed in 68 patients, directly after referral, and in an additional 5 patients either PE or DVT was diagnosed during 3 months of follow-up (1 DVT and 4 PE, no fatal events). Hence, a total number of 73 patients (12.2%) were diagnosed with VTE. Table 2.3 details the patient characteristics.

Table 2.3 Characteristics of all study participants (n=598).

Characteristic	Value
Age - years	
Mean $\pm$ SD	48 years $\pm$ 16
Range	18-91 years
Females – no. (%)	425 (71.0 %)
Diagnosis of VTE § – no. (%)	73 (12.2%)
Unexplained sudden onset dyspnoea – no. (%)	329 (55.0%)
Pain on inspiration – no. (%)	465 (77.8%)
Unexplained cough – no. (%)	188 (31.4%)
Signs and symptoms suggestive for DVT – no. (%)	57 (9.5 %)
PE most likely diagnosis – no. (%)	333 (55.7%)
Heart rate >100 bpm – no. (%)	111 (18.6%)
Immobilisation or surgery – no. (%)	94 (15.7%)
Previous DVT or PE – no. (%)	84 (14.0%)
Haemoptysis – no. (%)	21 (3.5 %)
Active malignancy – no. (%)	26 (4.3%)
Wells PE rule	
Score $\geq$ 2 – no. (%)	361 (60.4%)
Score >4 – no. (%)	176 (29.4%)
Simplify point-of care D-dimer positive – no. (%)	220 (36.8%)

SD= standard deviation; PE= pulmonary embolism; DVT= deep vein thrombosis; VTE= venous thromboembolism. § VTE composite reference standard, including 3 months of follow-up.

## Results of the Wells PE rule

In 422 patients the score was  $\leq$ 4, and in 237 patients the score was <2. In these patients, 21 (5.0%; 95%CI 3.1–7.5) and 7 (3.0%; 95%CI 1.2–6.0) VTE events were observed, respectively. In patients with a score >4 on the Wells PE rule, 52 (29.5%; 95%CI 22.9–36.9) VTE events were noted. (Figure 2.1)

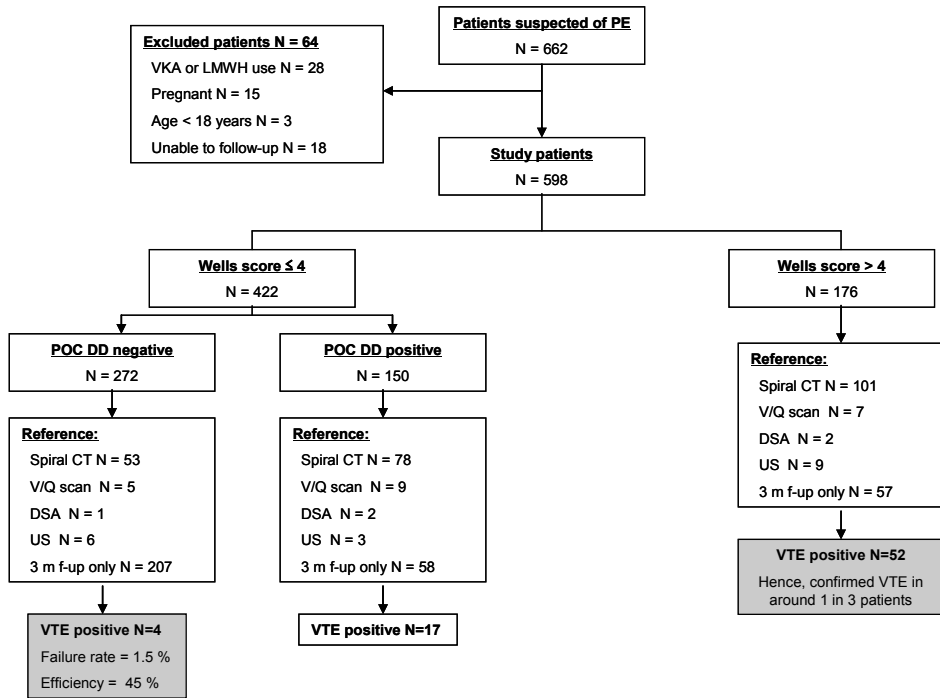


Figure 2.1 Flowchart of all study patients.

PE= pulmonary embolism; VKA= vitamin K antagonist; LMWH= low-molecular weight heparin; CT= computed tomography; V/Q= ventilation perfusion; DSA= digital subtraction angiography; US= ultrasound; 3 m f up= 3 months follow-up; POC= point of care; Quant= quantitative; DD= dimer; VTE= venous thrombo-embolism.

## Combining the Wells PE rule with D-dimer testing

Uninterpretable (Clearview Simplify) point-of-care D-dimer test results occurred in 39 patients (6.5% of all patients). According to the study protocol, these tests were evaluated as positive test results in all analyses.

If a Wells threshold at  $\leq 4$  was combined with a negative point-of-care D-dimer test, 4/272 patients in this low-risk category were diagnosed with PE: failure rate 1.5% (95% CI 0.4-3.7; Table 2.4). The efficiency of this strategy was 45% (272/598). The sensitivity and specificity of Wells  $\leq 4$  combined with a negative Simplify D-dimer test were 94.5% (95% CI 86.6–98.5) and 51.0% (95% CI 46.7–55.4) respectively. In 168 patients with a score  $< 2$  on the Wells PE rule, the point-of-care D-dimer test was also negative. In these ‘very low-risk’ patients, 2 cases of PE were observed, yielding a failure rate of 1.2% (95% CI 0.1–4.2) and an efficiency of 28% (168/598). The sensitivity and specificity of this strategy were 97.3% (95% CI 90.5–99.7) and 31.6% (95% CI 27.7–35.8) respectively. See Table 2.4.

Table 2.4 Diagnostic parameters of the Wells rule with a qualitative POC or a quantitative D-dimer test in primary care

Parameter % (95% CI)	Simplify POC D-dimer test Wells $\leq 4$	Simplify POC D-dimer test Wells $< 2$
Efficiency §	45.5% (41.4 – 49.6)	28.1% (24.5 – 31.9)
Failure rate ¥	1.5 % (0.4-3.7)	1.2 % (0.1-4.2)
Sensitivity	94.5% (86.6 – 98.5)	97.3% (90.5 – 99.7)
Specificity	51.0% (46.7 – 55.4)	31.6% (27.7 – 35.8)
PPV	21.2% (16.9 – 26.0)	19.8% (15.8 – 24.3)
NPV	98.5% (96.3 – 99.6)	98.8% (95.8 – 99.9)

POC= point-of-care; DD= D-dimer; CI= confidence interval; PPV= positive predictive value; NPV= negative predictive value; § Efficiency is defined as the proportion of all study patients in whom PE was excluded based on Wells below various cut-off values and a negative D-Dimer test; ¥ The PE failure rate is defined as the proportion of patients in whom PE was excluded based on Wells below various cut-off values and a negative D-Dimer test, *with symptomatic and proven VTE during 3 months follow-up*

### Low-risk patients with PE

Four patients classified as ‘low-risk’ (Wells score  $\leq 4$  and a negative point-of-care D-dimer) were diagnosed with PE. These cases are described in more detail in Table 2.5. They were adjudicated by an independent adjudication committee at the end of the study. The committee concluded that in one case (patient #3 in Table 2.5) a diagnosis of PE was questionable. In this patient, doubt was based upon a re-evaluation of the spiral CT scan images, which were non-conclusive due to an inadequate amount of contrast. Reanalyzing our results with this patient as not having PE yielded a lower failure rate: the PE failure rate became 1.1% (95% CI 0.2–3.2) and 0.6% (95% CI 0.0–3.3) for the thresholds of  $\leq 4$  and  $< 2$  on the Wells PE rule, respectively.

Table 2.5 Detailed description of 5 patients classified as ‘low-risk’ (Wells PE rule score  $\leq 4$  and a negative - either qualitative point-of-care or quantitative - D-dimer test) but diagnosed as PE.

Patient #	Description	POC DD	PE diagnosed by
# 1	F, 63 years. Acute onset of pain on inspiration, but no shortness of breath. Wells PE rule*= 0 points	Uninterpretable ¥	Spiral CT, directly after referral.
# 2	M, 75 years. Acute onset of pain on inspiration, no shortness of breath. Wells PE rule*=1.5 points (prior VTE).	Negative	Spiral CT, directly after referral.
# 3	F, 25 years. Acute onset of pain on inspiration and shortness of breath. Patient used oral contraceptives. Wells PE rule*=0 points	Negative	Spiral CT, directly after referral.
# 4	F, 80 years. Subacute progressive shortness of breath, after a flight trip. Wells PE rule*= 3 points (prior VTE and immobilisation).	Negative	Spiral CT, directly after referral.
# 5	F, 30 years. Acute onset of pain on inspiration, but no shortness of breath. Patient used oral contraceptives. Wells PE rule*= 3 points (PE most likely diagnosis).	Negative	Spiral CT, directly after referral.

POC= point-of-care; DD= D-dimer; VTE= venous thrombo-embolism; PE= pulmonary embolism; CT= computed tomography, M= male, F= female, \* Wells-PE-rule as scored by primary care physician, #= number, ¥ Uninterpretable Simplify results were analyzed as a positive test result.

## Discussion

The present study validated the Wells PE rule combined with a qualitative point-of-care D-dimer test in 598 patients suspected of PE in a primary care setting. Using this strategy 45% of these patients were classified as being at 'low-risk for PE', based on a threshold score  $\leq 4$  on the Wells PE rule and a negative point-of-care D-dimer test. In these patients a proportion of 1.5% PE cases was observed. In addition, lowering the threshold of the Wells PE rule to  $< 2$  combined with qualitative point-of-care D-dimer testing yielded an even lower failure rate (1.2%), but at the cost of a lower efficiency (28%). These results are in accordance with studies performed in secondary care, as documented in a recent meta-analysis on the performance of several clinical decision rules, including the Wells PE rule combined with a qualitative and quantitative D-dimer test.<sup>18</sup>

### Strengths and limitations

This is the first study to validate the Wells PE rule in a primary care setting, in a large population of almost 600 patients with suspected PE. Yet, for full appreciation of the observed results some aspects require comments.

First, the reference standard of PE consisted of various combinations of laboratory and imaging procedures – including 3 months of follow-up – to diagnose or refute a case of PE – this is differential verification bias. Although primary care physicians were asked to refer all patients to secondary care regardless of the result of point-of-care D-dimer assay or the score of the Wells PE rule – secondary care physicians were not explicitly blinded to these results obtained in primary care. Consequently, differential verification was (at least partly) dependent upon our index test under study: patients with a low score on the Wells PE rule and a negative D-dimer test more often did not undergo imaging tests for PE. Although such a combined reference approach is common in the field of diagnostic studies in PE, differential verification could lead to an over optimistic estimate of the PE failure rate.<sup>19</sup> For example, in patients with a low score on the Wells PE rule and a negative D-dimer test smaller, subsegmental, PE could be missed if these patients only received follow-up as a reference. However, missing such subsegmental PE is less relevant from a clinical perspective.<sup>20</sup>

Moreover, our study followed common clinical practice from both academic and non-academic hospitals in many parts of the world, increasing the generalizability of our results.

Second, in 57 patients no initial imaging to diagnose or refute acute PE was performed in secondary care – despite a high Wells score and despite the fact that both national and international guidelines recommend to do so. Rather, these patients were followed-up in primary care. All final diagnoses made in these patients are summarized in Table 2.6. During follow-up, in 2 of these patients VTE was diagnosed: both with confirmed DVT shortly after referral (Wells score in primary care 6.0 in both



patients). Although we do not know all results of the Wells score and D-dimer testing in secondary care, a reason for not subjecting the referred high risk patients to imaging could be a discrepancy in the clinical probability assessment between the primary care physician and the hospital. This discrepancy may be explained by differences in scoring the subjective item of the Wells rule “PE more likely than an alternative diagnosis” and differences in the result of the primary care point-of-care D-dimer test used in our study and the quantitative D-dimer tests used in secondary care.

Third, an independent adjudication committee re-evaluated all 4 patients that were “missed” by a low score on the Wells PE rule ( $\leq 4$  or  $< 2$ ) in combination with a negative point-of-care D-dimer assay. They concluded that in 1 case a diagnosis of PE was questionable. Reanalyzing this patient as not having PE would result in an – albeit small – decrease of the PE failure rates. As in reality this patient was treated with anticoagulants based on the presumed diagnosis of PE, we chose to analyze this patient as having PE for the main analyses, yielding the failure rates as presented in Figure 2.1 and Table 2.4. However, possibly, our results can be even more optimistic than the presented failure rates of Figure 2.1 and Table 2.4

Table 2.6 Final diagnoses made in 57 patients where no initial imaging was performed, despite a high Wells score (see also Figure 2.1).

Final diagnosis	n
Myalgia or thoracic chest pain	26
Pneumonia or respiratory tract infection	16
Thoracic trauma	2
Heart failure	2
Acute coronary syndrome	1
Pericarditis	1
Exacerbation COPD	1
Panic disorder	1
Obesity (Pickwick syndrome)	1
Diabetic ketoacidosis	1
Sarcoidosis	1
Airway obstruction	1
Unknown	1
Venous thrombo-embolism during follow-up #	2

# both patients diagnosed with DVT shortly after referral

Fourth, results of the point-of-care Simplify D-dimer were uninterpretable in 39 patients (6.5% of all study patients). This indicates that, although point-of-care D-dimer testing can be easily performed in a primary care domain, interpretation of a result for this qualitative assay can sometimes be difficult. In a meta-analysis on point-of-care D-dimer testing, it was shown that this difficulty in reading a test result for an older qualitative point-of-care D-dimer assay (SimpliRED D-dimer assay) resulted in much heterogeneity in the pooled analysis for this assay.<sup>7</sup> As a consequence, most

experts agree that this older SimpliRED D-dimer assay should no longer be recommended for use in daily clinical practice. Theoretically, the same problem could arise in the future for the qualitative Simplify D-dimer assay as more studies become available for this assay. However, in the present study, the results of most Simplify D-dimer tests were easily interpreted. In addition – as we did in all our analyses – we believe a solution for this difficulty in reading some of the Simplify D-dimer tests is to classify uninterpretable results as “positive”. This effectively prevents missing a PE diagnosis because of uninterpretable Simplify D-dimer test results, and is only needed in a small minority of all tested patients.

Finally, at the end of our inclusion phase we were confronted with a gradual decline in inclusion rates. We were able to include 272 low-risk patients, 81% of our predefined sample size. The expected number of PE cases was a bit higher than expected and thus the confidence limits were wider as well. Accordingly, while the point estimate of our failure rate (1.5%) was lower than 2.0%, the confidence interval did cross the predefined 2.0% limit. However, as described above, there are no formal methods for power calculations of model validation studies and, moreover, there is much discussion among clinicians on what proportion is still acceptable as upper limit. Where many previous studies addressed an upper limit of 4% being still acceptable<sup>5,15</sup>, we were conservative in our a-priori sample size considerations by setting it at 2.0%. It was based on the aim of the original derivation study of the Wells PE rule, which was to determine a score that is able to designate PE unlikely such that a negative D-dimer in these patients would result in a rate (i.e. point estimate) of PE close to 2.0%<sup>5</sup>. In this original derivation study their PE failure rate was 2.2% with a 95% confidence interval of 1% to 4%. In addition, in the PIOPED II study on the diagnostic accuracy of spiral CT-scanning in suspected PE, the failure rate was 1.7% with a 95% confidence interval of 0.7% to 3.9%.<sup>15</sup> Our results are in line with these previous studies. Increasing the number of included patients would (very likely) not change our point estimate of the failure rate but only narrow the confidence interval. Considering all above aspects and the undefined acceptable proportions – as applies to most diagnostic contexts – we believed that including more patients would not lead to different inferences about the rule’s benefits in primary care.

## Clinical implications

PE is a potentially life threatening disease. At the same time, its diagnosis is difficult as signs and symptoms can be relatively mild. In our previous study on excluding deep vein thrombosis with a clinical decision rule and D-dimer testing<sup>21</sup>, many participating physicians asked whether a similar approach would be possible for suspected PE. The present validation study indeed demonstrated that such an approach would also be feasible for PE in primary care: a Wells score  $\leq 4$  combined with a qualitative point-of-care D-dimer test ruled out PE in 4-5 out of 10 patients, with a failure rate of less than 2%, that is considered safe by most published consensus statements.<sup>5,15</sup> Such a PE

rule-out strategy makes it possible for primary care physicians to safely exclude PE in a large proportion of suspected patients during the consultation of the patient, thereby reducing costs and patient burden (e.g. contrast nephropathy with spiral CT scanning) that are associated with an unnecessary referral to secondary care.

## Conclusion

Excluding PE using a Wells score  $\leq 4$  combined with a negative qualitative D-dimer test, is safe whereas using a threshold  $< 2$  is even safer. Future studies, in which patient management is actually guided by the Wells PE rule and point-of-care D-dimer testing, are indicated to evaluate the feasibility of such an approach in reducing costs and patient burden.

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# Chapter 3

## Alternative diagnoses of pulmonary embolism in primary care

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## Abstract

### Introduction

Pulmonary Embolism (PE) often presents with non-specific symptoms and is a frequently missed diagnosis. A list of alternative diagnoses of PE might help the primary care physician when his differential diagnosis includes PE. This study aims to report the most common alternative diagnoses in patients in whom the primary care physician suspected PE. Additionally, we investigate whether the Wells rule combined with a point-of-care D-dimer test not only may exclude PE but also other serious diagnoses.

### Methods

This study is a secondary analysis of the Amsterdam Maastricht Utrecht study on thromboembolism that validated the use of the Wells clinical decision rule for PE combined with point-of-care D-Dimer testing in patients suspected of PE in primary care. After medical history and physical examination, all patients were referred to secondary care and diagnosed according to local hospital protocols. Patients were followed-up for 3 months.

### Results

The most frequent alternative diagnoses after excluding PE (n=516) were: nonspecific thoracic pain / dyspnoea (42.6%), pneumonia (13.0%), myalgia (11.8%), asthma/COPD (4.8%), panic disorder/hyperventilation (4.1%) and respiratory tract infection (2.3%). Patients with a Wells score of >4 or a positive D-Dimer test were significantly more often diagnosed with a clinically serious disease that needs immediate medical treatment.

### Conclusion

In primary care patients suspected of PE, the most common alternative diagnoses besides PE were thoracic pain/dyspnoea e.c.i., pneumonia and myalgia. A low probability of PE according the Wells rule and point-of-care D-dimer testing may also help to exclude other serious diseases than PE.

## Introduction

Pulmonary embolism (PE) often presents with non-specific mild symptoms and is a frequently missed but potentially life-threatening diagnosis. In patients presenting with sudden unexplained (or deterioration of existing) dyspnoea, pain on inspiration and/or unexplained cough symptoms primary care physicians have to differentiate between frequently occurring clinically less serious diseases such as myalgia and more rare serious diseases such as PE and pneumonia. Several clinical decision rules to exclude PE have been proposed and validated.<sup>1</sup> One of the most validated and used clinical decision rule is the Wells rule.<sup>2</sup> The Amsterdam Maastricht Utrecht Study on thrombo-embolism (Amuse-2) recently showed the safety of the use of the Wells clinical decision rule for PE combined with D-dimer testing in primary care.<sup>3</sup>

The Wells rule combines 7 items into a score to calculate the pretest probability of PE. (Table 3.1) The rule includes the attending physician's judgment of whether an alternative diagnosis is less or more likely than PE. The subjective character of this specific criterion and its moderate reproducibility is the main point of criticism to the Wells rule.<sup>4</sup> However, clinical judgment has been shown to improve the accuracy of clinical decision rules for PE.<sup>5</sup> Furthermore, Klok et al. showed that the subjective criterion has a high predictive value in comparison to the other variables of the Wells rule.<sup>6</sup> A list of alternative diagnoses of PE might thus help physicians in judging this subjective criterion and in judging the probability of PE in suspected patients.

Bagattini et al. investigated common alternative diagnoses of PE in secondary care. They found that the most frequent discharge diagnoses in emergency ward patients in whom PE was ruled out were nonspecific chest pain, bronchopneumonia, and heart failure.<sup>7</sup> Alternative diagnoses of PE as seen in primary care, however, have not been investigated yet. In this secondary analysis of the Amuse-2 study we aim to report the most common alternative diagnoses in patients in whom the primary care physician suspected PE. Additionally, we investigated whether the Wells rule combined with a point-of-care D-dimer test may not only exclude PE but also other serious diagnoses.

Table 3.1 Wells clinical decision rule for pulmonary embolism.

Variable	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
PE more likely than an alternative diagnosis	3.0
Heart rate >100/min	1.5
Immobilization (>3days) or surgery in the previous 4 weeks	1.5
Previous PE or DVT	1.5
Haemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0

DVT= deep vein thrombosis; PE= pulmonary embolism.



## Methods

### Study design and population

This study is a preplanned sub-analysis of the Amuse-2 data: a prospective cohort-study evaluating the safety of the diagnostic strategy of the Wells PE rule and a point-of-care D-dimer test in ruling out PE in primary care patients in the Netherlands between July 2007 and December 2010.<sup>2,3</sup> We enrolled patients suspected of PE. Suspicion of PE was based on the presence of at least one of the following symptoms: unexplained (sudden) dyspnoea, deterioration of existing dyspnoea, pain on inspiration, or unexplained cough.

### Data collection

After written informed consent, the primary care physician documented information on the patient's history and physical examination and applied the Wells PE rule using a standard form. Subsequently the point-of care Simplify D-dimer test (Clearview, Inverness Medical, Bedford, UK) was performed. Primary care physicians were asked to refer all patients to secondary care for further diagnostic work-up regardless of the outcome of the Wells rule and the point-of-care D-dimer test. In secondary care, the diagnostic strategy was based on current guidelines and routine care protocols. We retrieved medical information, including hospital discharge letters, about the investigations done to establish the diagnosis. In addition, all patients were followed up for 3 months. After these 3 months, primary care physicians were asked to document the final diagnosis of each patient by completing a case record form. The primary care physician could choose one or more of the following predefined diagnoses: PE, deep vein thrombosis (DVT), pneumonia, (exacerbation of) chronic obstructive pulmonary disease (COPD), coronary insufficiency, aneurysm aortae, trauma thorax, malignancy, pneumothorax, myalgia, panic disorder, nonspecific thoracic pain / dyspnoea or other. When 'other' was chosen, the primary care physician was asked to write down the patient's final diagnosis. No criteria for the clinical diagnoses were provided. If more than one final diagnosis was reported, the main diagnosis explaining the signs and symptoms which originally resulted in PE suspicion was included in the current analyses.

### Outcomes

The primary outcome of this sub-study is the prevalence of each alternative diagnosis after excluding PE in primary care patients suspected of PE. In order to analyze the association between the clinical probability for PE (as assessed by Wells-score and result of D-dimer test) and the type or severity of the final diagnosis, we divided the alternative diagnoses in two categories:

- 1) Clinical serious diseases, leading to immediate medical treatment including pneumonia, pneumothorax, pleuritis, pericarditis, atelectasis, aneurysm aortae thoracalis, heart failure, asthma / COPD, respiratory tract infection, endocarditis, atrial fibrillation and lung cancer,
- 2) Clinical less serious diseases, not leading to any treatment other than supportive care (e.g. pain-killing in case of musculoskeletal pain) including nonspecific thoracic pain / dyspnoea, myalgia and panic disorder / hyperventilation.

At least two investigators assessed the 3-months follow-up forms completed by the primary care physician and hospital discharge letters before assigning patients to one of the two above described categories. In case of disagreement a third investigator was involved and disagreements were resolved by discussion.<sup>8</sup>

## Statistical analysis

Statistical analyses were performed by using IBM Statistical Package for the Social Sciences software (version 19; SPSS; Chicago, IL, USA).

Descriptive statistics were used to describe the baseline characteristics and to report the prevalence of the alternative diagnoses. Corresponding ninety-five percent confidence intervals (95% CI) were calculated for each alternative diagnosis by using Fisher's exact test. In order to investigate the association between the probability of PE and type or severity of the alternative diagnosis, we performed subgroup analyses for patients with a Wells score >4 or a positive point-of-care D-Dimer test and patients with a Wells score of ≤4 and a negative point-of-care D-Dimer test. A threshold of 4 was introduced based on previous studies showing a high efficiency and safety at this cut-off point.<sup>2,3</sup> Odds ratios (OR) and corresponding 95%CI for the alternative diagnoses by probability of PE were calculated by Mantel-Haenszel common odds ratio.

Missing values on items of the Wells PE rule or point-of-care Simplify D-dimer test results were observed in 24 patients. Missing data was not completely at random and therefore deletion of the subjects with missing values would not only lead to a loss of statistical power but also to biased results.<sup>9</sup> To minimize the effect of selective missing, we imputed missing values using multiple imputation techniques. Imputation techniques are based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects.<sup>10,11</sup>

## Results

Over a three-year period, primary care physicians collected data of 662 patients suspected of PE. One or more of the predefined exclusion criteria were met in 64 patients, leaving 598 patients. VTE was present in 73 patients (prevalence 12.2%). Since a clear final diagnosis was missing in 9 (1.5%) patients, a total of 516 patients in

whom PE was excluded were included in the analyses of the current study. One hundred and forty-nine patients (29%) were classified as having a clinically serious disease and 367 patients (71%) as having a clinically less serious disease. (Figure 3.1)

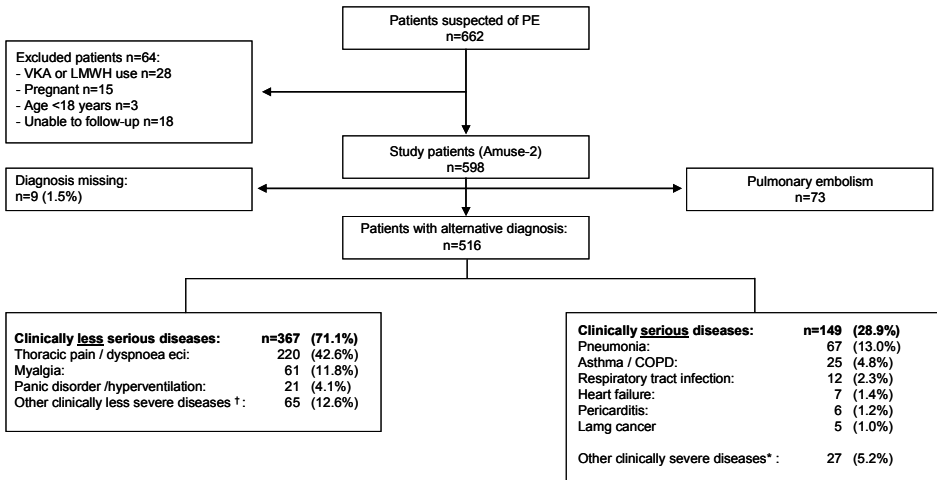


Figure 3.1 Flow chart study population.

PE= Pulmonary Embolism; VKA= Vitamin K Antagonist; LMWH= Low Molecular Weight Heparin; COPD= Chronic Obstructive Pulmonary Disease.

\* other clinically severe diseases: coronary insufficiency (n=3), atrial fibrillation (n=3), pleuritis (n=3), pneumothorax (n=2), atelectasis (n=2), rib fracture (n=2), obstructive sleep apnoea syndrome (n=2), multiple myeloma (n=1), metastatic colon carcinoma (n=1), endocarditis (n=1), lymphadenopathy etc (n=1), urosepsis diabetes (n=1), diabetes mellitus de novo (n=1), sarcoidosis (n=1), acute aortic dissection (n=1), systemic lupus erythematosus (n=1), Langerhans cell histiocytosis (n=1). † other clinically less severe diseases: other diagnoses (e.g. bronchial hyperactivity, collaps etc, trauma thorax, influenza, sinusitis) made by a PCP or hospital physician not leading to any treatment other than supportive care (e.g. painkilling).

Baseline characteristics of both groups are shown in Table 3.2. The mean age was 47 years and 72% was female. Patients with a clinically less serious disease were younger than patients with a clinically serious disease. Patients diagnosed with a serious disease were more likely to have presented with an unexplained sudden onset of dyspnoea, unexplained cough, a heart rate of more than 100 beats per minute and haemoptysis. Furthermore, patients with a clinically serious disease were more likely to have a Wells risk score of more than 4 points or a positive point-of-care D-Dimer test than patients with a less serious disease. (Table 3.2)

Table 3.2 Baseline characteristics of the study population.

Baseline characteristics:	Alternative final diagnoses		
	Clinically serious disease n=149	Clinically less serious disease n=367	OR (95% CI)
<b>Demographics</b>			
Age – years			
mean ± SD	52 ± 16	45 ± 16	-
range	18 - 88	17 - 91	-
Females – no. (%)	99 (66.4%)	270 (73.6%)	-
<b>Signs and symptoms</b>			
Unexplained sudden onset dyspnoea – no. (%)	94 (63.1%)	189 (51.5%)	1.6 (1.1 – 2.4)
Pain on inspiration – no. (%)	116 (77.9%)	294 (80.1%)	0.9 (0.5 – 1.4)
Unexplained cough – no. (%)	63 (42.3%)	98 (26.7%)	2.0 (1.3 – 3.0)
<b>Wells CDR for PE</b>			
Signs and symptoms suggestive for DVT – no. (%)	11 (7.4%)	18 (4.9%)	1.5 (0.7 – 3.4)
PE most likely diagnosis – no. (%)	88 (59.1%)	179 (48.8%)	1.5 (1.0 – 2.2)
Heart rate >100 bpm – no. (%)	51 (34.2%)	34 (9.3%)	5.1 (3.1 – 8.3)
Immobilisation or surgery – no. (%)	20 (13.4%)	50 (13.6%)	1.0 (0.6 – 1.7)
Previous DVT or PE – no. (%)	9 (6.0%)	56 (15.3%)	0.4 (0.2 – 0.7)
Haemoptysis – no. (%)	9 (6.0%)	7 (1.9%)	3.3 (1.2 – 9.0)
Active malignancy – no. (%)	7 (4.7%)	13 (3.5%)	1.3 (0.5 – 3.4)
Wells PE rule score >4 – no. (%)	44 (29.5%)	78 (21.3%)	1.6 (1.0 – 2.4)
Simplify point-of-care D-Dimer positive – no. (%)	64 (43.0%)	100 (27.2%)	2.0 (1.4 – 3.0)

OR= odds ratio; CI= confidence interval; SD= standard deviation; CDR= clinical decision rule; PE= pulmonary embolism; DVT= deep vein thrombosis; bpm= beats per minute.

## Common alternative diagnoses

The most common alternative diagnoses after excluding PE were thoracic pain / dyspnoea e.c.i. (42.6%), pneumonia (13.0%), myalgia (11.8%), asthma/COPD (4.8%), panic disorder/hyperventilation (4.1%), respiratory tract infection (2.3%), heart failure (1.4%), pericarditis (1.2%) and lung cancer (1.0%). Other less frequent clinically severe diagnoses were coronary insufficiency, atrial fibrillation, pleuritis, pneumothorax, atelectasis, rib fracture, obstructive sleep apnoea syndrome, multiple myeloma, metastatic colon carcinoma, endocarditis, lymphadenopathy e.c.i., diabetes mellitus de novo, urosepsis in a patient with diabetes mellitus, sarcoidosis, acute aortic dissection, systemic lupus erythematosus and Langerhans cell histiocytosis. Other diagnoses in the group of clinically less severe diseases were bronchial hyperreactivity, collapse e.c.i., trauma thorax, influenza, sinusitis and other diagnoses made by a PCP or hospital physician not leading to any treatment other than supportive care, e.g. painkilling. (Figure 3.1)

## Alternative diagnoses by probability for PE

There was a significant association between probability for PE and severity of the alternative diagnoses,  $p=0.001$ . This seems to represent that patients with a Wells score of  $>4$  or a positive point-of-care D-Dimer test were 1.9 (95% CI 1.3–2.9) times more likely to have a clinical severe disease leading to medical treatment than patients with a Wells score of  $\leq 4$  and a negative point-of-care D-Dimer test. Mainly pneumonia was strongly associated with a high risk class (OR 2.6; 95% CI 1.5–4.5,  $p=0.001$ ). No difference was seen in the prevalence of respiratory tract infection between high risk and low risk patients. Patients with a high probability of PE seemed to be diagnosed 70% less often (OR 0.3; 95% CI 0.2–0.5) with a clinically less severe disease than patients with a low probability. (Table 3.3)

Table 3.3 Odds Ratios for alternative diagnoses by probability for pulmonary embolism.

	High probability: Wells $>4$ or positive D-dimer n=254 n (%; 95% CI)	Low probability: Wells $\leq 4$ and negative D-dimer n=262 n (%; 95% CI)	Total n=516 OR (95% CI; p-value)
Clinically less serious diagnoses	161 (63.4%; 57.1–69.3)	206 (78.6%; 73.2–83.4)	0.5 (0.3–0.7)
Nonspecific thoracic pain / dyspnoea	97 (38.2%; 32.2–44.5)	123 (46.9%; 40.8–53.2)	0.7 (0.5–1.0)
Myalgia	23 (9.1%; 5.8–13.3)	38 (14.5%; 10.5–19.4)	0.6 (0.3–1.0)
Panic disorder / hyperventilation	8 (3.1%; 1.4–6.1)	13 (5.0%; 2.7–8.3)	0.6 (0.3–1.5)
Other clinical less serious diagnosis*	33 (13.0%; 9.1–17.8)	32 (12.2%; 8.5–16.8)	1.1 (0.6–1.8)
Clinically serious diagnoses	93 (36.6%; 30.7–42.9)	56 (21.4%; 16.6–26.8)	2.1 (1.4–3.1)
Pneumonia	47 (18.5%; 13.9–23.8)	20 (7.6%; 4.7–11.5)	2.7 (1.6–4.8)
Asthma / COPD	10 (3.9%; 1.9–7.1)	15 (5.7%; 3.2–9.3)	0.7 (0.3–1.5)
Respiratory tract infection	6 (2.4%; 0.9–5.1)	6 (2.3%; 0.8–4.9)	1.0 (0.3–3.2)
Other clinical serious diagnosis <sup>†</sup>	30 (32.3%; 22.9–42.8)	15 (16.1%; 9.3–25.2)	2.2 (1.2–4.2)

COPD= chronic obstructive pulmonary disease; CI= confidence interval. <sup>¶</sup> adjusted for age. \* other clinical less severe diagnoses: other diagnoses (e.g. bronchial hyperactivity, collaps eci, trauma thorax, influenza, sinusitis) made by a PCP or hospital physician not leading to any treatment other than supportive care (e.g. painkilling). <sup>†</sup> other clinical severe diagnoses: coronary insufficiency (n=3), atrial fibrillation (n=3), pleuritis (n=3), pneumothorax (n=2), atelectasis (n=2), rib fracture (n=2), obstructive sleep apnoea syndrome (n=2), multiple myeloma (n=1), metastatic colon carcinoma (n=1), endocarditis (n=1), lymphadenopathy eci (n=1), urosepsis diabetes (n=1), diabetes mellitus de novo (n=1), sarcoidosis (n=1), acute aortic dissection (n=1), systemic lupus erythematosus (n=1), Langerhans cell histiocytosis (n=1).

## Discussion

### Main findings

In this analysis of a large prospective study performed in primary care including patients suspected of PE, we found that the most common alternative diagnoses of PE were thoracic pain / dyspnoe e.ci., myalgia and pneumonia. To our knowledge, this is

one of the first studies presenting alternative diagnoses of PE in suspected primary care patients and our results correspond to reported alternative diagnoses in secondary care in the literature.<sup>7</sup>

Furthermore, we showed that high risk patients, with either a positive Wells-rule or positive D-dimer test, in whom the diagnosis of PE was excluded, were more often diagnosed with clinically serious diseases than low risk patients. More than 60% of the patients with a clinically serious disease had a Wells score of >4 or a positive D-Dimer test.

## Interpretation

Our results are consistent with previously published studies showing a high proportion of patients with clinically serious diseases in patients with a high clinical probability of PE.<sup>12,13</sup> The association in our study between risk class and severity of the final diagnosis may be partly explained by high D-dimer levels. It is known from literature that pneumonia<sup>14</sup>, malignancy<sup>12,15</sup>, coronary syndromes<sup>16,17</sup> and heart failure<sup>18</sup> is associated with high D-dimer levels. This corresponds with our finding of an increased proportion of having pneumonia in patients with a positive D-Dimer test result. Unfortunately, a significant association between D-dimer and malignancy, heart failure or coronary syndrome could not be noted due to the small number of patients in the subgroups resulting in large 95% CI. Additional to D-Dimer, also the items 'heart rate >100 beats per minute' and 'haemoptysis' of the Wells clinical decision rule have contributed to the association between the probability for PE and severity of the alternative diagnosis. From these results we may conclude that a low Wells score and negative D-dimer test not only exclude PE, but also reduces the probability of other clinically serious diseases for which patients need to be referred to the hospital. This emphasizes the usefulness of the diagnostic strategy of the Wells rule combined with point-of-care D-dimer testing in primary care.

## Limitations

Some limitations of this study have to be mentioned. First, although we asked primary care physicians to refer all patients to secondary care, 17% of the patients were not sent to the hospital for further diagnostic work-up. No referral to secondary care usually means less systematic diagnostic work-up. This may have resulted in an underreporting of less clinically serious diagnoses in those patients without referral and thus selection bias can not be excluded. Nevertheless, all patients were followed-up in primary care for three months and the reported final diagnosis according to the primary care physician for these patients was included in the present analysis. For 1.5% of the patients no alternative diagnosis was reported. All these patients had a follow-up without VTE.

Second, in 30% of the patients without a confirmed PE but with a clinically serious alternative diagnosis, it was not clear if objective testing was performed to confirm these diagnoses. In these patients the presence of the alternative diagnoses may thus be mainly based on clinical features. Since this also occurs in daily clinical primary care, we think that our study is still a good representation of daily practice.

Third, the original study was designed to validate the diagnostic strategy of excluding PE in primary care by using the Wells clinical decision rule for PE and point-of-care D-dimer testing. Therefore, potentially important characteristics of the alternative diagnoses may not have been recorded. Hence, we were not able to identify risk factors and predictors for the alternative diagnoses. This deserves more attention in future studies.

## Conclusion

In conclusion, we found that the most common alternative diagnoses, besides PE, in primary care patients suspected of PE were nonspecific thoracic pain / dyspnoea, pneumonia and myalgia. Furthermore, we found that a low probability of PE may not only exclude PE but also other serious diseases. Otherwise, patients with a high probability of PE but without PE, often have a clinically serious diagnosis that needs medical treatment. This emphasizes the usefulness of the Wells rule and D-dimer point-of-care testing in the differentiation between high and low risk patients for clinically serious diseases in primary care patients suspected of PE. Although approximately 80% of the primary care patients with a high probability of PE will be not diagnosed with PE, referral to secondary care seems still warranted to diagnose and treat potential other clinical serious diseases.

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# Chapter 4

## Clinical decision rules for excluding pulmonary embolism: a meta-analysis

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*Annals of Internal Medicine* 2011;155:448-460

## Abstract

### **Background**

Clinical probability assessment combined with D-dimer testing is used to exclude pulmonary embolism (PE). To compare test-characteristics of gestalt (physicians' unstructured estimate) and clinical decision rules for evaluating adults with suspected pulmonary embolism and to assess failure-rate (missed cases) when used in combination with D-dimer testing.

### **Methods**

We searched Medline and Embase for articles in English, French, German, Italian, Spanish and Dutch, published between 1966 and June 2011. Three reviewers operating in pairs of two selected prospective studies conducted in consecutive patients suspected of PE. Studies provided PE-probability estimate using gestalt or decision rule as compared to an appropriate reference standard. We extracted data on study characteristics, test performance and prevalence, constructed 2\*2-tables and assessed methodological quality.

### **Results**

Fifty-two studies, including 55268 patients were selected. Meta-analysis was performed on studies investigating gestalt (n=15; sensitivity 0.85/specificity 0.51), Wells-rule at cut-off <2 (n=19;0.84/0.58), Wells-rule at cut-off ≤4 (n=11;0.60/0.80), Geneva-rule (n=5;0.84/0.50) and revised Geneva-rule (n=4;0.91/0.37). Increasing prevalence of PE was associated with higher sensitivity and lower specificity. Combining a decision rule or gestalt with a D-dimer test seemed safe for all strategies except for combining the less sensitive Wells4 with the less sensitive qualitative D-dimer.

### **Conclusions**

Combined with sensitive D-dimer tests all rules and gestalt are safe to exclude PE .We advocate physicians to use a standardized rule because of the lower specificity of gestalt. The choice of rule and D-dimer test must be different for physicians working in different settings.

## Introduction

Pulmonary embolism (PE) has an estimated annual incidence of 2-3 cases per 1000 persons and has a high fatality rate if left untreated.<sup>1</sup> A major problem in diagnosing PE is that signs and symptoms are often non-specific and the vast majority of suspected patients does not have PE.<sup>2</sup> Every day a wide variety of doctors – such as primary care physicians, pulmonologists, internists, surgeons and emergency physicians – are facing the diagnostic dilemma of not missing PE while avoiding expensive and possible harmful diagnostic procedures like multi-detector computerised tomography-scanning. Diagnostic strategies in patients suspected of PE initially focus on identifying patients in whom PE can be ruled out.<sup>3</sup> In these strategies the first step is to assess clinical probability using either empirical clinical assessment ('gestalt') or a standardized clinical decision rule. The most widely used clinical decision rule is the Wells rule which includes the physician's judgment of whether PE is more likely than an alternative diagnosis. This criterion however is subjective. New rules, such as the Geneva-, Pisa-, Charlotte- and PERC-rules, containing only objective items were developed. (see appendix I for a full description of rules) Only if clinical probability is low an additional D-dimer test is performed. If clinical probability is not low the patient is referred for additional pulmonary vascular imaging without performing D-dimer testing.<sup>4</sup> Both quantitative and qualitative D-dimer tests are used. Quantitative tests are more sensitive but less specific than qualitative tests.<sup>5</sup> Qualitative tests can be used as a point-of-care test.

Because dispute about the relative merits of gestalt and different rules remained, we performed a systematic review and meta-analysis to compare the sensitivity and specificity of gestalt and different clinical decision rules, using the novel bivariate analysis approach.<sup>6</sup> Moreover we assessed the failure-rate and efficiency of gestalt and rules when used in combination with a D-dimer test. We focussed on their role as a triage tool to exclude PE without referral for imaging tests.

## Methods

### Data sources and searches

We performed a systematic search to identify studies using gestalt or a decision rule in assessing clinical probability of PE. We searched Medline and Embase for articles in English, French, German, Italian, Spanish and Dutch, published between 1966 and June 2011.

Key-words were: pulmonary embolism, epidemiologic research design, epidemiologic studies, predictive value of tests, probability, sensitivity and specificity (the full search strategy is available at [www.annals.org](http://www.annals.org)). Finally, we examined reference lists of selected articles.

## Study selection

To be eligible for inclusion, studies had to fulfil the following criteria:

1. Study population consisted of consecutive patients (age  $\geq 16$  years) with symptoms or signs suspected by a physician to be caused by acute pulmonary embolism (PE).
2. Original, prospectively collected data.
3. Containing an estimate of the clinical probability of PE using gestalt or a clinical decision rule. Gestalt was defined as a physicians' unstructured clinical probability estimate after collecting routine-data (data from patient history, physical examination with or without basic laboratory tests, electrocardiography or a chest x-ray). A clinical decision rule had to be based on a multivariable logistic regression model and had to provide a structured estimate of the probability of PE.
4. Assessment of clinical probability was performed blinded to the results of a D-dimer test or any pulmonary vascular imaging.
5. Studies that derived a clinical decision rule should have included a sufficient number of patients with confirmed pulmonary embolism ( $n > 50$ ) to ensure a minimum level of accuracy of the derived rule.<sup>7</sup>
6. Diagnosis of pulmonary embolism was confirmed by an appropriate (composite) reference standard (such as ventilation-perfusion lung scanning, computerised tomography, pulmonary angiography or autopsy). Diagnosis of deep venous thrombosis as surrogate for the diagnosis of PE was also accepted.<sup>8</sup> In case the diagnosis was refuted without pulmonary imaging (for example in patients with a negative D-dimer test result) we required a clinical follow-up period of at least 45 days.
7. Allowing construction of a 2\*2 table from which we could extract the number of patients with a true-positive-, false-positive-, true-negative- and false-negative test result.
8. To be included in the meta-analysis of rule and gestalt in combination with D-dimer testing we required that D-dimer testing was performed in all patients with low-probability assessment.

Three reviewers operating in pairs of two identified potentially eligible articles. They participated equally. Any disagreements were resolved by discussion between the reviewers.

## Data extraction and quality assessment

Three reviewers operating in pairs of two extracted independently study-characteristics from each included study including: mean (or median) age of patients, proportion outpatients, prevalence of PE (including follow-up period) and type of verification (full description of study-characteristics is available at [www.annals.org](http://www.annals.org)). If information on any of these predefined characteristics was missing in the original

publication, authors were contacted to provide these data. To construct 2\*2 tables, PE-probability assessment had to be dichotomized. In studies not reporting dichotomized data, we dichotomized by taking the lowest probability-category (Wells<2, Geneva<5, revised Geneva<4, simplified revised Geneva  $\leq 1$ , Pisa  $\leq 10\%$ , (see appendix I) versus the other probability categories. Between studies using gestalt the cut-off score for the lowest probability category varied between <10% and <40%.

Finally, based on the constructed 2\*2 tables, the number of true-positives, false-positives, true-negatives and false-negatives were extracted from each study.

The methodological quality of the selected studies was assessed independently by three reviewers operating in pairs of two using the Quadas instrument.<sup>9</sup> The instrument includes 14 quality items, which are all scored as “Yes” (indicating absence of bias), “No” (risk of bias present), or “Unclear”. All discrepancies were resolved by discussion between the three reviewers.

## Data synthesis and analysis

### *Meta-analysis of data from gestalt and rules alone*

Based on the number of true-positives, false-positives, true-negatives and false-negatives sensitivity and specificity together with 95% confidence intervals (95% CI) were calculated (Wilson’s method) and presented in forest plots.

The bivariate model for diagnostic meta-analysis was used to obtain summary estimates of sensitivity and specificity.<sup>6,10</sup> The bivariate approach simultaneously models pairs of (logit transformed) sensitivity and specificity from studies, thereby incorporating any correlation that might exist between sensitivity and specificity. The model uses a random effects approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical and methodological differences between studies. We analyzed data from different rules within a single model in order to obtain summary estimates of sensitivity and specificity for each rule and to subsequently test whether these summary values were significantly different from each other. This model was fitted allowing the between-study variation in sensitivity and specificity to be different across rules. For a rule to be included in the meta-analysis we required a minimum of four studies to account for inter-study variability and assure a reliable assessment of summary estimates of sensitivity and specificity using the bivariate approach.

We extended the basic bivariate model with study-level covariates to assess the impact of bias caused by specific design and patient population characteristics on sensitivity, specificity or both. Three study characteristics, this is type of study (derivation-study: a study for developing the rule or management-study: a study in which the rule was actually used in clinical practice), type of verification method and prevalence, were examined.

### *Meta-analysis of data from rules and gestalt in combination with D-dimer test results*

This combination of tests is used as a diagnostic strategy to exclude PE. Studies therefore address the question whether it is safe to exclude PE and send patients home without anticoagulant treatment when the rule shows low probability and the D-dimer test is negative.

As these studies aim to evaluate a diagnostic strategy, rather than the characteristics of a specific test, failure rate is the outcome measure used in such studies.<sup>4</sup> Failure rate is defined as the proportion of patients with symptomatic and confirmed venous thrombo-embolism during follow-up divided by the total number of patients with negative test results on both rule and D-dimer test ('missed cases') We used a random-effects model to combine these logit transformed proportions to estimate the overall failure rate for each combination of gestalt or decision rule with D-dimer. Covariates were added to the model to examine whether summary failure rates were different depending on the type of rule or type of D-dimer test used. We considered a strategy using clinical probability assessment in combination with a D-dimer test to exclude PE safe if the failure rate was below 2% with a maximum upper confidence limit of 2.7% (being the upper confidence limit of the three-month thrombo-embolic rate of patients suspected of PE but with a normal pulmonary angiography).<sup>11</sup> Another outcome measure that is relevant is the efficiency of the diagnostic strategy. Efficiency is expressed as the number of patients that receive a negative test result on both the rule and the D-dimer test among all included patients ('successful avoidance of imaging'). This is also a proportion and was analysed in the same manner as the failure rate. SAS 9.1, in particular the non-linear mixed models procedure (PROC NLMIXED), was used in the analyses.

### Role of funding source

The study was funded by the Dutch Heart Foundation. The funder played no role in question formulation, searches and data collection, data interpretation, manuscript preparation or approval of the manuscript for publication.

## Results

### Study selection

The search yielded 14642 citations and 313 studies were retrieved for detailed reading of which 52 studies met our inclusion criteria.

## Study characteristics

Included studies were all published in English between 1990 and 2011. In 52 studies 55268 patients (median 753, range 77-8138) were included. PE was diagnosed in 8987 patients (overall prevalence 16%, range 4-44%). The mean age of included patients ranged from 45-72 years (full description of study-characteristics of included studies is available at [www.annals.org](http://www.annals.org)).

## Index tests (clinical decision rules) under study

Five different clinical decision rules were identified: the Wells rules (Wells2 (cut-off<2), Wells4 (cut-off≤4)<sup>12</sup> and the simplified Wells rule<sup>13</sup>), the Geneva rules (original<sup>14</sup>, revised<sup>15</sup> and simplified revised<sup>16</sup>), the Pisa-rules (original<sup>17</sup> and revised<sup>18</sup>), the Charlotte rule<sup>19</sup> and the PERC-rule (Pulmonary Embolism Rule-out Criteria).<sup>20</sup> (Appendix I of this thesis). The Geneva-rule (original) and Pisa-rules use additional diagnostics (electrocardiography, chest x-ray); the other rules all use clinical data only.

## Quality assessment

All studies used the appropriate cross-sectional study design and collected data prospectively. Differential disease verification as potential source of bias was present in 63% of the studies. This means, for example, that patients with a positive clinical decision rule underwent pulmonary vascular imaging as reference test, whereas patients with a negative decision rule and a negative D-dimer test did not undergo this reference test but only received follow-up. In addition uninterpretable test results were not always reported (37%).

## Results of individual studies

Figures 4.1 and 4.2 show the *forest plots* of sensitivity and specificity of individual studies. Results varied considerably both between and within rules. The confidence-intervals for specificity were substantially smaller than for sensitivity due to the larger numbers of patients not having PE. The low sensitivity of the Charlotte-studies and the high sensitivity of the Pisa-studies was striking. Outliers were (partly) explained by cut-off differences. For example, Perrier 2005<sup>21</sup> (Geneva-rule), Righini<sup>22</sup> (revised Geneva), Parent<sup>23</sup> (gestalt) and Elias<sup>24</sup> (gestalt) used high cut-off levels. Accordingly, fewer patients were classified as false-positives but more patients as false-negatives, leading to higher specificities and lower sensitivities respectively.

The forest-plot for specificity clearly shows the lower specificity of gestalt-studies (with a low cut-off) and PERC-studies versus the studies using other decision rules.



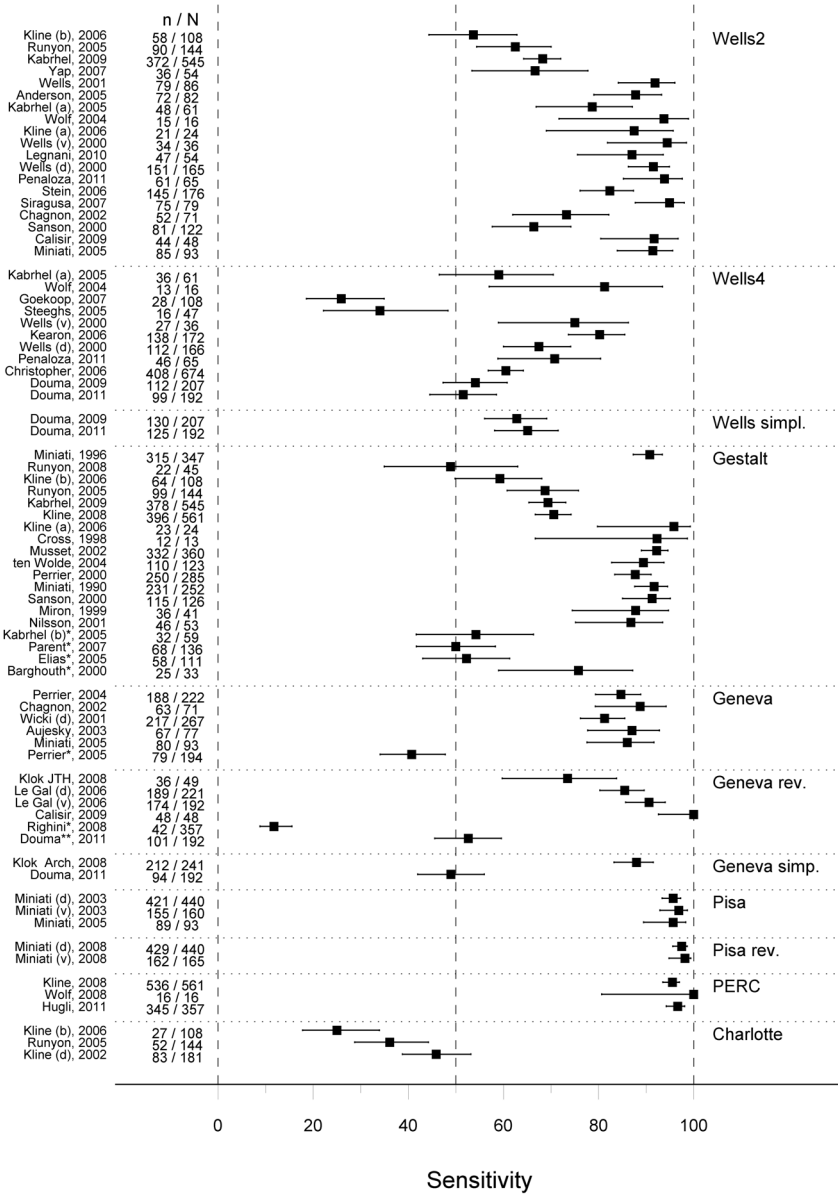


Figure 4.1 Forest plot of sensitivity of gestalt and different decision rules. Studies ordered from low to high prevalence of pulmonary embolism, and by type. n/N= proportion of patients with pulmonary embolism (N) who have a positive test (n). Wells2= Wells with cut-off<2, Wells4= Wells with cut-off≤4, Wells simpl.=Wells simplified ,Geneva rev.= revised Geneva with trichotomized cut-off, Geneva simp.=revised Geneva simplified, Pisa rev.= Pisa revised, PERC=Pulmonary Embolism Rule-out Criteria, (d): derivation-study, (v) validation-study, (a,b) author published two studies in same year, \* study with high-cut-off excluded from meta-analysis, \*\* study with revised Geneva dichotomized cut-off.

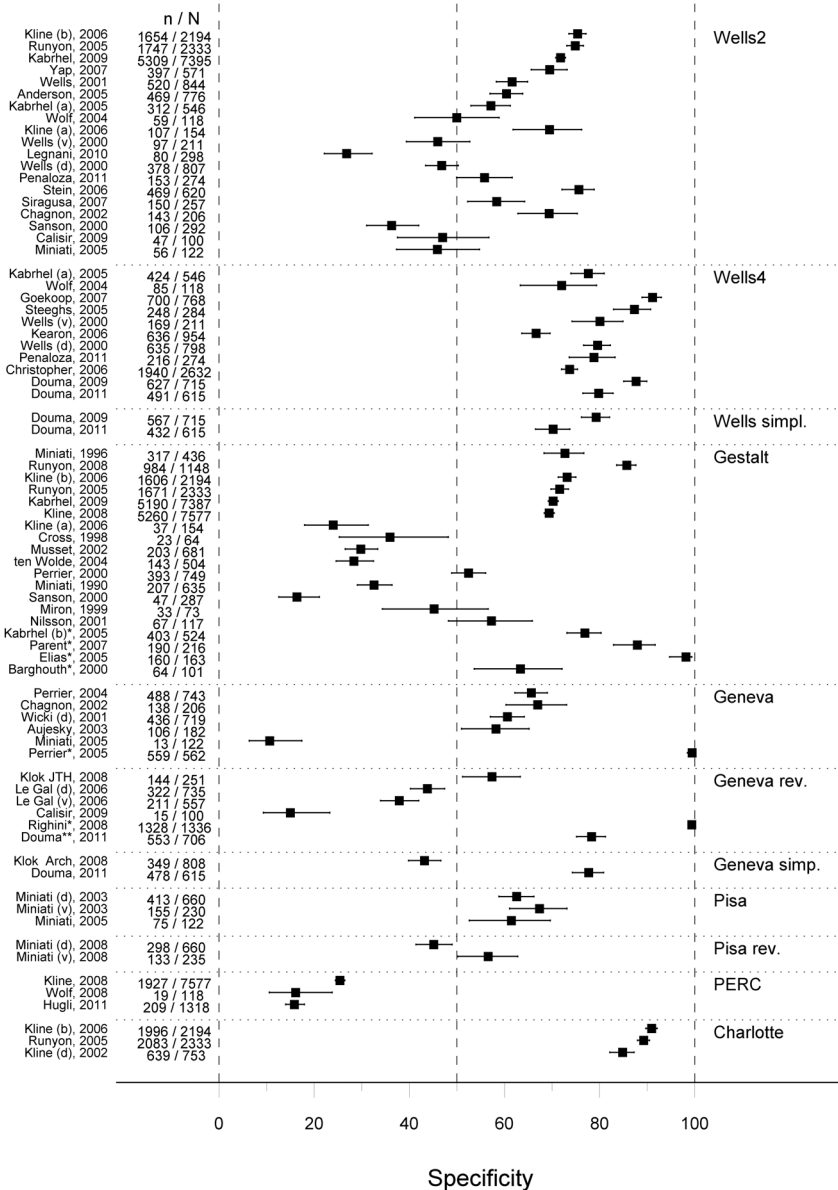


Figure 4.2 Forest plot of specificity of gestalt and different decision rules. Studies ordered from low to high prevalence of pulmonary embolism, and by type of rule. n/N= proportion of patients without pulmonary embolism (N) who have a negative test (n). Wells2= Wells with cut-off<2, Wells4= Wells with cut-off≤4, Wells simpl.=Wells simplified, Geneva rev.= revised Geneva with trichotomized cut-off, Geneva simp.=revised Geneva simplified, Pisa rev.= Pisa revised, PERC=Pulmonary embolism Rule-out Criteria, (d)= derivation-study, (v)= validation-study,(a,b)= author published two studies in same year, \* study with high-cut-off excluded from meta-analysis, \*\* study with revised Geneva dichotomized cut-off.

## Sensitivity and specificity of gestalt and different clinical decision rules

A pooled analysis using the bivariate model was performed in studies using gestalt (n=19), Wells2 (n=19), Wells4 (n=11), Geneva (n=6) and revised Geneva (n=6). For the other clinical decision rules less than four studies were available and therefore could not be included in the meta-analysis.

For gestalt, Geneva and revised Geneva the meta-analysis was performed with 15 instead of 19 studies, 5 instead of 6 and 4 instead of 6 studies, respectively. One study used revised Geneva with a dichotomized cut-off<sup>25</sup> and in six studies<sup>21-24,26,27</sup> the cut-off was regarded too high (probability >40%) to be useful for excluding PE and were excluded from meta-analysis.

Table 4.1 shows the pooled sensitivity and specificity of gestalt, Wells2, Wells4, Geneva and revised Geneva. For both sensitivity and specificity differences between Wells4 and the other rules/gestalt were statistically significant (p<0.01). For specificity also the difference between Wells2 and the revised Geneva was statistically significant (p=0.026). Other differences between the rules or gestalt were not significant.

The summary estimates of sensitivity indicate that a negative test result from any clinical decision rule alone is insufficient for decision-making. Even for the revised Geneva it would mean that 9% (1 minus sensitivity) of patients with PE are classified as false negatives and therefore would be left untreated.

The between study variability for sensitivity and specificity was substantial for all rules and gestalt.

Table 4.1 Pooled sensitivity and specificity of gestalt and different decision rules.

Type of decision rule	No. of studies	Prevalence in %	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Estimated sensitivity at prevalence 15% # (95% CI)	Estimated specificity at prevalence 15% # (95% CI)
Gestalt	15	16.7	0.85 (0.78-0.90)	0.51 (0.39-0.63)	0.83 (0.81-0.84)	0.52 (0.43-0.62)
Wells2*	19	14.7	0.84 (0.78-0.89)	0.58 (0.52-0.65)	0.85 (0.80-0.89)	0.58 (0.52-0.63)
Wells4**	11	16.3	0.60 (0.49-0.69)	0.80 (0.75-0.84)	0.58 (0.47-0.68)	0.81 (0.76-0.85)
Geneva	5	29.0	0.84 (0.81-0.87)	0.50 (0.29-0.72)	0.76 (0.71-0.79)	0.61 (0.41-0.78)
Revised Geneva	4	23.7	0.91 (0.73-0.98)	0.37 (0.22-0.55)	0.82 (0.78-0.86)	0.45 (0.32-0.59)

# A theoretical population with PE-prevalence of 15%; \* Wells2= Wells-rule with cut-off <2; \*\* Wells4= Wells-rule with cut-off ≤4.

## Covariate analysis

The prevalence of PE in the included studies had a significant impact on sensitivity and specificity for gestalt, Wells-, and Geneva-rules. The direction of the effect was similar across the rules: increasing prevalence was associated with higher sensitivity and lower specificity. For example a change in prevalence from 5% to 30% is accompanied by an increase in sensitivity for the gestalt from 0.63 to 0.90, Wells2 from 0.67 to 0.91, Wells4 from 0.34 to 0.72, Geneva from 0.53 to 0.85 and revised Geneva from 0.63 to 0.90.

Because overall prevalence for PE was different between gestalt, Wells-, and Geneva-rules we performed an additional analysis adjusting for these differences in prevalence by adding it as a covariate to the model. Table 4.1 demonstrates the accuracy of the different rules in a virtual population with a prevalence of PE of 15% (overall prevalence included studies 16%). Because the actual prevalence in gestalt and Wells-studies is near 15% their accuracy hardly changed while sensitivity of the (revised) Geneva is considerably lower and specificity higher.

To study the influence of type of verification we classified studies into three groups. In group 1 all patients underwent pulmonary vascular imaging. In group 2 PE was excluded based on a negative decision rule or gestalt combined with a negative D-dimer test including follow-up. In group 3, PE was excluded solely on a negative D-dimer test including follow-up. Both sensitivity and specificity of gestalt, Wells-rules and Geneva-rules did not vary significantly across type of verification (data not shown).

To study the influence of type of study we excluded studies deriving a new rule from the meta-analysis and re-analyzed the remaining studies. Both sensitivity and specificity of gestalt, Wells-, and Geneva-rules did not change (data not shown).

## Adding D-dimer testing to the result of a clinical assessment

A total of 20 studies reported data of combining the result of clinical assessment with D-dimer testing. Some studies reported on more than one rule or gestalt. One study failed to perform D-dimer testing on all patients with a low probability assessment<sup>28</sup> and 4 studies used a high-cut-off and were excluded from analysis.<sup>21-24</sup> Failure rate and efficiency of individual studies are shown in Figure 4.3 and 4.4. Rule or gestalt was 12 times combined with a quantitative D-dimer test, 11 times with a qualitative D-dimer test (Table 4.2). The failure rate for all studies was 0.7% (95% CI 0.5-1.0) with an overall efficiency of 35%. Studies using a qualitative D-dimer test yielded a higher failure rate of 1.0% (95% CI 0.8-1.3) however with a higher efficiency of 45% as compared to a failure rate of 0.4% (95% CI 0.2-0.7) ( $p < 0.01$ ) and an efficiency of 27% ( $p < 0.01$ ) for studies using a quantitative D-dimer test. Using a qualitative D-dimer test the failure rate of Wells4 doubled in comparison with Wells2 (1.7% versus 0.9%). Using Wells4 in combination with a quantitative D-dimer test lowered the failure rate to 0.5%.

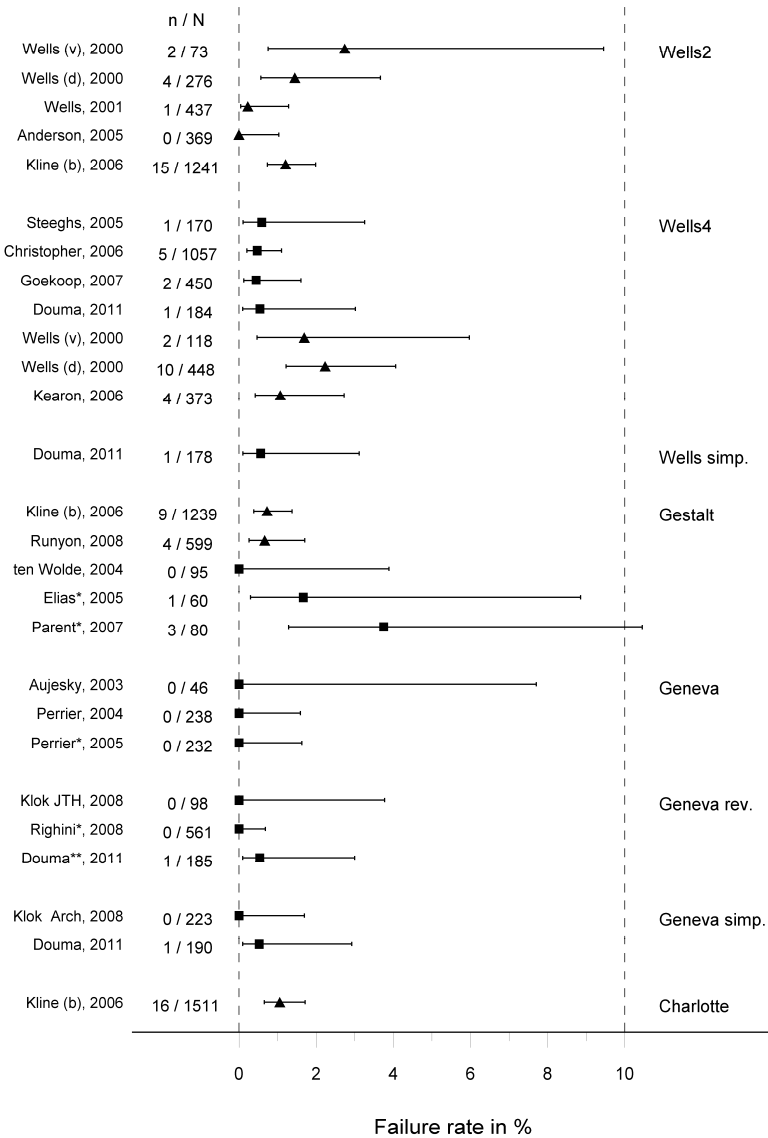


Figure 4.3 Forest plot of the failure rate of gestalt and the different decision rules. ■ = Quantitative D-dimer test, ▲ = Qualitative D-dimer test, n/N= patients with symptomatic and confirmed venous thrombo-embolism during follow-up (n) divided by the total number of patients with negative results on both rule or gestalt and D-dimer test(N), Wells2= Wells with cut-off <2, Wells4= Wells with cut-off ≤4, Wells simp.=Wells simplified ,Geneva rev.= revised Geneva with trichotomized cut-off, Geneva simp.=Geneva simplified, (d) derivation-study, (v) validation-study, (b) author published two studies in same year, \* study with high-cut-off excluded from analysis, \*\* study with revised Geneva dichotomized cut-off.

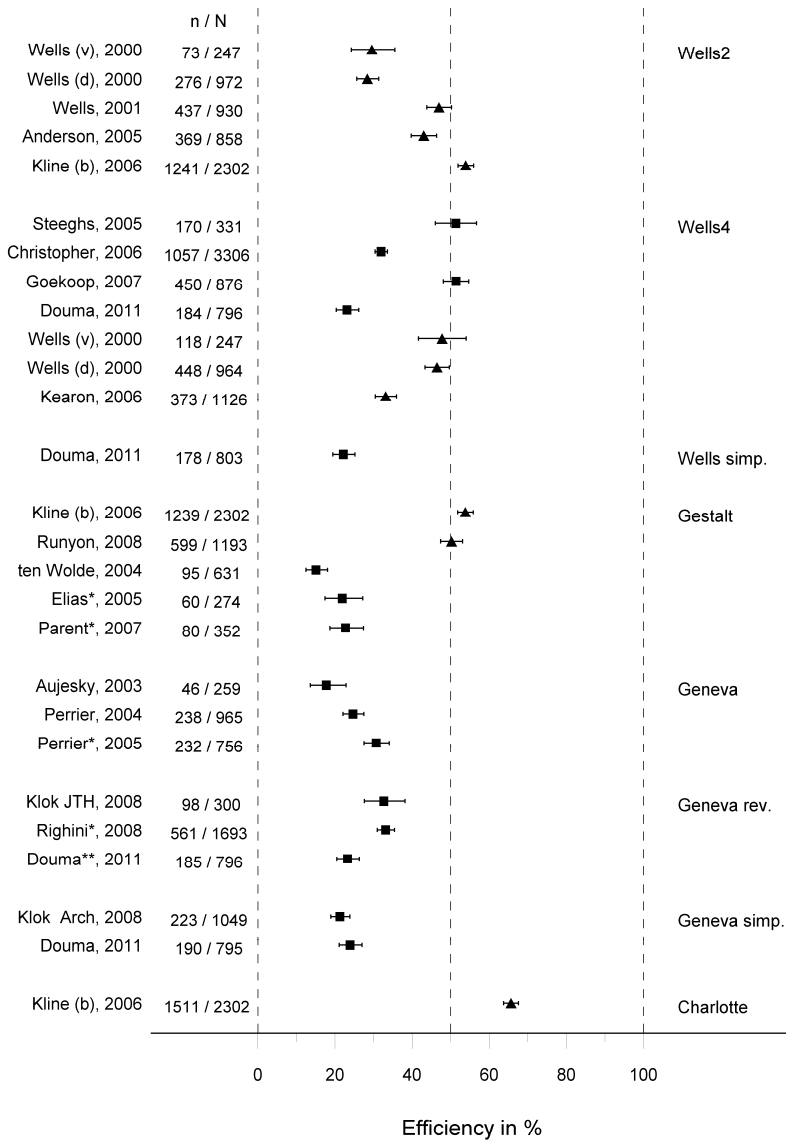


Figure 4.4 Forest plot of the efficiency of gestalt and different decision rules. ■ = Quantitative D-dimer test , ▲= Qualitative D-dimer test, n/N= number of patients with a negative result on both the rule or gestalt and the D-dimer test (n) divided by all included patients (N). Wells2= Wells with cut-off <2, Wells4= Wells with cut-off ≤4, Wells simp.=Wells simplified, Geneva rev.= revised Geneva with trichotomized cut-off, Geneva simp.= Geneva simplified, (d) derivation-study, (v) validation-study, (b) author published two studies in same year, \* study with high-cut-off excluded from analysis, \*\* study with revised Geneva dichotomized cut-off.

Table 4.2 Failure rate and efficiency of gestalt and the different decision rules either combined with a quantitative or a qualitative D-dimer test.

Rule/gestalt	No.	No. pat.	Prevalence PE in %	Failure rate (95% CI) in %	Efficiency (95% CI) in %
All	23	24.384	14.0	0.7 (0.5- 1.0)	35% (30- 41)
Quantitative D-dimer					
All	12	10.941	21.1	0.4 (0.2- 0.7)	27% (22- 34)
Wells4	4	5.320	19.2	0.5 (0.2- 0.9)	39% (31- 47)
Geneva	2	1.224	24.4	0.0 (0.0- 1.3)	21% (14- 31)
Simpl.Geneva	2	1.856	23.3	0.3 (0.0-1.7)	23% (15-33)
Qualitative D-dimer					
All	11	13.443	8.3	1.0 (0.8- 1.3)	45% (39- 52)
Gestalt	2	3.495	4.4	0.7 (0.4-1.2)	52% (40- 64)
Wells4	3	2.337	16.0	1.7 (1.0- 2.8)	42% (32- 52)
Wells2	5	5.309	9.0	0.9 (0.6- 1.5)	40% (33- 48)

We only show separate results of a rule/ gestalt + D-dimer when minimal two studies are available. No: number of times a rule/ gestalt+ D-dimer was studied; No pat: number of patients included. *Simpl. Geneva*=simplified revised Geneva.

The two gestalt-studies using a qualitative D-dimer had an unexpectedly high efficiency, which is likely due to the low prevalence (4% and 5%) in both studies.<sup>29,30</sup> Despite having a low cut-off (<15%) both studies had significantly higher specificity than the summary estimate for specificity.

## Discussion

We were able to perform a pooled bivariate analysis of gestalt, Wells2 and Wells4 (Wells-rule with cut-off <2 and ≤4), Geneva and revised Geneva in their ability to exclude pulmonary embolism. Gestalt, Wells2 and the Geneva-rules had similar, high sensitivity for detecting pulmonary embolism. None of them however was sensitive enough to exclude pulmonary embolism on its own. The specificity of gestalt and the revised Geneva was considerably lower generating more false-positives and more unnecessary computerised tomography-scanning. Increasing prevalence of PE was associated with higher sensitivity and lower specificity, yielding fewer false negatives and more false positives.

A strategy to exclude PE using a combination of clinical probability assessment and a quantitative D-dimer test seemed safe for gestalt, the Wells-, and the Geneva-rules. When using a less sensitive qualitative D-dimer test the 95% CI exceeded our pre-specified threshold of 2.7% failure-rate for Wells4. The more sensitive gestalt and Wells2 were safe in combination with a qualitative D-dimer.

Our findings are in line with a previous meta-analysis showing that different clinical decision rules had similar accuracy in assessing clinical probability.<sup>31</sup> Our findings are also in line with a previous review and meta-analysis showing that PE can be safely

excluded combining low-clinical probability and negative D-dimer test.<sup>32,33</sup> However in these studies neither gestalt nor the importance of specificity of rules and prevalence of PE were reported.

Our meta-analysis has potential limitations. Firstly, we found substantial heterogeneity in sensitivity and specificity within gestalt-, Wells-, and Geneva-studies correlating with differences in PE-prevalence. Increasing prevalence was associated with higher sensitivity and lower specificity. Differences in prevalence can be an indirect reflection of differences in case-mix of included patients. In studies with lower disease prevalence more patients may be in an early stage of the condition which hampers detection.<sup>34-36</sup> This can lead to more false negatives (lower sensitivity). PE-prevalence in included studies ranged from 5 to 44%. Studies performed in the United States (prevalence 8%) and Canada (13%) had considerably lower PE-prevalence as compared to studies performed in Europe (26%). In North-America a low threshold for testing for PE for medico-legal concerns results in low prevalence.<sup>37</sup> In Europe, preselection by primary care physicians results in higher prevalence.

Another explanation for heterogeneity is remaining differences in threshold. In the gestalt-studies threshold-differences are clearly present as defining a low probability in the different gestalt-studies ranges from <10% to <40%. These threshold differences are highly implicit. In the Wells-studies such implicit threshold-differences are also important as one of the seven items in the Wells-rule is rather subjective: 'PE is as likely as or more likely than an alternative diagnosis'. A positive score on this item counts three points, substantially influencing test-positivity (and thus both sensitivity and specificity).

Secondly, different reference standards to diagnose or exclude PE were used in the included studies. Adding different types of reference-methods used as a covariate to the bivariate model did not influence sensitivity or specificity of gestalt, Geneva-, and Wells-rules. The inclusion of studies that used methods of excluding PE without imaging but with uneventful follow-up could lead to a small overestimation of both sensitivity and specificity of gestalt or rule, as a patient with a negative test result but a small subsegmental embolus could be missed when managed with uneventful follow-up only.<sup>38</sup>

Thirdly, we included studies reporting data from both gestalt and rule, using the same study population. In these studies physicians might have been influenced using both gestalt and rule. Because of the limited number of studies available we were not able to perform a covariate-analysis.

Finally, our analysis is based only on published studies and publication bias may be a concern. We didn't look for publication bias.

In a high PE-prevalence population (i.e. a selected population as in a population referred by general practitioners) applying a high sensitive/low specific decision rule (Wells2, Geneva) is less desirable. The high prevalence decreases the already moderately or low specificity leading to an absolute increase of patients classified as false positive by the rule. As a consequence too many patients are referred for



pulmonary vascular imaging. A less sensitive/more specific rule (Wells4) is recommended in this setting. The lower sensitivity of Wells4 urges combination with a high sensitive quantitative D-dimer test.

In a low prevalence unselected population (i.e. emergency department or in primary care) a highly sensitive rule such as Wells2 or Geneva is recommended as a lower PE prevalence lead to a further decrease of the sensitivity, yielding too many false negatives. In this setting it is possible to safely exclude PE using the more sensitive Wells2 and a less sensitive qualitative (point-of care) D-dimer test.

## Conclusion

None of the rules nor gestalt is sensitive enough to exclude PE safely on its own. Combined with sensitive D-dimer tests all rules and gestalt are safe to exclude PE. However it is not just sensitivity of the rule that matters. A lower specificity (and thus more false-positives) of the rule increases the number of patients that are referred for pulmonary vascular imaging, without D-dimer testing. Compared to other rules gestalt and revised Geneva had lower specificity.

The clinician using gestalt tends to act as safe as possible by assigning the patient a higher probability in order not to miss a case of PE, causing more false-positives and causing more patients to be exposed to subsequent unnecessary pulmonary imaging. We advocate physicians to use a standardized decision rule instead of gestalt. Physicians should be aware that the sensitivity of a decision rule increases and specificity decreases with increasing prevalence. As prevalence of PE is an indirect reflection of the case-mix of their population, physicians should use the diagnostic strategy that fits the situation best. In high prevalence situations (a referred population) a rule with higher specificity is desirable, e.g. the Wells4 rule, while in a lower prevalence situation (emergency department or primary care) a more sensitive rule is desirable, e.g. the Wells2 rule or the Geneva rule. As all reviewed studies were performed in a hospital situation (emergency department, referred patients and inpatients), a diagnostic strategy to exclude pulmonary embolism in primary care without imaging must be evaluated before implementing such a strategy.

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# Part II

## Treatment of Pulmonary Embolism in Secondary Care





# Chapter 5

**Fixed dose subcutaneous low molecular weight  
heparins versus adjusted dose unfractionated  
heparin for venous thromboembolism**

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*Cochrane database systematic reviews, 2010;8:CD001100*

## Abstract

### Background

Low molecular weight heparins (LMWH) have been shown to be effective and safe in preventing venous thromboembolism (VTE), and may also be effective for the initial treatment of VTE. We aim to determine the effect of LMWH compared with unfractionated heparin (UFH) for the initial treatment of VTE.

### Methods

Trials were identified by searching the Cochrane Peripheral Vascular Diseases Group's Specialised Register and CENTRAL. Colleagues and pharmaceutical companies were contacted for additional information. Randomised controlled trials comparing fixed dose subcutaneous LMWH with adjusted dose intravenous or subcutaneous UFH in people with VTE were included. At least two reviewers assessed trials for inclusion and quality, and extracted data independently.

### Results

Twenty-three studies were included (n=9587). Thrombotic complications occurred in 165/4541 (3.6%) participants treated with LMWH, compared with 226/4301 (5.3%) treated with UFH (odds ratio (OR) 0.70; 95% confidence intervals (CI) 0.57-0.85, 19 trials). Thrombus size was reduced in 53% of participants treated with LMWH and 45% treated with UFH (OR 0.69; 95% CI 0.59-0.81, 12 trials). Major haemorrhages occurred in 44/3860 (1.1%) participants treated with LMWH, compared with 77/3984 (1.9%) treated with UFH (OR 0.58; 95% CI 0.40 to 0.83, 20 trials). In nineteen trials, 199/4553 (4.3%) participants treated with LMWH died, compared with 245/4221 (5.8%) treated with UFH (OR 0.77; 95% CI 0.63-0.93). Nine studies (n = 4451) examined proximal thrombosis; 2192 participants treated with LMWH and 2259 with UFH. A subgroup analysis showed statistically significant reductions favouring LMWH in thrombotic complications and major haemorrhage. By end of follow up, 80 (3.6%) participants treated with LMWH had thrombotic complications, compared with 143 (6.3%) treated with UFH (OR 0.57; 95% CI 0.44-0.75). Major haemorrhage occurred in 18 (1.0%) participants treated with LMWH, compared with 37 (2.1%) treated with UFH (OR 0.50; 95% CI 0.29-0.85). Nine studies showed a statistically significant reduction favouring LMWH with respect to mortality. By the end of follow up, 3.3% (70/2094) of participants treated with LMWH had died, compared with 5.3% (110/2063) treated with UFH (OR 0.62; 95% CI 0.46-0.84).

### Conclusion

Fixed dose LMWH is more effective and safer than adjusted dose UFH for the initial treatment of VTE. LMWH, compared to UFH, significantly reduces the incidence of thrombotic complications, the occurrence of major haemorrhage during initial treatment and overall mortality at follow up.

## Background

### Description of the condition

Venous thromboembolism (presence of a blood clot in the veins) has an incidence in the general population of approximately 0.1% per year. Its main manifestations are leg complaints, due to deep venous thrombosis in the lower limb (blood clot in the deep veins of the leg), and signs of dyspnea (shortness of breath) and pleuritic thoracic pain (chest pain) when a thrombus (clot) becomes dislodged and embolises in the pulmonary circulation. Recent evidence suggests that although people may only complain about either deep venous thrombosis or pulmonary embolism, in many cases the pathological manifestations are shared between these two clinically distinct conditions.<sup>1,2</sup> Therefore, they are referred to as one disease and are treated with comparable anticoagulant regimens.

### Description of the intervention

Anticoagulant therapy is the treatment of choice for most patients with venous thromboembolism.<sup>3</sup> Patients are usually treated with heparin for five to ten days and then with oral anticoagulants for a minimum of three months. Heparin is administered by either continuous intravenous infusion or twice daily subcutaneous injection.<sup>4-6</sup> The evidence supporting initial treatment with heparin comes from a randomised placebo-controlled trial which demonstrated that a regimen of intravenous heparin plus oral anticoagulants was more effective in preventing recurrence than oral anticoagulants alone.<sup>7</sup> It is standard practice to monitor heparin dosage by the activated partial thromboplastin time (APTT) and adjust the dose to maintain the anticoagulant effect within a defined therapeutic range. Laboratory monitoring is necessary because the anticoagulant response to heparin is highly variable among people with venous thromboembolism, as well as in an individual, and there is evidence that a minimum anticoagulant effect is required for optimum clinical efficacy.<sup>8,9</sup>

### Why it is important to do this review

In the past decade a number of low molecular weight heparin preparations and heparinoids have been developed for clinical use. Compared with unfractionated heparin, low molecular weight heparin preparations have a longer plasma half-life, less inter-individual variability in anticoagulant response to fixed doses, and, in animal models, a more favourable antithrombotic to haemorrhagic ratio.<sup>10,11</sup> As a result of their pharmacokinetic properties, a stable and sustained anticoagulant effect is achieved when low molecular weight heparins are administered subcutaneously, once or twice daily, without laboratory monitoring. Although most experience with low molecular weight heparins has been in the prevention of venous thromboembolism, where they have been shown to be safe and effective<sup>12</sup>, there is accumulating

evidence that these new anticoagulants are also safe and effective for the treatment of venous thromboembolic events.

## Objectives

The purpose of this critical review was to evaluate the efficacy and safety of fixed dose subcutaneous low molecular weight heparin compared to adjusted dose unfractionated heparin (intravenous (i.v.) or subcutaneous (s.c.)) for the initial treatment of people with acute deep venous thrombosis or pulmonary embolism.

## Methods

### Criteria for considering studies for this review

#### *Types of studies*

Randomised controlled clinical trials (RCTs) with prospective follow up.

#### *Types of participants*

People with venous thromboembolism (acute deep venous thrombosis or pulmonary embolism) confirmed by objective tests.

#### *Types of interventions*

Initial treatment (usually the first 5 to 14 days) with fixed dose subcutaneous low molecular weight heparin and adjusted dose unfractionated heparin (i.v. or s.c.).

#### *Types of outcome measures*

##### Primary outcome

(a) Incidence of symptomatic recurrent venous thromboembolism (deep venous thrombosis or pulmonary embolism) during the initial treatment and during follow up.

##### Secondary outcomes

- (a) Change in thrombus size based on pre- and post-treatment venograms.
- (b) Frequency of major haemorrhagic episodes during initial treatment or within 48 hours after treatment cessation.
- (c) Overall mortality at the end of follow up.

## Search methods for identification of studies

### *Electronic searches*

The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched April 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (last searched *Library Issue 2*, 2010) for publications describing (or which might describe) RCTs that compared low molecular weight heparins against unfractionated heparin for the treatment of venous thromboembolism. Details of the search strategy used to search CENTRAL are available at [www.cochrane.org](http://www.cochrane.org). The Specialised Register is maintained by the Trials Search Co-ordinator and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library*.

### *Searching other resources*

The reference lists of papers resulting from these searches were reviewed. In addition, information about possible RCTs was sought through personal communication with colleagues and representatives of pharmaceutical companies. There were no language restrictions.

## Data collection and analysis

### *Selection of studies*

The evaluation of additional eligible studies for this updated review was performed by PE and checked by MP. There was 100% agreement about the classifications of the RCTs between the reviewers.

Studies were excluded if:

- (1) they were dose-ranging studies using higher doses of low molecular weight heparin than are currently in use;
- (2) they used low molecular weight heparin intravenously;
- (3) they adjusted low molecular weight heparin dosages after initiation of treatment;
- (4) the difference in initial treatment was confounded by differences in concomitant medication or long-term medication;
- (5) they did not use a true low molecular weight heparin (by true low molecular weight heparin we mean that no compounds other than heparins are present);
- (6) the administration of unfractionated heparin was suboptimal (i.e. not in adjusted dose);
- (7) the report was an abstract with incomplete data.

### *Data extraction and management*

Data extracted included route of administration and intensity of heparin therapy, intensity of oral anticoagulant therapy, and the performance of independent assessment of study outcomes. Data on outcomes were only extracted if the assessment of the specific outcome was blinded.

In addition, the following data were extracted:

- (1) The incidence of symptomatic recurrent deep venous thrombosis and pulmonary embolism during the initial treatment and during follow up (if active follow up was conducted prospectively at the study centres); whether this was assessed by persons unaware of treatment assignment; and if valid criteria for the diagnosis of recurrent venous thromboembolism were used.

The diagnosis of recurrent deep venous thrombosis was accepted if one of the following criteria was met:

- (a) a new constant intraluminal filling defect not present on the last available venogram;
- (b) if the venogram was not diagnostic, either an abnormal <sup>125</sup>I-fibrinogen leg scan or abnormal impedance plethysmogram or ultrasound result that had been normal before the suspected recurrent episode.<sup>13</sup>

The diagnosis of pulmonary embolism was accepted if one of the following criteria was met:

- (a) a segmental defect on the perfusion lung scan that was unmatched on the ventilation scan or chest röntgenogram;
  - (b) positive pulmonary angiography;
  - (c) pulmonary embolism at autopsy.
- (2) The number of participants in each group with improved venographic score, if pre- and post-treatment venograms were obtained and were assessed by persons unaware of treatment assignment.
  - (3) The frequency of major haemorrhagic episodes during initial treatment. Haemorrhages were classified as major if they were intracranial, retroperitoneal, led directly to death, necessitated transfusion or they led to the interruption of antithrombotic treatment or (re)operation. All other haemorrhages were classified as minor.
  - (4) The overall mortality at the end of follow up specified for participants with or without malignant disease, if active follow up was prospectively conducted at the study centres.

### *Assessment of risk of bias in included studies*

#### *Methodological quality*

For this updated review, a risk of bias table was completed by two authors (PE and MP). The risk of bias was assessed for all new and previously included studies

according to the guidelines given in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.0 (The Cochrane Collaboration, 2008). The following domains were assessed by a score of 'Yes' (i.e. low risk of bias), 'No' (i.e. high risk of bias) or 'Unclear' (uncertain risk of bias):

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation treatment: was allocation adequately concealed?
3. Blinding: was knowledge of the allocated interventions adequately prevented during the study?
4. Incomplete data: were incomplete outcome data adequately addressed?
5. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?
6. Other potential threats to validity: was the study apparently free of other studies that could put it at risk of bias?

Disagreements were resolved by discussion and consensus.

#### *Measures of treatment effect*

The change in thrombus size between pre- and post-treatment venograms was classified as improved or not, based on the criteria used to measure thrombus size in each study. The incidence of venographic improvement and of each of the other outcomes for the different treatments was used to calculate an odds ratio separately for each trial. These odds ratios were then combined across studies, giving due weight to the number of events in each of the two treatment groups in each separate study using the Peto procedure, which assumes a fixed treatment effect.<sup>14,15</sup>

All these analyses were performed for the individual low molecular weight heparin preparations for venous thromboembolism (i.e. deep venous thrombosis and pulmonary embolism combined), and some were performed for proximal deep venous thrombosis and pulmonary embolism separately.

An analysis for all low molecular weight heparin preparations combined was performed if the treatment effects of the individual low molecular weight heparin preparations were compatible with each other, in view of the biochemical heterogeneity as well as the heterogeneity in animal experiments.

The validity of combining the trials was addressed with a statistical test of homogeneity, which considers whether differences in treatment effect over individual trials are consistent with natural variation around a constant effect.<sup>14</sup>

#### *Subgroup analysis and investigation of heterogeneity*

The following subgroup analyses were performed: an analysis in participants with pulmonary embolism, an analysis in participants with venous thromboembolism with or without malignant disease, an analysis of studies with subcutaneous UFH versus LMWH and studies with intravenous UFH versus LMWH, an analysis with adequate



concealment or allocation prior to randomisation and finally a separate analysis to explore trend over time.

In all analyses, the validity of combining the trials was addressed with a statistical test of homogeneity.

## Results

### Description of studies

#### *Results of the search*

For this update the search of the Specialised Register yielded 107 additional reports to trials and 1463 additional citations were retrieved from the search of CENTRAL. The CENTRAL results were screened by reading titles and abstracts.

#### *Included studies*

In this updated review, one study<sup>16</sup> was added to the original meta-analyses. In total, twenty-three studies were truly randomised trials, published between 1988 and the end of 2004, with a total of 9587 participants. Thirteen of the twenty-three studies included participants with symptomatic deep venous thrombosis of the leg without symptoms of pulmonary embolism. In five of these thirteen studies people with distal deep venous thrombosis were included as well as people with proximal deep venous thrombosis. In seven studies participants were included if they had symptomatic deep venous thrombosis of the leg, with or without symptomatic pulmonary embolism or asymptomatic deep venous thrombosis of the leg with symptomatic pulmonary embolism or symptomatic deep venous thrombosis or pulmonary embolism. In two studies participants with pulmonary embolism only were included. All studies used objective diagnostic tests to confirm the diagnosis. All of the included studies considered fixed dose subcutaneous low molecular weight heparin once daily<sup>17-21</sup>, twice daily<sup>16,22-37</sup> or both<sup>38</sup> compared with adjusted dose intravenous unfractionated heparin<sup>17-21,23,24,26-31,33,34,36-38</sup> or subcutaneous unfractionated heparin<sup>16,25,32</sup> or both<sup>22</sup>. Eight different preparations of low molecular weight heparin were identified (nadroparin, tinzaparin, enoxaparin, dalteparin, CY 222, certoparin, ardeparin and reviparin). Ten trials did not have any post-randomisation exclusions or losses to follow up. Eleven trials reported the number of participants lost to follow up which ranged from 1.0% to 12.7%. One trial did not report the dropouts 'Characteristics of included studies are available at [www.cochrane.org](http://www.cochrane.org)').

*Excluded studies*

Twenty one trials were excluded for the following reasons: dosage of unfractionated heparin was not adjusted (four trials<sup>39-42</sup>; dose-ranging study (three trials<sup>43-45</sup>; low molecular weight heparin dosage was adjusted (four trials<sup>46-49</sup>); intravenous administration of low molecular weight heparin (four trials<sup>50-53</sup>); results from participants treated for venous thrombosis of the upper limb and for pulmonary embolism could not be distinguished from those of participants with leg vein thrombosis and the outcome was incompletely evaluated (four trials<sup>54-57</sup>); and difference in long-term treatment between the two treatment regimens (two trials<sup>58,59</sup>).

## Risk of bias in included studies

*Allocation (selection bias)*

In twelve of the twenty-three included studies, the assigned treatment was adequately concealed prior to allocation, while in the other eleven trials concealment of allocation was unclear, based on the information given in the publication (Characteristics of the included studies are available at [www.cochrane.org](http://www.cochrane.org)).

*Blinding (performance bias and detection bias)*

In the majority of the included studies treatment allocation was not blinded due to the difference in route of administration between subcutaneous low molecular weight heparin and intravenous unfractionated heparin. Even the three studies<sup>16,25,32</sup> about subcutaneous unfractionated heparin versus subcutaneous low molecular weight heparin were not blinded for treatment allocation due to an initial intravenous bolus in the unfractionated heparin group. There is only one<sup>18</sup> double blinded clinical trial in which patients received either intravenous unfractionated heparin with subcutaneous placebo or subcutaneous low molecular weight heparin with intravenous placebo. However, twenty-one studies were blinded for outcome assessment. In two studies<sup>26,27</sup> the blinding was unclear.

## Effects of intervention

None of the trials individually demonstrated statistically significant protection from recurrent symptomatic venous thromboembolic complications during the initial treatment period. One trial<sup>23</sup> showed that low molecular weight heparin conferred statistically significant protection from recurrent symptomatic venous thromboembolic complications at the end of follow up; only one study<sup>18</sup> demonstrated a statistically significant reduction in major haemorrhage and mortality after treatment with low molecular weight heparin. Three studies<sup>23,32,34</sup> showed a

statistically significant reduction in thrombus size between pre-treatment and post-treatment venograms in favour of low molecular weight heparin.

#### *Recurrent venous thromboembolism (Graph 1.1-1.5)*

The occurrence of symptomatic recurrent venous thromboembolism was evaluated during the initial treatment period<sup>17,19,21,24,26,28-37</sup>, at three months follow up<sup>16,18,21-24,26,30-32,34,36-38</sup> and at six months follow up.<sup>19,28-30,34,35</sup> Combining all trials with long-term follow up gave a comparison of recurrent thromboembolism at the end of follow up. Analysis of the pooled data from these studies demonstrated a statistically significant reduction in recurrent venous thromboembolic events with low molecular weight heparin during the initial treatment period (OR 0.68; 95% CI 0.48-0.97), at three and six months follow up (OR 0.71; 95% CI 0.56-0.90 and OR 0.68; 95% CI 0.48 to 0.96, respectively) and at the end of follow up (OR 0.70; 95% CI 0.57-0.85). During the initial treatment 51 (1.7%) of the 3030 participants allocated to low molecular weight heparin had thrombotic complications versus 74 (2.4%) of the 3030 of the participants allocated to unfractionated heparin. After a follow up of three months, the period in most of the studies for which oral anticoagulant therapy was given, 122 (3.6%) of the 3382 participants treated with low molecular weight heparin had a recurrent thrombotic event versus 164 (5.2%) of the 3169 participants treated with unfractionated heparin. The results of all individual trials include the observed common odds ratio and their individual 95% confidence interval. Hence, there was no indication of heterogeneity and the statistical test for heterogeneity was negative.

#### *Major haemorrhage during the initial treatment (Graph 1.6)*

Twenty of the included trials evaluated the occurrence of major haemorrhage during the initial treatment.<sup>16-22,24-26,28-37</sup> Analysis of the pooled data showed a statistically significant reduction in major haemorrhagic complications in favour of low molecular weight heparin (OR 0.58; 95% CI 0.40-0.83). Of the individual trials, only one trial using tinzaparin demonstrated a statistically significant reduction in major haemorrhage (OR 0.19; 95% CI 0.06-0.59), whereas two studies using enoxaparin and reviparin showed a statistically non-significant increase in major haemorrhage favouring unfractionated heparin (OR 1.70; 95% CI 0.42-6.87 and OR 1.26; 95% CI 0.49-3.19, respectively). At the end of the initial treatment period, 44 (1.1%) of the 3860 participants in the low molecular weight heparin group versus 77 (1.9%) of the 3984 participants in the unfractionated heparin group suffered a major haemorrhage.

#### *Overall mortality at the end of follow up (Graph 1.7)*

Nineteen studies prospectively evaluated the overall mortality at the end of follow up.<sup>16,18-21,23,24,26-32,34-38,55</sup> Overall mortality at the end of follow up was significantly lower in participants treated with low molecular weight heparin (OR 0.77; 95% CI 0.63-0.93). In the low molecular weight heparin group 199 (4.4%) of the 4553

participants died versus 245 (5.8%) of the 4221 participants in the unfractionated heparin group.

*Venographic assessment (Graph 1.8)*

Venograms were obtained before and after heparin treatment in twelve studies.<sup>17,19,20,23,25,27-29,32-34,36</sup> In all studies, these venograms were adjudicated by investigators unaware of treatment allocation. The combined results of the twelve studies demonstrated a reduction of thrombus size in 53% of the participants treated with low molecular weight heparin and in 44% of participants treated with unfractionated heparin. Low molecular weight heparin was associated with a better venographic outcome (OR 0.69; 95% CI 0.59-0.81), compared with unfractionated heparin. Of the individual low molecular weight heparin preparations, a statistically significant better venographic outcome was observed for nadroparin (OR 0.54; 95% CI 0.37-0.79), reviparin (OR 0.59; 95% CI 0.43-0.80) and ardeparin (OR 0.37; 95% CI 0.14-0.99).

*Analysis in participants with proximal deep venous thrombosis (Graph 2.1-2.5)*

Of the 4451 participants with proximal deep venous thrombosis enrolled in nine studies<sup>18,22,23,28,30,31,34-36</sup>, 2192 were assigned to receive low molecular weight heparin and 2259 to receive unfractionated heparin. Five preparations of low molecular weight heparin were used: nadroparin (three trials, 864 participants), tinzaparin (one trial, 432 participants), enoxaparin (two trials, 634 participants), reviparin (one trial, 763 participants) and certoparin (two trials, 1758 participants).

At the end of follow up 80 (3.6%) of the 2192 participants treated with low molecular weight heparin had a symptomatic recurrent venous thromboembolic event versus 143 (6.3%) of the 2259 participants treated with unfractionated heparin. This reduction was statistically significant in favour of low molecular weight heparin (OR 0.57; 95% CI 0.44-0.75). The reduction in the incidence of symptomatic recurrent deep venous thrombosis as well as the reduction in the incidence of pulmonary embolism with low molecular weight heparin treatment was also statistically significant (OR 0.63; 95% CI 0.42-0.95 and OR 0.42; 95% CI 0.26-0.70, respectively).

Analysis of the pooled data showed a statistically significant reduction in major haemorrhagic complications in favour of low molecular weight heparin (OR 0.50; 95% CI 0.29-0.85). At the end of the initial treatment period, 18 (1.0%) of the 1804 participants in the low molecular weight heparin group versus 37 (2.1%) of the 1785 participants in the unfractionated heparin group suffered a major haemorrhage.

Overall mortality at the end of follow up demonstrated a statistically significant reduction in favour of low molecular weight heparin (OR 0.62; 95% CI 0.46-0.84). In the low molecular weight heparin group 70 (3.3%) of the 2094 participants died versus 110 (5.3%) of the 2063 participants in the unfractionated heparin group.

*Analysis in participants with pulmonary embolism (Graph 3.1)*

The reduction of venous thromboembolic events in participants with pulmonary embolism was not statistically significant (OR 0.88; 95% CI 0.48-1.63).

*Analysis in participants with venous thromboembolism with or without malignant disease (Graph 4.1-5.1)*

Six studies evaluated mortality at the end of follow up in participants with malignant disease.<sup>18,19,21,32,34,37</sup> One of these studies<sup>34</sup> showed a statistically significant reduction in deaths at the end of follow up with low molecular weight heparin (OR 0.16; 95% CI 0.03-0.72). Combining the six studies also demonstrated a statistically significant reduction in overall mortality in participants with cancer who were treated with low molecular weight heparin (OR 0.53; 95% CI 0.33-0.85). In participants without cancer who received low molecular weight heparin, the reduction in overall mortality of approximately 3% was not statistically significant (OR 0.97; 95% CI 0.61-1.56).

*Analysis of studies subcutaneous UFH versus LMWH and studies of intravenous UFH versus LMWH (Graph 6.1-7.1)*

In three studies the UHF in the control group was administered subcutaneously.<sup>16,25,32</sup> The analysis of the pooled data from these studies demonstrated a reduction in recurrent venous thromboembolism at the end of follow up in favour of low molecular weight heparin (OR 0.82; 95% CI 0.40-1.67), although this was not statistically significant. Neither the reduction in major haemorrhagic episodes during initial treatment (OR 0.40; 95% CI 0.42-1.33), nor the overall mortality at the end of follow-up (OR 0.92; 95% CI 0.41-2.04) was statistically significant after treatment with low molecular weight heparin. In the studies which compared LMWH with intravenous UFH, we found a reduction in recurrent venous thromboembolism (OR 0.69; 95% CI 0.56-0.85) as well as in major haemorrhages (OR 0.60; 95% CI 0.41-0.88) as well as in overall mortality (OR 0.76; 95% CI 0.62-0.93) with significant confidence intervals.

*Analysis of studies with adequate concealment of allocation prior to randomisation (Graph 8.1-8.6)*

Twelve studies had clear concealment of allocation prior to randomisation, based on the information given in the publication.<sup>16-18,21,24,27,29-31,35,37,38</sup> The analysis of the pooled data from these studies demonstrated a reduction in recurrent venous thromboembolism during the initial treatment period as well as at the end of follow-up in favour of low molecular weight heparin (OR 0.80; 95% CI 0.55-1.16 and OR 0.81; 95% CI 0.64-1.03, respectively), although this was not statistically significant. Neither the reduction in major haemorrhage (OR 0.61; 95% CI 0.46-1.05) nor the reduction in the overall mortality at the end of follow up (OR 0.82; 95% CI 0.66-1.02) was

statistically significant after treatment with low molecular weight heparin. The reduction in the thrombus size, however, was statistically significant in favour of low molecular weight heparin (OR 0.62; 95% CI 0.43-0.90).

#### *Trends over time (Graph 9.1-9.4)*

In order to investigate trend over time, we performed analyses in which all studies were ordered by their date of publication. The forest plots of these analyses do not show an obvious trend over time.

## Discussion

Our review on low molecular weight heparin for the initial treatment of venous thromboembolism includes more than 9000 participants and indicates that this drug is not only more efficacious than unfractionated heparin, but is also safer with regard to major bleeding episodes and mortality. Many of the included papers reported on the other advantages of low molecular weight heparin over unfractionated heparin. Firstly, the route of administration (subcutaneous once or twice daily) is more convenient, which increases the mobility of participants with venous thromboembolism. Secondly, the pharmacokinetics are more predictable, which abolishes the need for laboratory monitoring and subsequent dose adjustments. Hence, low molecular weight heparin can be advocated as the standard therapy for patients with confirmed venous thromboembolism. Treatment in an outpatient setting has been demonstrated to be feasible, safe and cost-effective for patients with deep venous thrombosis.<sup>30,31,60</sup>

We believe that our efficacy data are robust the 99% CI for the main outcome of recurrent venous thromboembolism, at end of follow up and at three months, was less than one (OR 0.70; 99% CI 0.53-0.91) and (OR 0.71; 99% CI 0.52-0.97). This was true for all of the other outcomes except recurrent venous thromboembolism at one month.

The tendency to improved efficacy with low molecular weight heparin treatment was not at the cost of a higher rate of major haemorrhage. On the contrary, a statistically significant reduction in major haemorrhage was demonstrated during the initial treatment period with low molecular weight heparin. In addition, overall mortality was reduced with low molecular weight heparin, compared with unfractionated heparin. However, the mechanism underlying this observation is unclear.

In the studies with adequate concealment of treatment allocation before randomisation, reductions in recurrent venous thromboembolism, major haemorrhages and overall mortality were also observed, albeit these were smaller than the overall reductions and were not statistically significant. An explanation for these differences in effect size could be that the overall reductions are possibly biased by including less adequate performed studies without adequate concealment.

Although these results are promising, there are a number of unresolved issues. Firstly, since only approximately 25% of the participants included in this critical review had a diagnosis of primary pulmonary embolism, it can be argued that more data are required before low molecular weight heparins can be recommended as the standard treatment for primary pulmonary embolism. Secondly, the combination of all preparations of low molecular weight heparin seems logical, and heterogeneity could not be identified. Current data do not discriminate between different LMWH preparations. However, studies with large sample sizes which include comparisons of different preparations are needed to determine whether the efficacy and safety of the individual low molecular weight heparins is actually comparable. Thirdly, Prandoni et al noted that the route of administration might be relevant to heparin efficacy.<sup>16</sup> When we limited a subgroup analysis to studies that used intravenous UFH, similar results as in the main analyses were observed. When the analysis was confined to those studies that use subcutaneous UFH, we still find a reduction in the incidence of recurrent venous thromboembolism and major haemorrhages, albeit these were not statistically significant. The lack of significance could be due to the smaller patient groups in this subgroup analysis.

We conclude that low molecular weight heparin can safely be adopted as the standard therapy in patients with deep venous thrombosis. In patients with pulmonary embolism, it would be prudent to await further results of new studies. If adequate support is available, low molecular weight heparin treatment can be administered at home in certain cases. In future, as low molecular weight heparin therapy becomes the standard treatment in patients with deep venous thrombosis, new drugs should be compared with low molecular weight heparin.

## Authors' conclusions

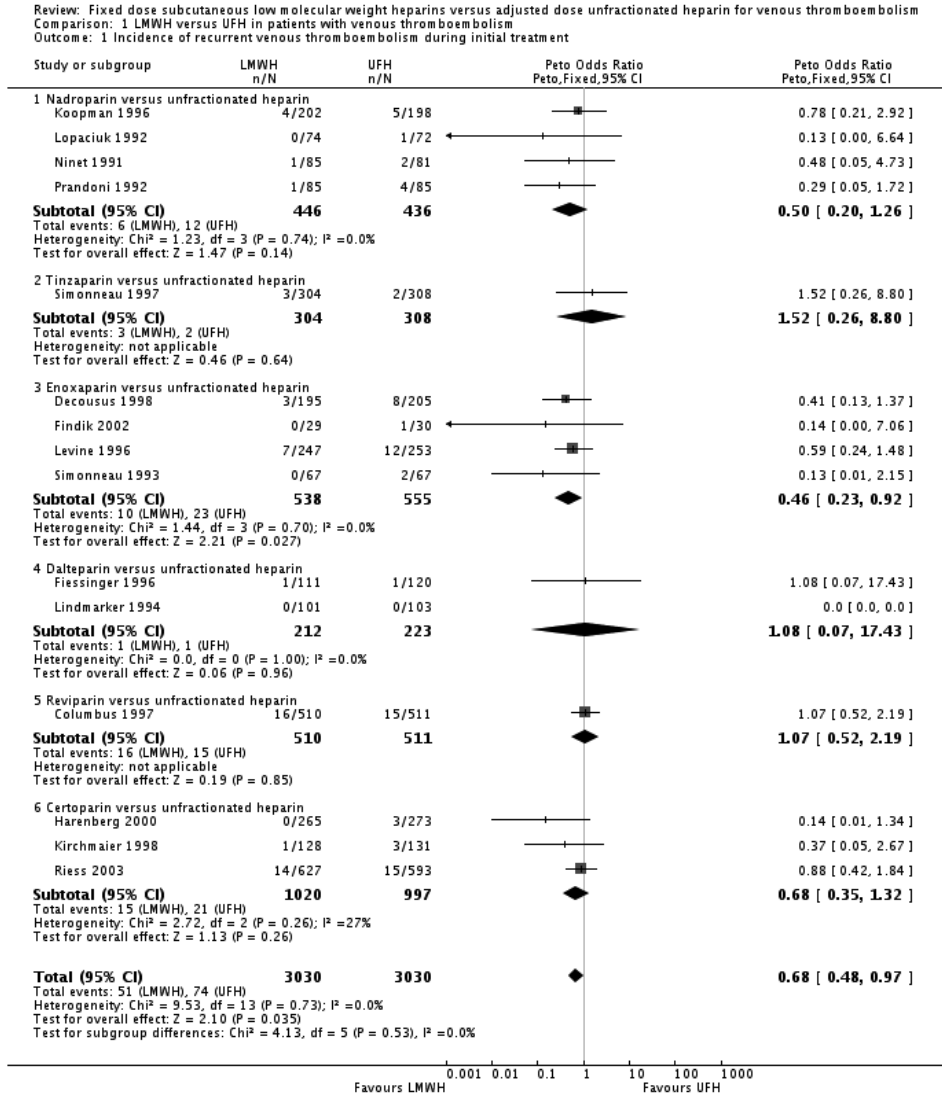
### *Implications for practice*

This systematic review suggests that low molecular weight heparin treatment can safely be adopted as the standard therapy in people with deep venous thrombosis.

### *Implications for research*

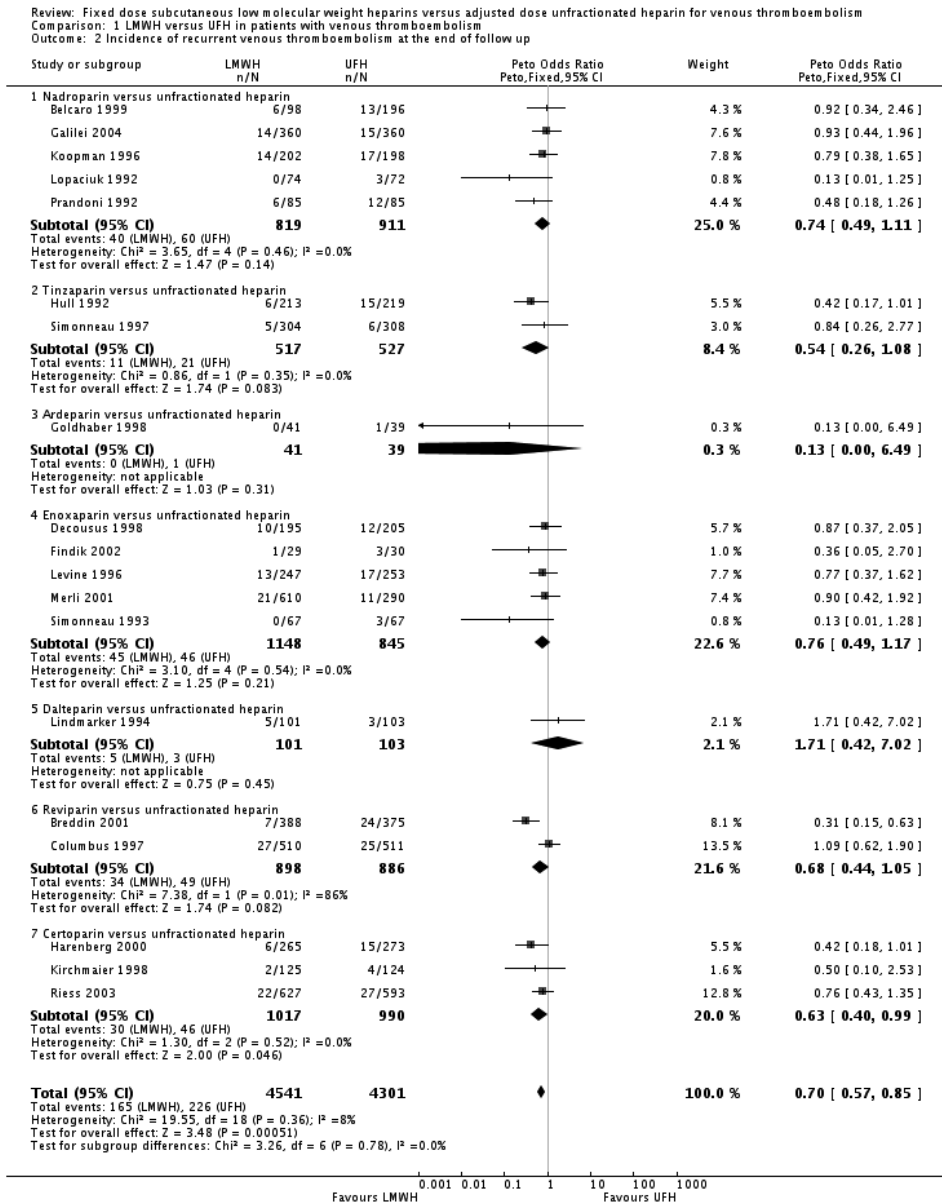
Further studies are required to compare low molecular weight heparin with unfractionated heparin in the treatment of patients with pulmonary embolism. In addition, a large RCT of at least two years' duration should be performed to determine the effects of dosing frequency on long-term sequelae of venous thromboembolism, such as the development of the post-thrombotic syndrome. Individual low molecular weight heparins could be compared with each other, and new drugs should now be compared with low molecular weight heparin.

Graph 1.1 Comparison 1: LMWH versus UFH in patients with thromboembolism. Outcome 1: Incidence of recurrent venous thromboembolism during initial treatment.



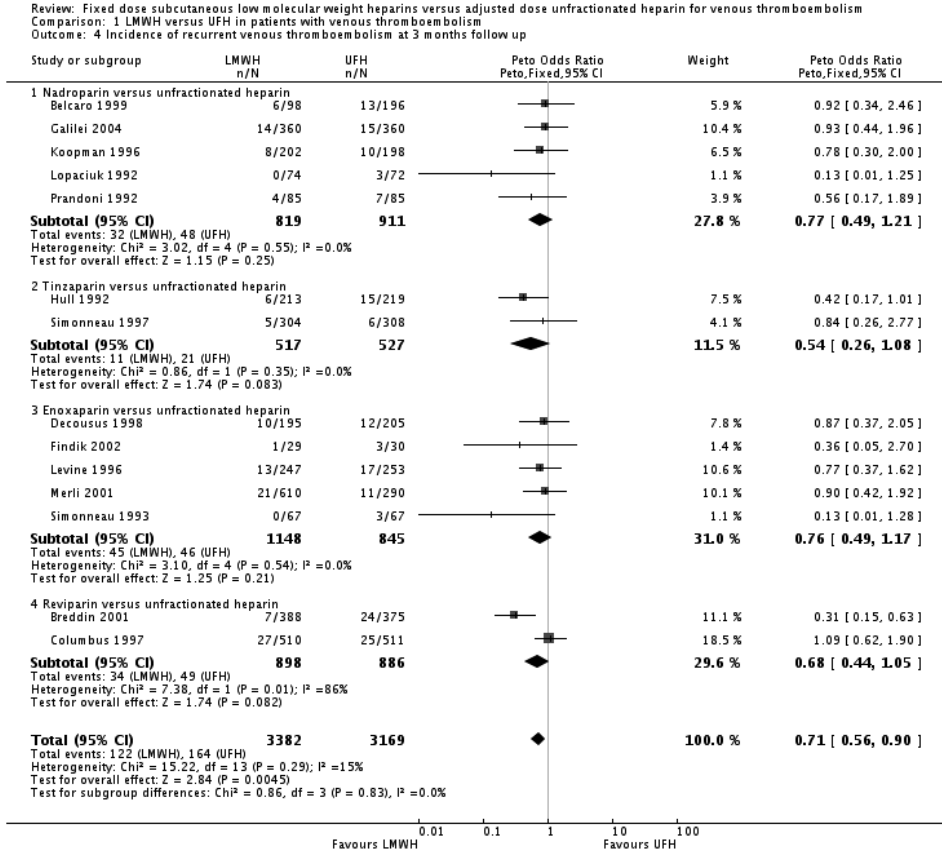


Graph 1.2 Comparison 1: LMWH versus UFH in patients with thromboembolism. Outcome 2: Incidence of recurrent venous thromboembolism at the end of follow up.



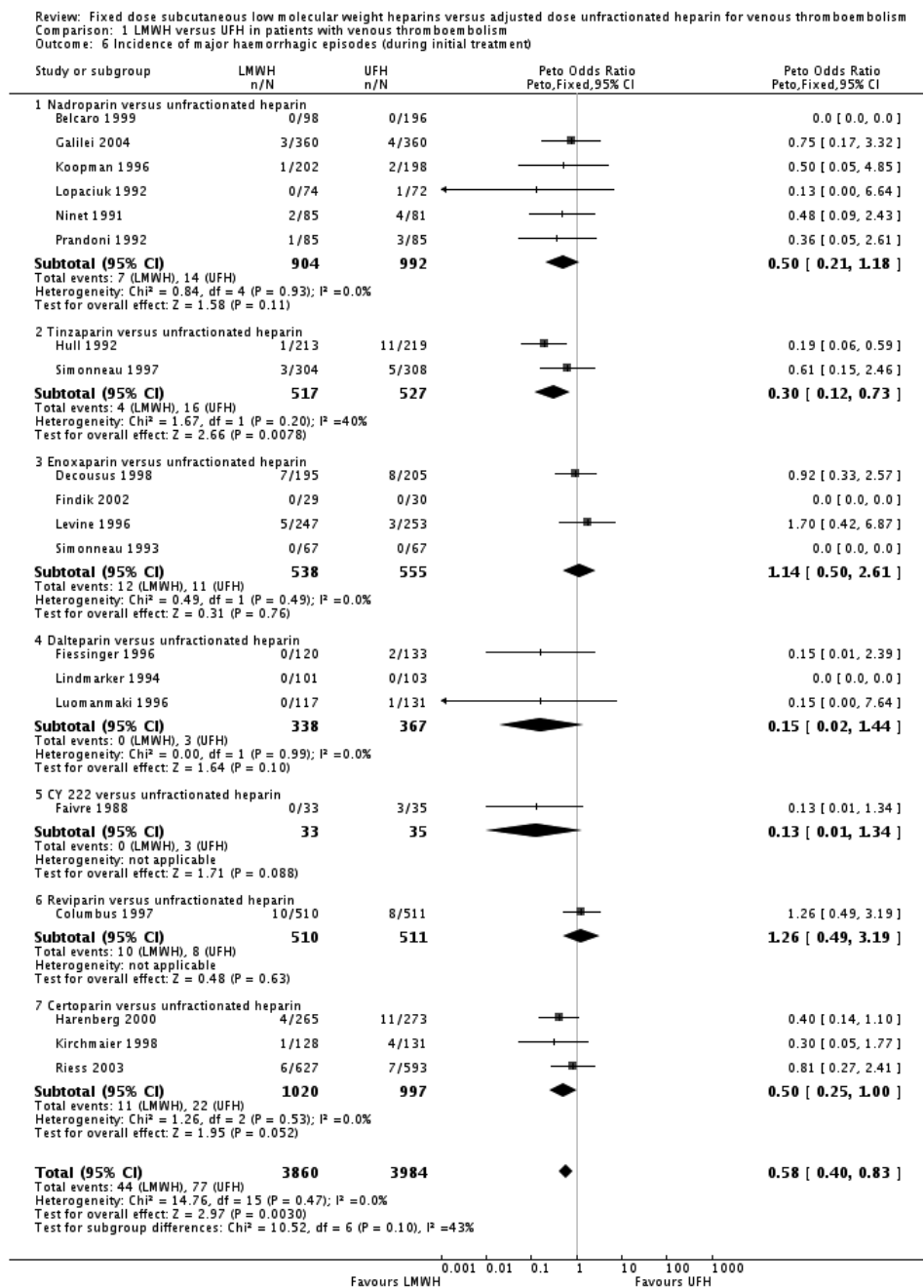


Graph 1.4 Comparison 1: LMWH versus UFH in patients with thromboembolism. Outcome 4: Incidence of recurrent venous thromboembolism at 2 months follow up.

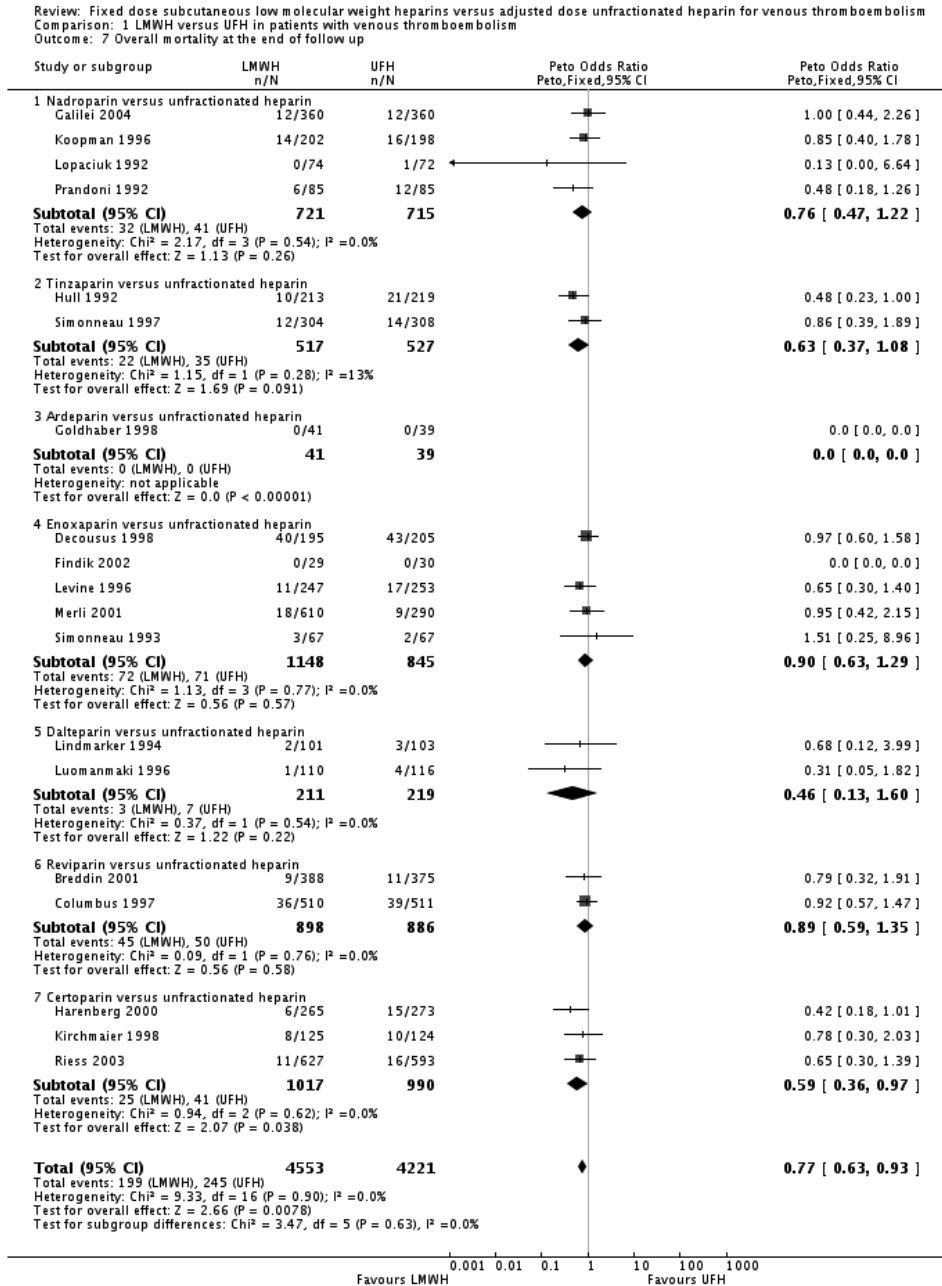




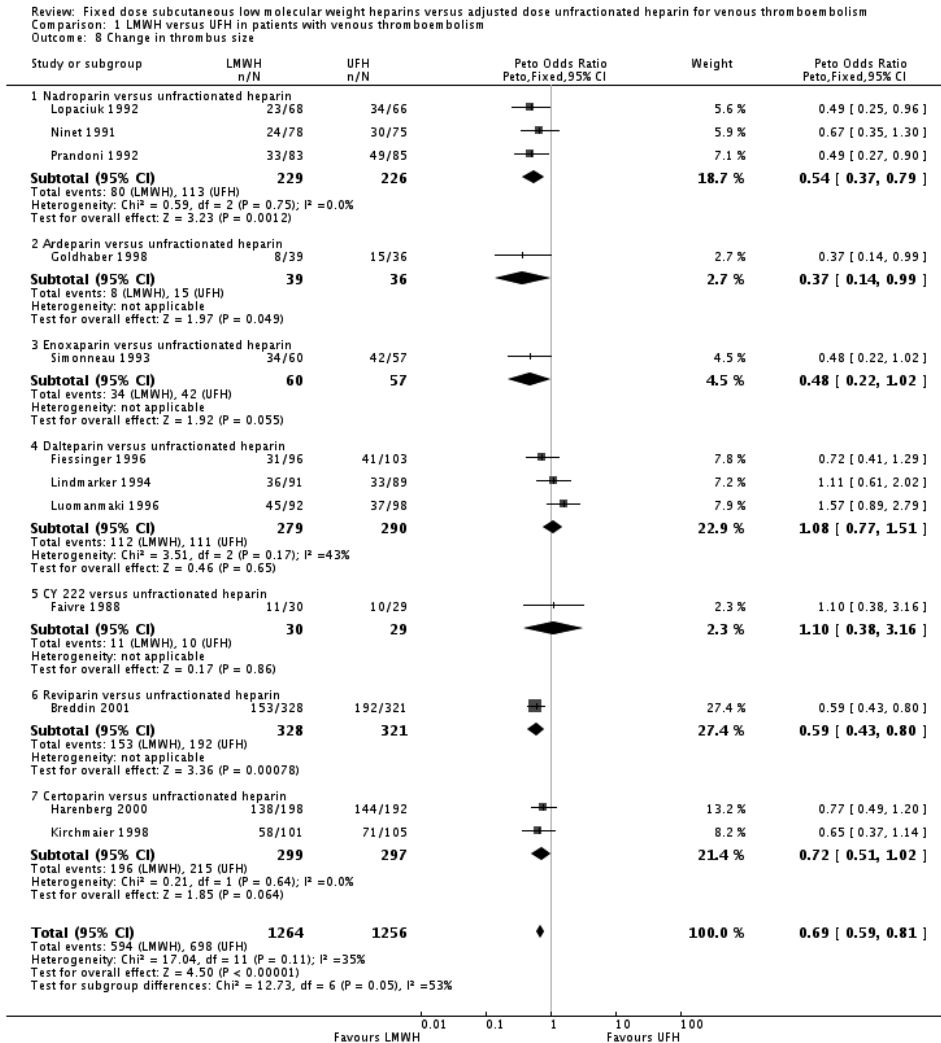
Graph 1.6 Comparison 1: LMWH versus UFH in patients with thromboembolism. Outcome 6: Incidence of major haemorrhagic episodes (during initial treatment).



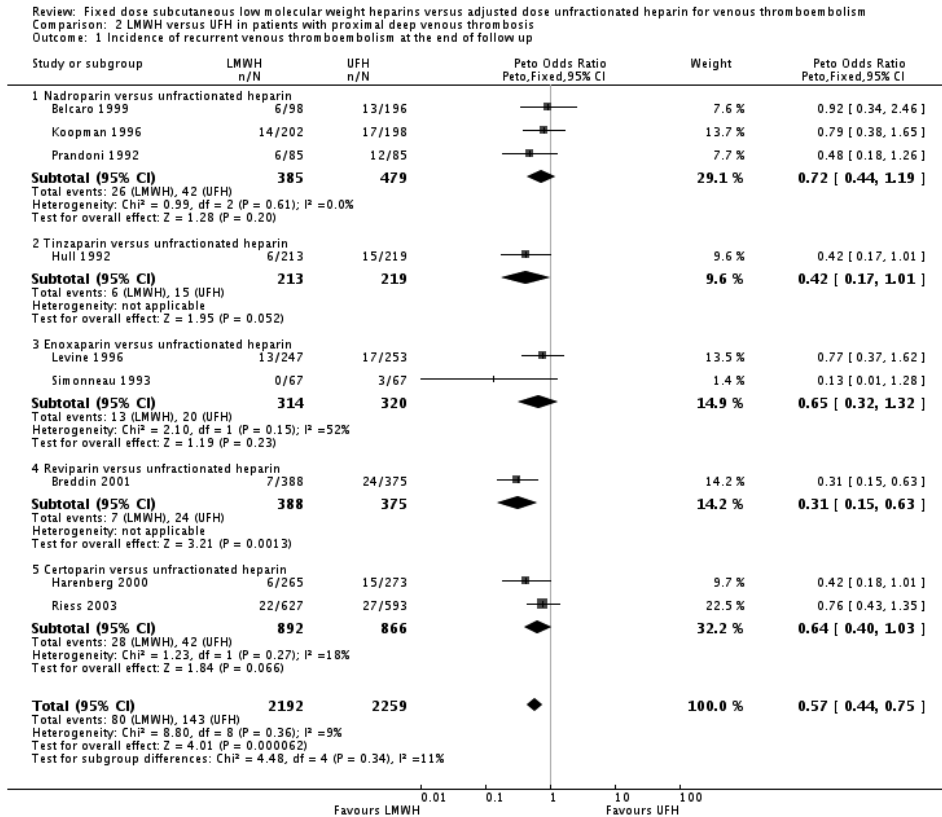
Graph 1.7 Comparison 1: LMWH versus UFH in patients with thromboembolism. Outcome 7: Overall mortality at the end of follow up.



Graph 1.8 Comparison 1: LMWH versus UFH in patients with thromboembolism. Outcome 8: Change in thrombus size.

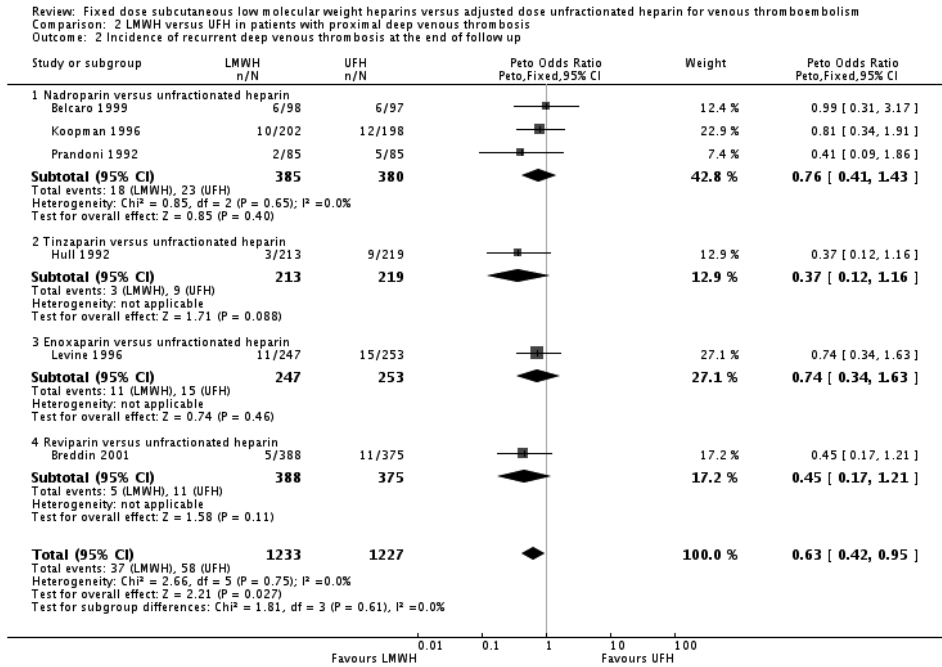


Graph 2.1 Comparison 2: LMWH versus UFH in patients with proximal deep venous thrombosis. Outcome 1: Incidence of recurrent venous thromboembolism at the end of follow up.

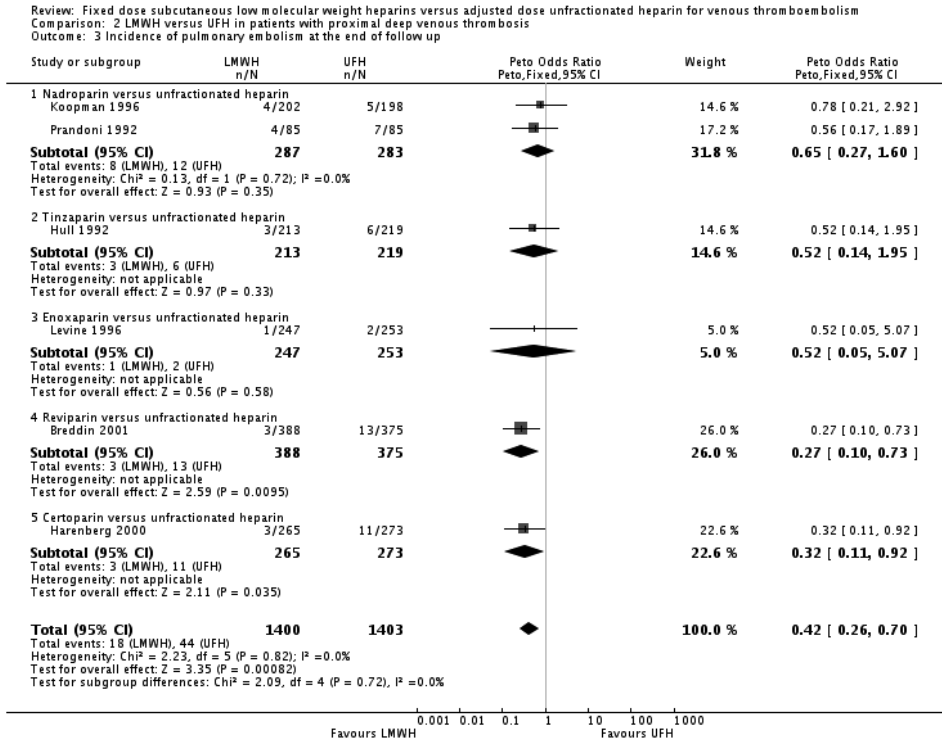




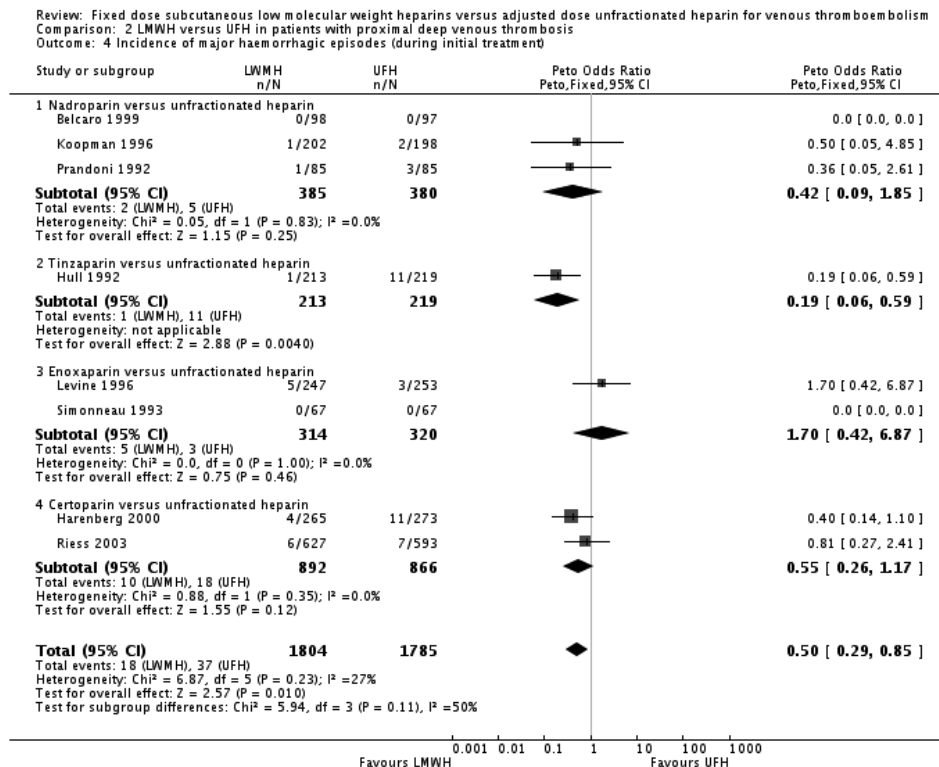
Graph 2.2 Comparison 2: LMWH versus UFH in patients with proximal deep venous thrombosis. Outcome 2: Incidence of deep venous thrombosis at the end of follow up.



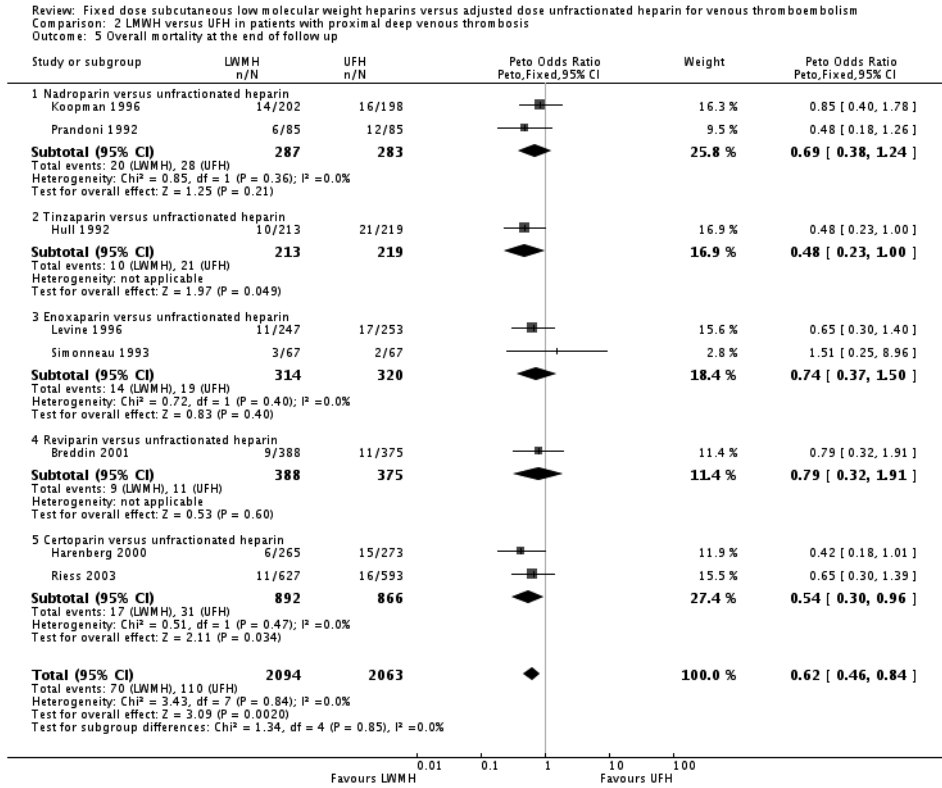
Graph 2.3 Comparison 2: LMWH versus UFH in patients with proximal deep venous thrombosis. Outcome 3: Incidence of pulmonary embolism at the end of follow up.



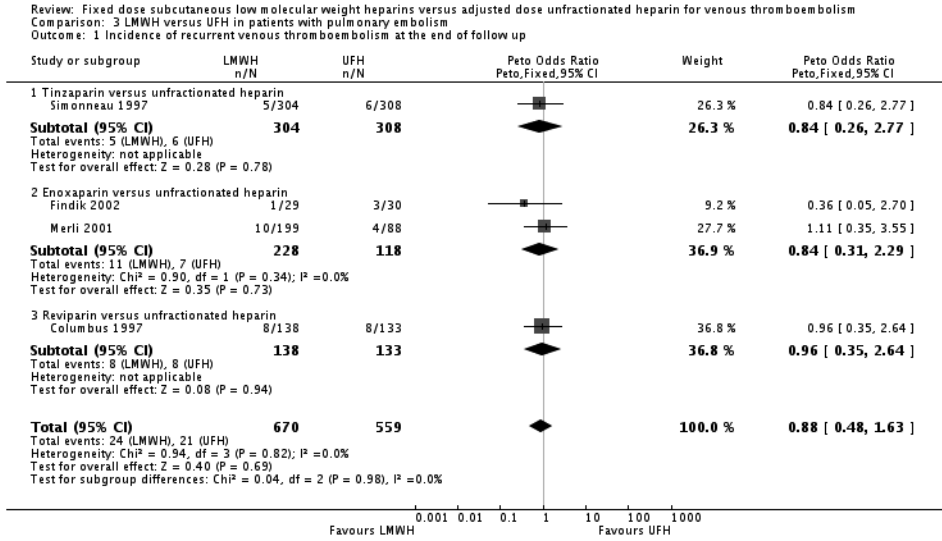
Graph 2.4 Comparison 2: LMWH versus UFH in patients with proximal deep venous thrombosis. Outcome 4: Incidence of major haemorrhagic episodes (during initial treatment).



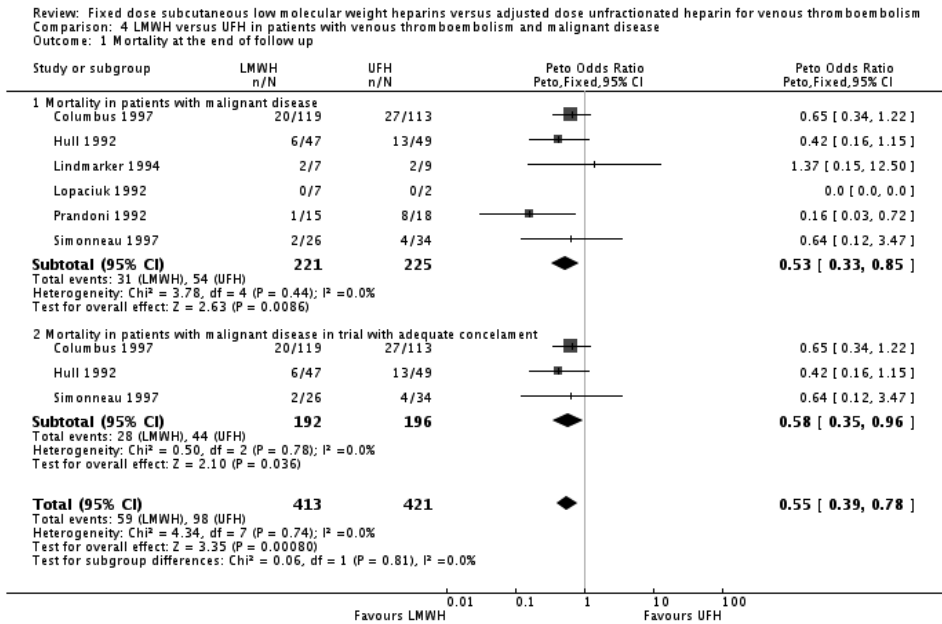
Graph 2.5 Comparison 2: LMWH versus UFH in patients with proximal deep venous thrombosis. Outcome 5: Overall mortality at the end of follow up.



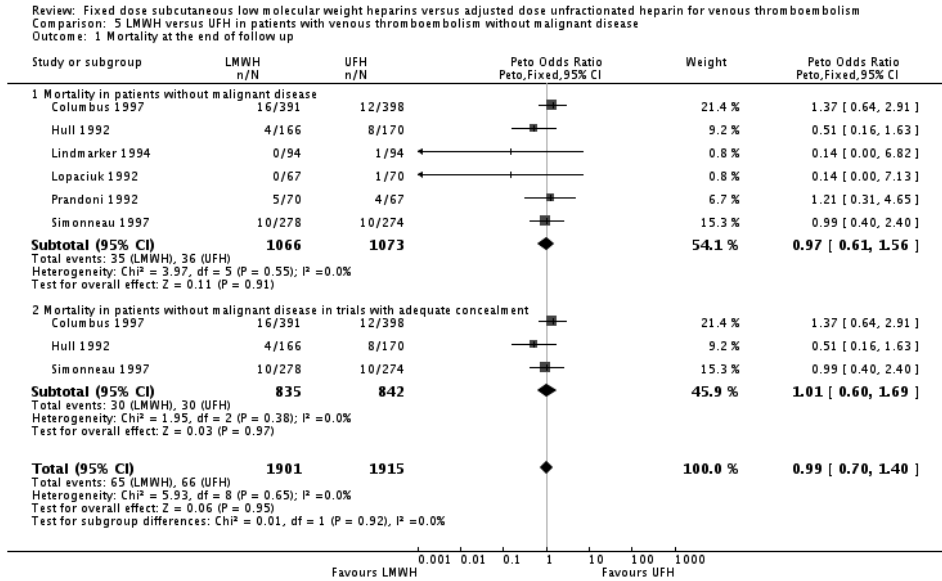
Graph 3.1 Comparison 3: LMWH versus UFH in patients with pulmonary embolism. Outcome 1: Incidence of recurrent venous thromboembolism at the end of follow up.



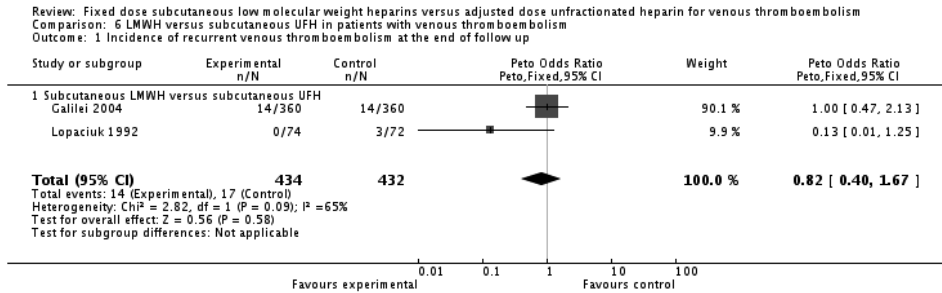
Graph 4.1 Comparison 3: LMWH versus UFH in patients with proximal deep venous thrombosis and malignant disease. Outcome 1: Mortality at the end of follow up.



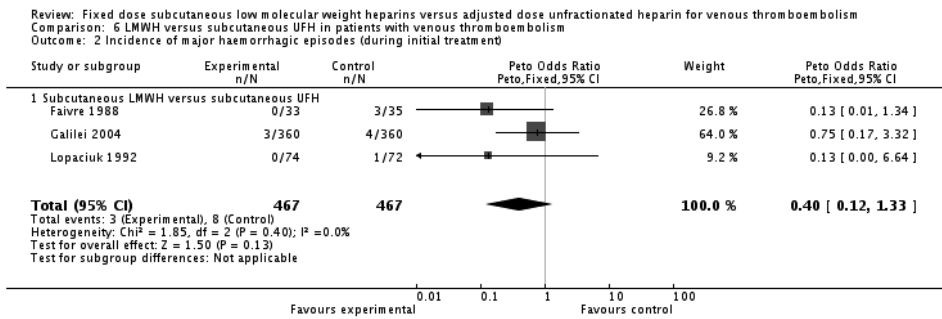
Graph 5.1 Comparison 5: LMWH versus UFH in patients with proximal deep venous thrombosis without malignant disease. Outcome 1: Mortality at the end of follow up.



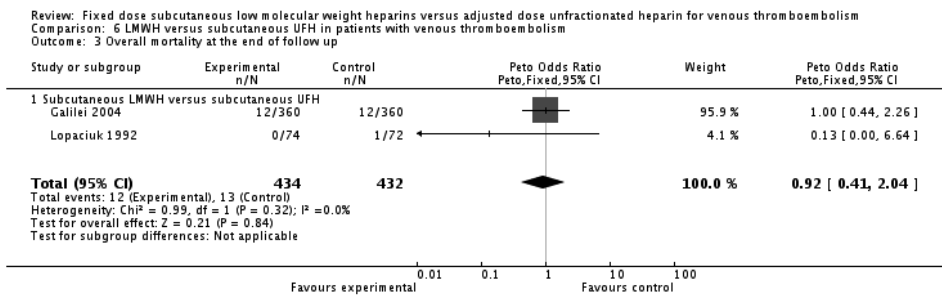
Graph 6.1 Comparison 6: LMWH versus subcutaneous UFH in patients with venous thromboembolism. Outcome 1: Incidence of recurrent venous thromboembolism at the end of follow up.



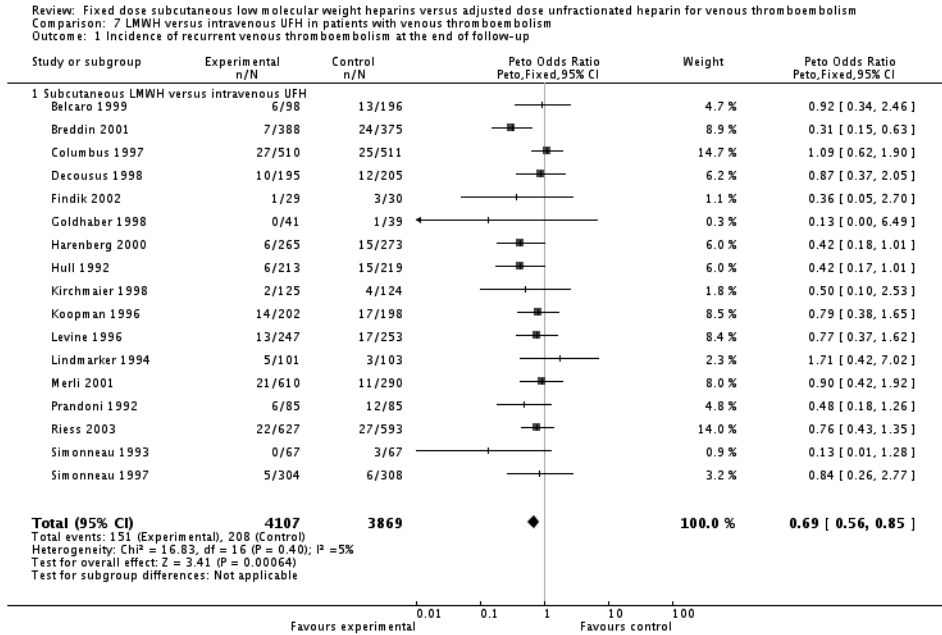
Graph 6.2 Comparison 6: LMWH versus subcutaneous UFH in patients with venous thromboembolism. Outcome 2: Incidence of major haemorrhagic episodes (during initial treatment).



Graph 6.3 Comparison 6: LMWH versus subcutaneous UFH in patients with venous thromboembolism. Outcome 3: Overall mortality at the end of follow up.

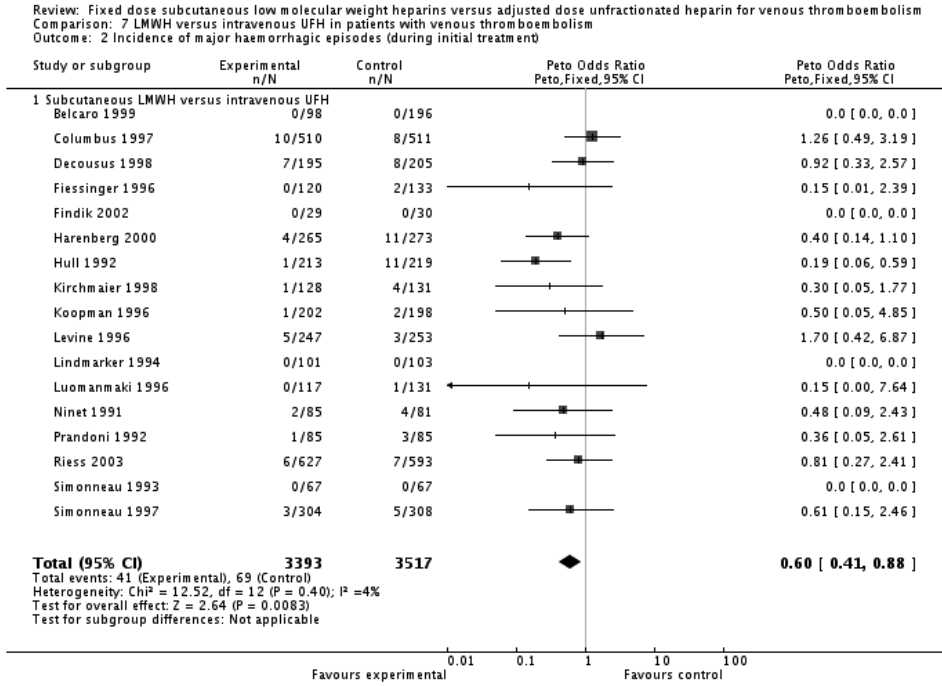


Graph 7.1 Comparison 7: LMWH versus intravenous UFH in patients with venous thromboembolism.  
Outcome 1: Incidence of recurrent venous thromboembolism at the end of follow up.

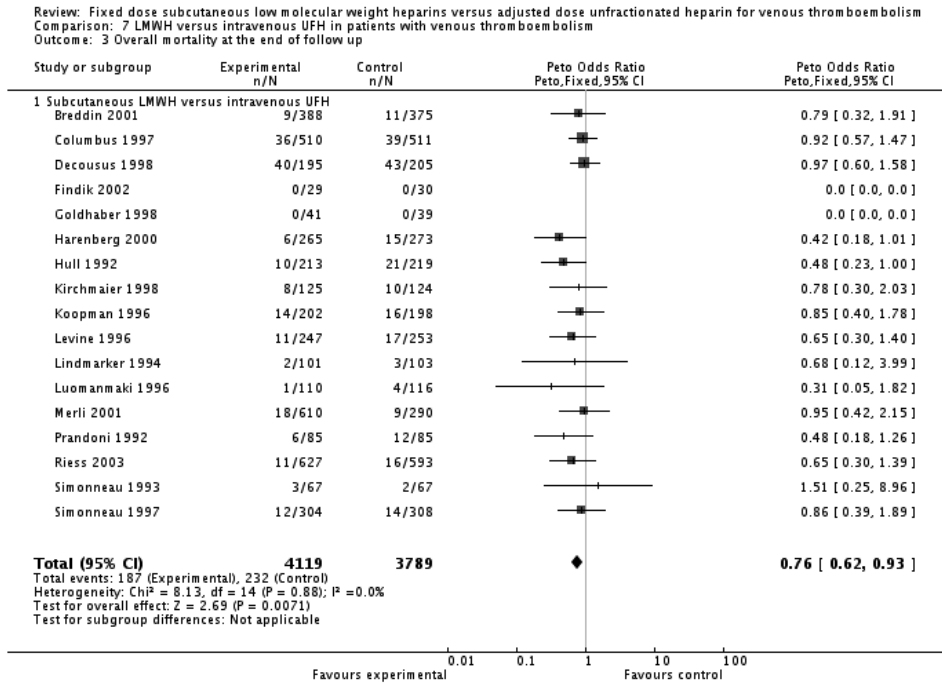




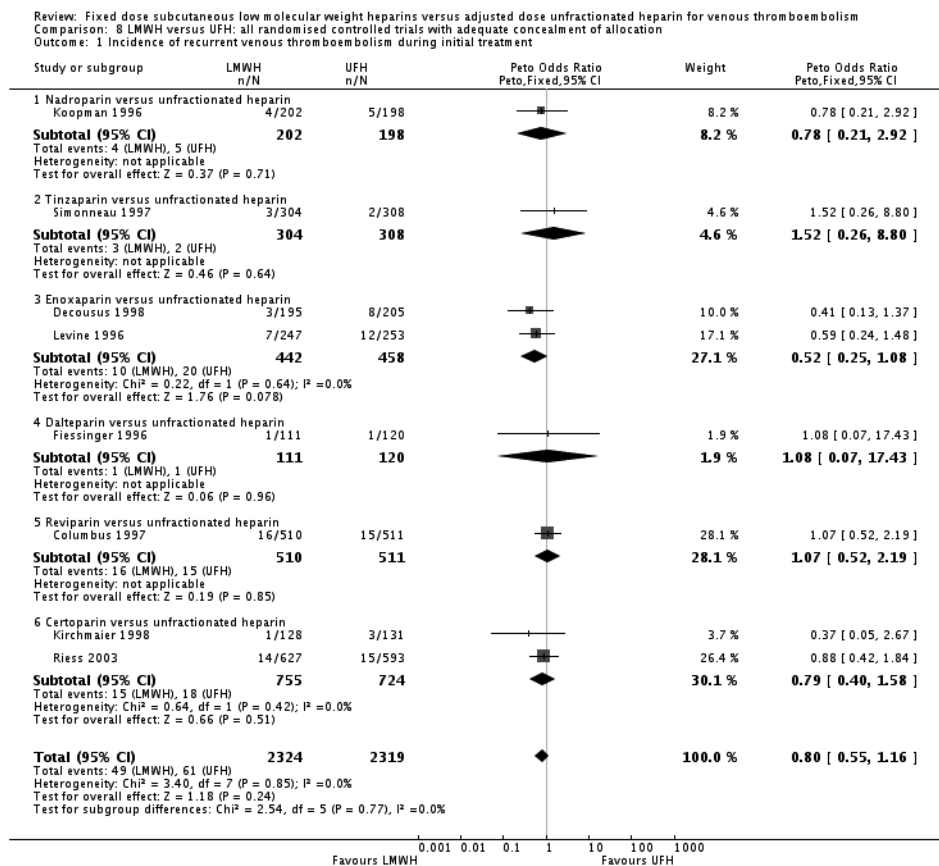
Graph 7.2 Comparison 7: LMWH versus intravenous UFH in patients with venous thromboembolism. Outcome 2: Incidence of major haemorrhagic episodes (during initial treatment).



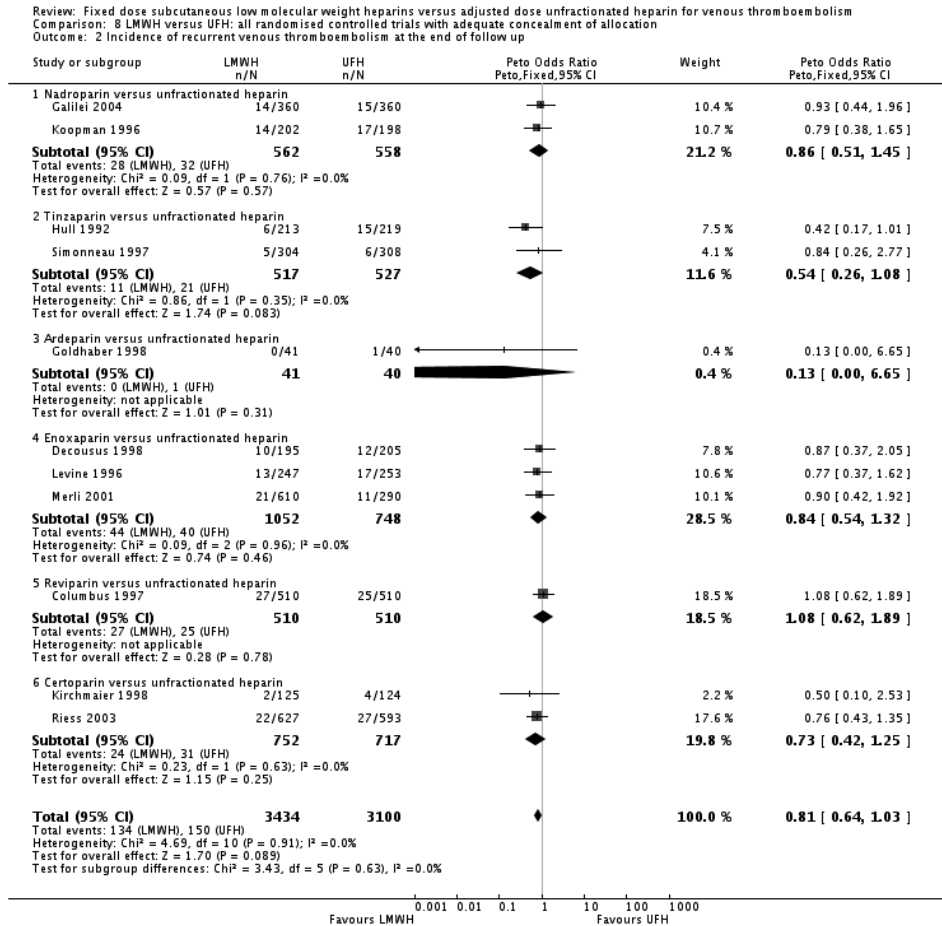
Graph 7.3 Comparison 7: LMWH versus intravenous UFH in patients with venous thromboembolism.  
Outcome 3: Overall mortality at the end of follow up.



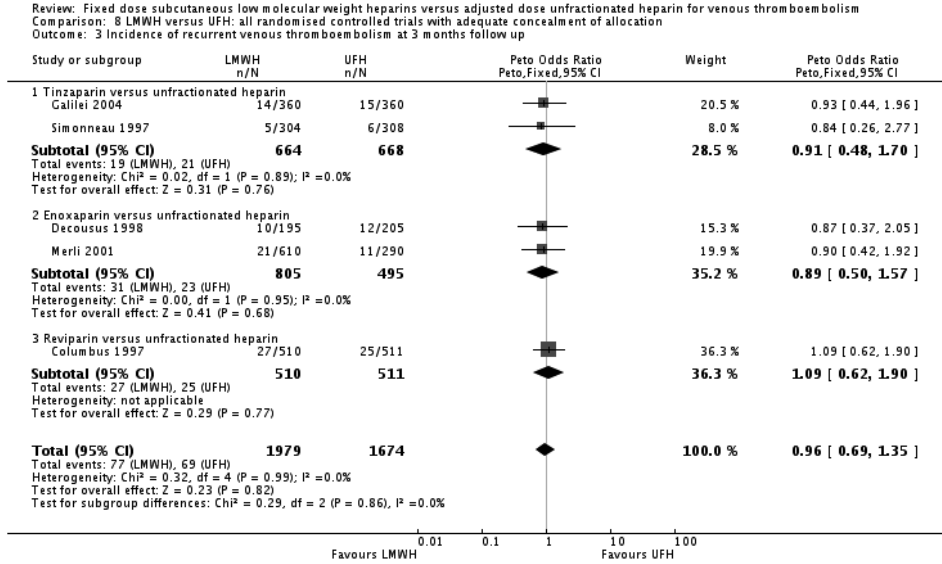
Graph 8.1 Comparison 8: LMWH versus UFH: all randomised controlled trials with adequate concealment of allocation. Outcome 1: Incidence of recurrent venous thromboembolism during initial treatment.



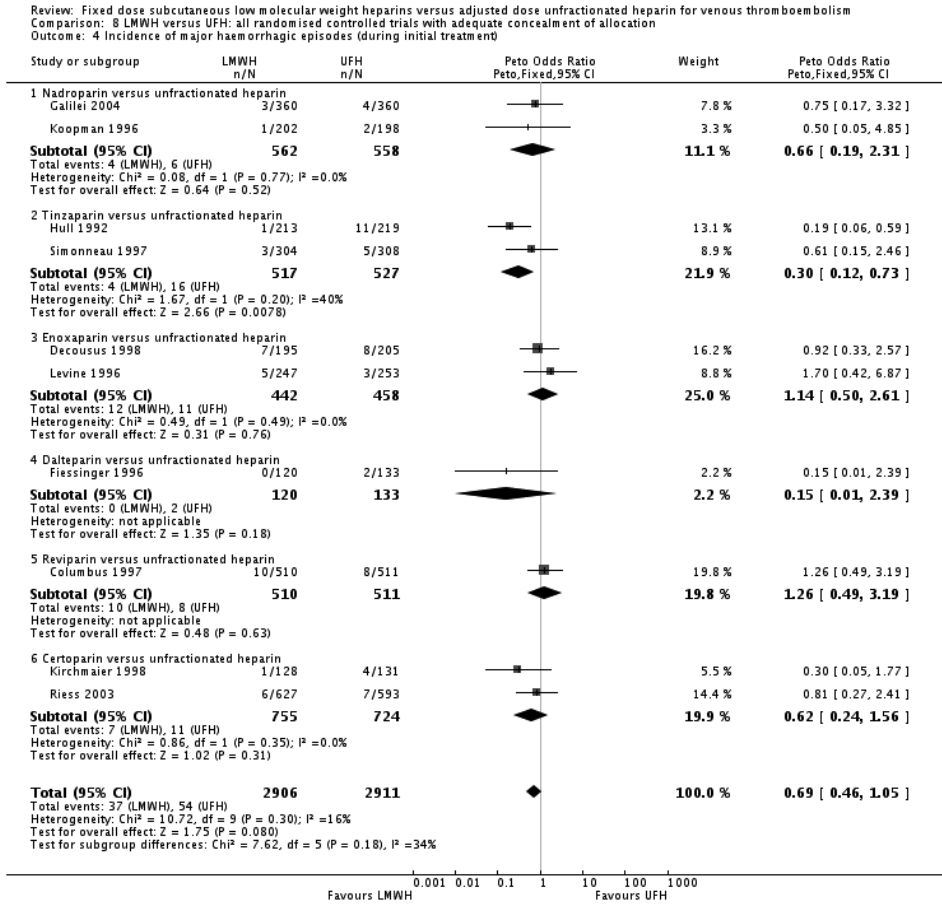
Graph 8.2 Comparison 8: LMWH versus UFH: all randomised controlled trials with adequate concealment of allocation. Outcome 2: Incidence of recurrent venous thromboembolism at the end of follow up.



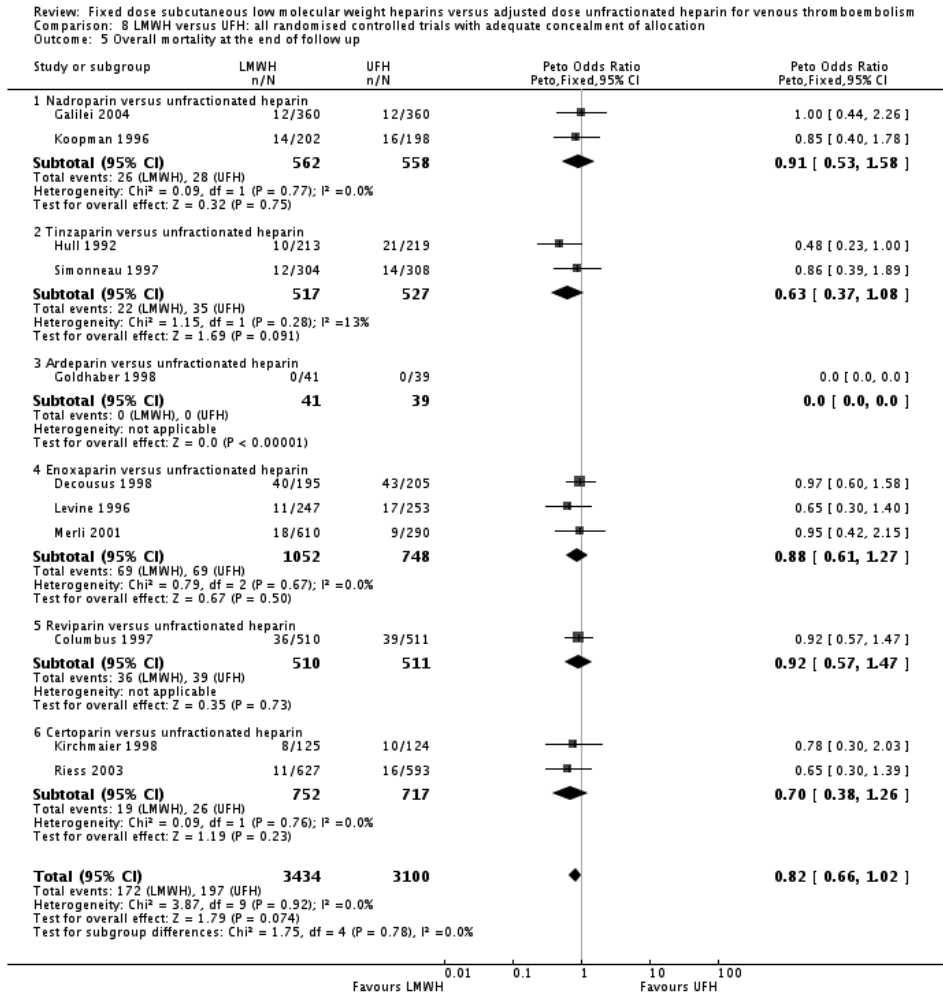
Graph 8.3 Comparison 8: LMWH versus UFH: all randomised controlled trials with adequate concealment of allocation. Outcome 3: Incidence of recurrent venous thromboembolism at 3 months follow up.



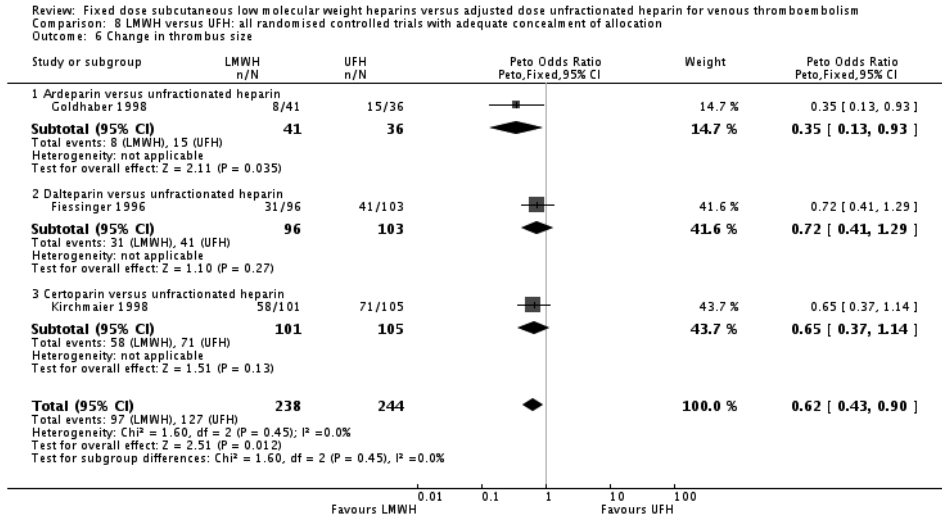
Graph 8.4 Comparison 8: LMWH versus UFH: all randomised controlled trials with adequate concealment of allocation. Outcome 4: Incidence major haemorrhagic episodes (during initial treatment).



Graph 8.5 Comparison 8: LMWH versus UFH: all randomised controlled trials with adequate concealment of allocation. Outcome 5: Overall mortality at the end of follow up.

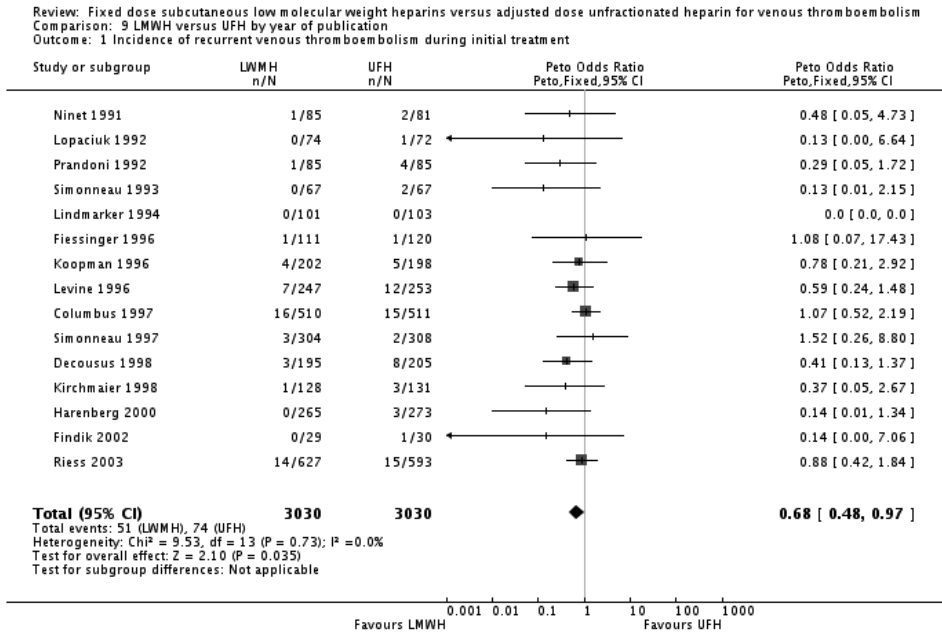


Graph 8.6 Comparison 8: LMWH versus UFH: all randomised controlled trials with adequate concealment of allocation. Outcome 6: Change in thrombus size.

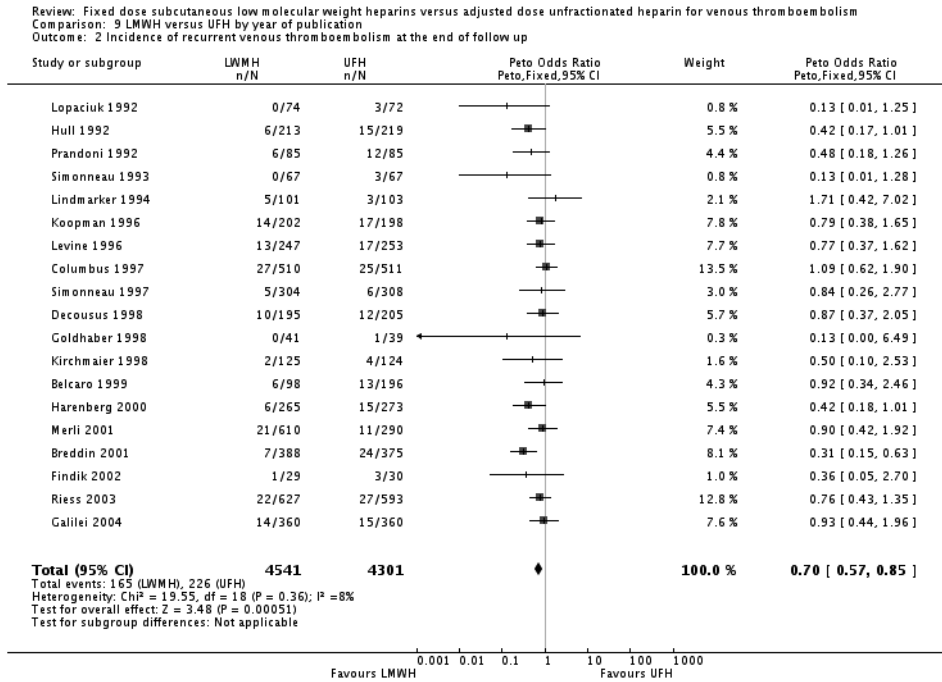




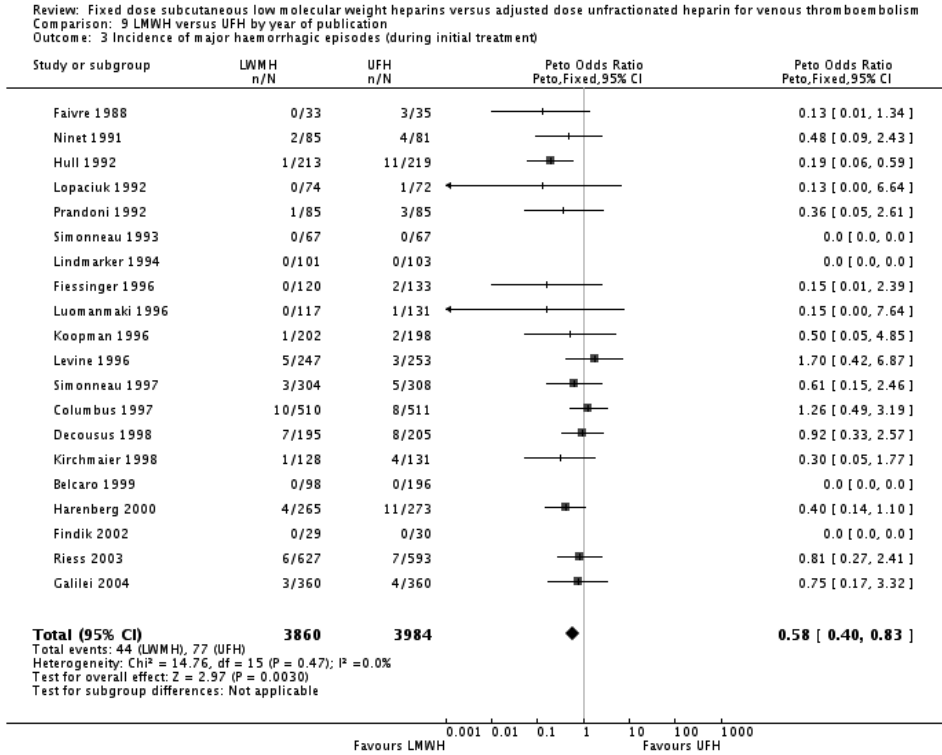
Graph 9.1 Comparison 9: LMWH versus UFH by year of publication. Outcome 1: Incidence of recurrent venous thromboembolism during initial treatment.



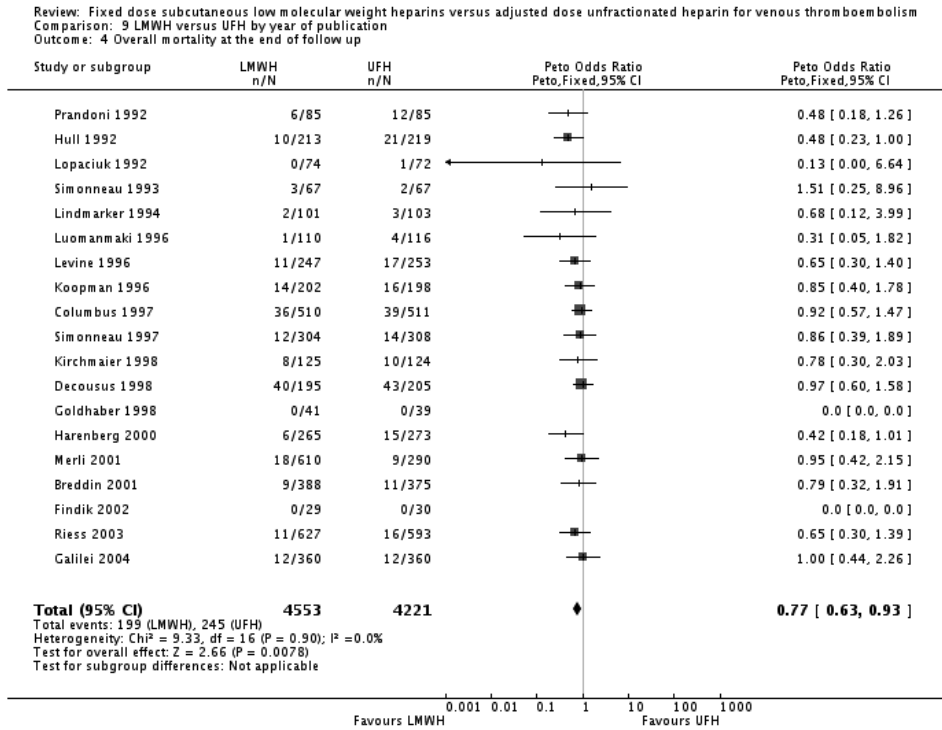
Graph 9.2 Comparison 9: LMWH versus UFH by year of publication. Outcome 2: Incidence of recurrent venous thromboembolism at the end of follow up.



Graph 9.3 Comparison 9: LMWH versus UFH by year of publication. Outcome 3: Incidence of major haemorrhagic episodes (during initial treatment).



Graph 9.4 Comparison 9: LMWH versus UFH by year of publication. Outcome 4: Overall mortality at the end of follow up.



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# Chapter 6

## Safety of outpatient treatment in acute pulmonary embolism

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*Journal of Thrombosis and Haemostasis, 2010;8: 2412-2417*

## Abstract

### **Background**

Data regarding outpatient treatment of pulmonary embolism (PE) is scarce. This study evaluates the safety of outpatient management of acute PE.

### **Methods**

This is a retrospective cohort study of consecutive patients presenting at the Ottawa Hospital with acute PE diagnosed between January 1, 2007 and December 31, 2008. PE was defined as an arterial filling defect on CTPA or a high probability V/Q scan. Patients were managed as outpatients if they were hemodynamically stable, did not require supplemental oxygenation and did not have contraindications to low molecular weight heparin therapy.

### **Results**

In this cohort of 473 patients with acute PE, 260 (55.0%) were treated as outpatients and 213 (45.0%) were admitted to the hospital. The majority of the patients were admitted because of severe co-morbidities (45.5%) or hypoxia (22.1%). No outpatient died of fatal PE during the 3 month follow-up period. At the end of follow-up, the overall mortality was 5.0% (95% CI: 2.7-8.4). The rates of recurrent venous thromboembolism (VTE) in outpatients were 0.4% (95% CI: 0.0-2.1) and 3.8% (95% CI: 1.9-7.0) within 14 days and 3 months, respectively. The rates of major bleeding episodes were 0% (95% CI: 0-1.4) and 1.5% (95% CI: 0.4-3.9) within 14 days and 3 months, respectively. Four (1.5%) outpatients were admitted to the hospital within 14 days.

### **Conclusion**

A majority of patients with acute PE can be managed as outpatients with a low risk of mortality, recurrent VTE and major bleeding episodes.

## Introduction

Patients with deep vein thrombosis (DVT) can be safely managed and treated as outpatients using subcutaneous low molecular weight heparins (LMWH).<sup>1,2</sup> However, the role of outpatient therapy in patients with pulmonary embolism (PE) is unclear and has been a matter of debate in literature.

A large majority of patients with PE are still systematically admitted to the hospital to avoid potential complications such as death, progressive right ventricular (RV) failure and major bleeding. Although the risk of fatal recurrent PE is higher in patients treated for PE than the risk of fatal PE in patients treated for DVT,<sup>3,4</sup> literature suggests that only 4.5% of PE-patients develop serious complications during the first 10 days of treatment.<sup>5</sup>

Small cohort studies and subgroup analyses of randomized controlled trials have investigated the outcomes of outpatient treatment for PE. Two systematic reviews, which include observational studies of patients diagnosed with symptomatic PE who were treated completely as outpatients or early discharge (within 3 days), concluded that outpatient therapy is safe in hemodynamically stable patients without hypoxia.<sup>6,7</sup> More recently, a randomized controlled trial was stopped early due to an increased mortality in the group of patients treated as outpatients.<sup>8</sup>

Outpatient treatment in patients with PE may be important to reduce hospitalizations and medical costs and hence save scarce health care resources. In order to counsel hemodynamically stable PE patients on the risks and benefits of outpatient treatment, clinicians require estimates of the rates for overall mortality, fatal PE, recurrent venous thromboembolism (VTE) and major bleeding at 14-days and 3 months. To address these knowledge gaps and assess the safety and feasibility of outpatient treatment of PE, we performed a retrospective study of patients diagnosed with PE and treated as outpatients at the Ottawa Hospital.

## Methods

### Study population

A retrospective cohort study of consecutive patients with suspected acute PE that underwent computed tomographic pulmonary angiography (CTPA) or lung ventilation/perfusion (V/Q) scan was conducted at the Ottawa Hospital Thrombosis Program, Ottawa, Canada. All reports of CTPA or V/Q scans conducted from January 1<sup>st</sup>, 2007 to December 31<sup>st</sup>, 2008 at The Ottawa Hospital, a large tertiary care center serving a catchment area greater than 1 million population, were reviewed. PE was defined as a pulmonary artery filling defect on CTPA or as a high probability V/Q scan. Patients diagnosed with PE during hospitalization, patients with chronic PE and patients in whom anticoagulation treatment was not initiated (e.g. palliative care

patients, small clinical non-significant PE) were excluded from the analyses. Patients were also excluded if they received treatment at another hospital or were followed-up by a health care professional out of the Ottawa Hospital. All included patients were followed for three months.

At our institution, the following patients are managed, as per hospital protocol, as outpatients: patients who do not have a systolic blood pressure of 100 mmHg or less, who have an oxygen saturation of 92% or more and do not require supplemental oxygen, who do not have contraindications for the use of LMWH (such as a high bleeding risk or renal failure) and who do not need hospitalization for other comorbidities (such as severe cancer, heart failure, chronic obstructive pulmonary disease, coronary artery disease, cerebrovascular events etc.). Outpatients with PE are treated with daily injections of LMWH for a minimum of 5 days with concomitant oral vitamin K antagonist (VKA). LMWH is discontinued if the International Normalized Ratio (INR) is above 2.0 on two consecutive readings. Outpatients are discharged home from the emergency department and are followed in the Outpatient Thrombosis Assessment and Treatment Unit within 24-48 hours of diagnosis, then again at 7 days and 3 months.

## Outcomes

The following variables were specified prior to data collection: 1) patient demographics; 2) reasons for hospitalization; 3) recurrent VTE and bleeding episodes; 4) death (date and cause). Data was extracted from hospital discharge reports and consultation notes from the Thrombosis Assessment and Treatment Unit. All outcomes were reviewed independently by two investigators (EG, PE). Disagreements on information were resolved by consensus or retrieving further information from other medical records.

The primary outcomes of this study were overall mortality and fatal recurrent PE. The cause of death was identified by a review of hospital records including death summaries. Secondary outcomes included recurrent VTE, major bleeding and VTE-related hospitalization at 14 days and 3 months of follow-up. Recurrent PE was defined as a new arterial filling defect on CTPA or a new mismatched area on a high probability V/Q-scan and recurrent DVT was defined as a new non-compressible venous segment on an ultrasound of the extremities. Major bleeding events were defined as: 1) fatal bleeding; 2) symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or 3) Bleeding causing a fall in hemoglobin level of  $20 \text{ g L}^{-1}$  ( $1.24 \text{ mmol L}^{-1}$ ) or more, or leading to transfusion of two or more units of whole blood or red cells.<sup>9</sup>

## Statistical analysis

Descriptive statistics were used to describe the patient characteristics and outcomes. Ninety-five percent confidence intervals (95% CI) and p-values were calculated for each event rate by using Fisher's exact test. A subgroup analysis was performed for patients without active cancer. The statistical analyses were performed using the Statistical Package for the Social Sciences software (version 16; SPSS; Chicago, IL, USA).

## Results

Over a two-year period, 4410 CTPA and 740 V/Q scans were carried out for suspected PE at The Ottawa Hospital. A total of 724 patients had a positive CTPA for PE and 115 patients had a high probability V/Q scan. A flow diagram including the reasons for patient's exclusion is depicted in Figure 6.1. A total of 473 patients presenting at the Ottawa Hospital with confirmed PE were included in the study. Two hundred and sixty (55.0%; 95% CI: 50.4–59.5) patients were managed entirely as outpatients and 213 (45.0%; 95% CI: 40.5–49.6) patients were admitted to the hospital.

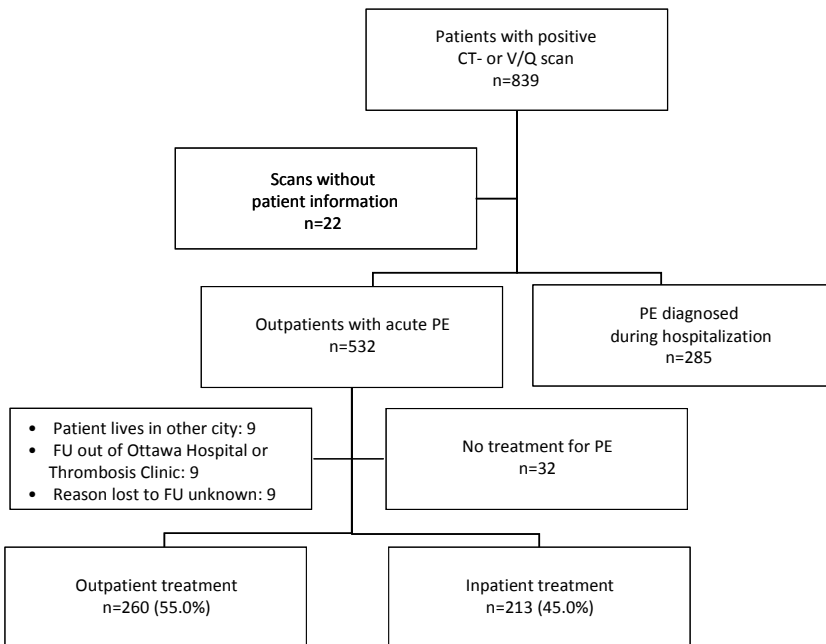


Figure 6.1 Flow diagram of the study. CT= computed tomography pulmonary angiography; V/Q= ventilation / perfusion; PE= pulmonary embolism; FU= follow-up.

Baseline characteristics of patients treated as outpatients and of those admitted to the hospital (inpatients) are shown in Table 1. Admitted patients were more likely to have had a previous diagnosis of heart failure whereas outpatients were more likely to have presented with chest pain. All outpatients were initially treated with LMWH. Most (70.4%) of the inpatients were also treated with LMWH while 25.8% received UFH (Table 6.1).

Table 6.1 Baseline characteristics of the cohort

	Outpatient treatment (n = 260)	Inpatient treatment (n=213)	
<b>Demographics</b>			
Female, n (%)	128 (49.2%)	106 (49.8%)	
Age, mean years (sd)	54.7 (17.1)	62.0 (17.5)	
	Outpatient treatment (n = 260)	Inpatient treatment (n = 213)	P-value
	N (%; 95% CI)	N (%; 95% CI)	
<b>Risk factors for VTE</b>			
Immobilization at least 3 days	40 (15.4%; 11.2 – 20.4)	35 (16.4%; 11.7 – 22.1)	0.801
Surgery in the previous 4 weeks	41 (15.8%; 11.6 – 20.6)	28 (13.1%; 8.9 – 18.4)	0.436
Previously objective diagnosed VTE	53 (20.4%; 15.9 – 25.8)	27 (12.7%; 8.5 – 17.9)	0.027
<b>Comorbidity</b>			
Active Cancer	83 (31.9%; 26.3 – 38.0)	86 (40.4%; 33.7 – 47.3)	0.067
Heart failure	4 (1.5%; 0.4 – 3.9)	15 (7.0%; 4.0 – 11.4)	0.004
COPD	9 (3.5%; 1.6 – 6.5)	18 (8.5%; 5.1 – 13.0)	0.027
CAD	22 (8.5%; 5.4 – 12.5)	27 (12.0%; 8.5 – 17.9)	0.172
Stroke	8 (3.1%; 1.3 – 6.0)	14 (6.6%; 3.6 – 10.8)	0.082
<b>Clinical presentation</b>			
Dyspnea	191 (73.5%; 67.7 – 78.7)	176 (82.6%; 76.9 – 87.5)	0.020
Chest pain	167 (64.2%; 58.1 – 70.1)	95 (44.6%; 37.8 – 51.6)	0.000
Hemoptysis	11 (4.2%; 2.1 – 7.4)	16 (7.5%; 4.4 – 11.9)	0.163
Syncope	2 (0.8%; 0.1 – 2.8)	13 (6.1%; 3.3 – 10.2)	0.001
Clinical symptoms of DVT	82 (31.5%; 25.9 – 37.6)	48 (22.5%; 17.1 – 28.8)	0.030
Heart rate >100 bpm	33 (12.7%; 8.9 – 17.4)	61(28.6%; 22.7 – 35.2)	0.000
SBP <100 mmHg	0 (0%; 0 – 1.4)	15 (7.0%; 4.0 – 11.5)	0.000
Arterial oxygen saturation <90%*	3 (1.2%; 0.2 – 3.3)	45 (21.1%; 15.9 – 27.3)	0.000
<b>Initial treatment</b>			
LWMH	260 (100%; 98.6 – 100.0)	150 (70.4%; 63.8 – 76.4)	0.000
UFH	0 (0%; 0.0 – 1.4)	55 (25.8%; 20.1 – 32.3)	0.000
Other initial treatment <sup>†</sup>	0 (0%; 0.0 – 1.4)	8 (3.8%; 1.6 – 7.3)	0.002

VTE= Venous ThromboEmbolism; COPD= Chronic Obstructive Pulmonary Disease; CAD= Coronary Artery Disease; DVT= Deep Vein Thrombosis; SBP= Systolic Blood Pressure; LMWH= Low Molecular Weight Heparin; UFH= Unfractionated Heparin. \*Saturation assessed with and without the administration of supplemental oxygen. <sup>†</sup> Other initial treatment: five patients received an IVC-filter, two patients received thrombolysis, one patient was treated with argatroban because of Heparin Induced Thrombocytopenia.

For the patients admitted to the hospital, the median length of admission was 6 days (range 1 to 209 days). Almost seventy-five percent of the inpatients were admitted for 10 days or less. The majority of these patients were admitted because of severe co-

morbidities (45.5%), hypoxia (22.1%), extensive PE (8.5%), hypotension (7.0%), renal dysfunction (6.6%), pain management (4.7%) or syncope (2.3%). The reason for admission was unclear in 7 (3.3%) patients.

## Overall Mortality and Fatal PE

Only one outpatient (0.4%; 95% CI: 0.0-2.1%) died within the first few weeks after the index PE (Table 6.2). This patient was initially sent home from the emergency room to be treated as an outpatient but was admitted within 24 hours of discharge. The patient was transferred to a palliative care facility after 10 days of hospitalization and died from progression of her metastatic cancer. After 3 months of follow-up, the overall mortality in the outpatient group was 5.0% (95% CI 2.7-8.4). No patient died of recurrent fatal PE (Table 6.2).

Table 6.2 Main outcomes.

	Outpatients treatment (n=260) <i>n</i> (%; 95% CI)	Inpatient treatment (n=213) <i>n</i> (%; 95% CI)	<i>p</i> -value
14 days follow-up			
Overall mortality	1 (0.4%; 0.0 – 2.1) <sup>†</sup>	27 (12.7%; 8.5 – 17.9) <sup>‡</sup>	0.000
PE-specific mortality	0 (0%; 0 – 1.4)	5 (2.3%; 0.8 – 5.4)	0.018
Recurrence VTE	1 (0.4%; 0.0 – 2.1)	4 (1.9%; 0.5 – 4.7)	0.180
Major haemorrhages*	0 (0%; 0.0 – 1.4)	13 (6.1%; 3.3 – 10.2)	0.000
Re-admissions	4 (1.5%; 0.4 – 3.9)	4 (1.9%; 0.5 – 4.7)	1.000
VTE / treatment related			
3 months follow-up			
Overall mortality	13 (5%; 2.7 – 8.4) <sup>§</sup>	57 (26.7%; 20.9 – 33.2) <sup>¶</sup>	0.000
PE-specific mortality	0 (0%; 0 – 1.4)	5 (2.3%; 0.8 – 5.4)	0.018
Recurrence VTE	10 (3.8%; 1.9 – 7.0)	10 (4.7%; 2.3 – 8.5)	0.654
Major haemorrhages*	4 (1.5%; 0.4 – 3.9)	17 (8.0%; 4.7 – 12.5)	0.001
Re-admissions	6 (2.3%; 0.9 – 5.0)	11 (5.2%; 2.6 – 9.1)**	0.135
VTE / treatment related			

PE= Pulmonary Embolism; VTE= Venous ThromboEmbolism. \* Major haemorrhage defined according to the Control of Anticoagulation Subcommittee (ISTH SSC 2004):

Fatal bleeding, and/or

Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or Bleeding causing a fall in hemoglobin level of 20 g L<sup>-1</sup> (1.24 mmol L<sup>-1</sup>) or more, or leading to transfusion of two or more units of whole blood or red cells.

<sup>†</sup> This outpatient received palliative care 10 days after PE; <sup>‡</sup> Five of these inpatients received palliative care at 14 days follow-up; <sup>§</sup> Three of these outpatients received palliative care at 3 months follow-up; <sup>¶</sup> No patients with palliative care; \*\* Nine patients with 1 re-admission and 2 patients with 2 readmissions.

In the inpatient group, 5 (2.3%; 95% CI 0.8–5.4) patients died because of fatal PE. All of these patients died within 7 days of the index PE diagnosis. The overall mortality was 12.7% (95% CI 8.5–17.9) within 14 days and 26.7% (95% CI 20.9–33.2) within 3 months.



The majority (76.4%) of patients died from cancer. In a subgroup analysis excluding patients with active cancer, the 3 months overall mortality in the outpatient and inpatient group was 0% (95% CI 0–2.1) and 9.4% (95% CI 5.0–15.9), respectively.

### Recurrent VTE and major bleeding episodes

One (0.4%; 95% CI 0.0–2.1) outpatient had recurrent PE within 14 days. At 3 months follow-up 10 outpatients (3.8%; 95% CI 1.9–7.0) developed recurrent VTE (Table 2). Four patients had DVT and 6 patients had recurrent PE. The incidence of recurrent VTE in hospitalized patients was similar at 14 days and 3 months ( $p=0.180$  and  $0.654$ , respectively).

None of the outpatients suffered from major bleeding during the first two weeks. Four (1.5%; 95% CI 0.4–3.9) outpatients, however, had a major bleeding during the 3 months follow-up (Table 6.2). The percentage of major bleeding episodes was higher in the inpatient group. Thirteen (6.1%; 95% CI 3.3–10.2) inpatients suffered from major bleeding episodes within 14 days after the index PE, and at 3 months follow-up 17 (8.0%; 95% CI 4.7–12.5) inpatients had a major bleeding episode (Table 6.2).

### Hospitalization during follow-up

Four (1.5%; 95% CI 0.4–3.9) outpatients were admitted to the hospital within 14 days of their index PE diagnosis. Outpatients were admitted either because of progressive shortness of breath ( $n=2$ ), presyncopal episode ( $n=1$ ) or heparin induced thrombocytopenia ( $n=1$ ). During the 3 months follow-up two more patients were admitted (one recurrent VTE; one major bleeding episode). Therefore, the VTE-related admission rate of outpatients at 3 months follow-up was 2.3% (95% CI 0.9–5.0) (Table 6.2). No differences were seen in the readmission rates between patients originally admitted and outpatients at the end of follow up ( $p=0.135$ ).

## Discussion

Our study suggests that outpatient PE treatment is feasible and safe in a majority of patients. To our knowledge, this is one of the largest cohort studies to evaluate the safety of outpatient treatment in low-risk patients with acute PE. More than 50% of the patients were treated as outpatient with a low subsequent risk of death, recurrent VTE and major bleeding episodes in the first 14 days. None of the outpatients died from PE and there is only one (0.4%) death from metastatic cancer within the first few weeks.

Our results are consistent with previously published smaller studies assessing outpatient management or an early discharge strategy (less than 3 days of

hospitalization) in patients with hemodynamically stable acute PE.<sup>8,10-20</sup> No PE-related deaths and only one death due to a major bleeding were reported in these studies. The overall short-term mortality in our study was 0.4% (95% CI 0–2.1%). Although this is consistent with previously reported cohort studies<sup>10,12,13,15-18</sup>, a recent randomized controlled trial reported an overall mortality of 2.8% within the first 10 days after the index PE. This study was stopped early due to this increased mortality in the outpatient group.<sup>8</sup> The reasons behind this discrepancy are unclear but might be explained by the difference in follow-up management between studies (in-person versus telephone follow-up). Short-term recurrent VTE in literature ranged from 0% to 3.2% and major bleeding from 0% to 2.3%.<sup>8,10,12,13,15-18</sup> Similarly, our results are consistent with prior studies assessing long-term outcomes in patients with PE treated as outpatients. The three months overall mortality in these studies ranged from 0% to 43.5%. The percentage of recurrent VTE and major bleeding ranged from 0% to 9.3% and 0% to 3.7%, respectively.<sup>8,10-20</sup>

In our cohort study, the decision whether patients with PE could be managed as outpatients or required hospitalization was based on the clinical judgment of the doctor at the emergency department. All hemodynamically stable patients that did not require supplemental oxygenation and had no contraindications to LMWH or significant co-morbidities were considered for outpatient management. Our rate of serious adverse events is higher in patients who were admitted to the hospital immediately after their index PE (Table 2) suggesting that these simple criteria are able to discriminate between low and high-risk patients.

Several studies investigated risk stratification in PE and developed risk-prediction models to identify patients with acute PE who are at low risk for adverse outcomes and could be treated as outpatients.<sup>21</sup> The most extensively validated models are the Geneva Prognostic Score (GPS) and the Pulmonary Embolism Severity Index (PESI).<sup>21-23</sup> Other studies have shown that patients with acute PE who have elevated cardiac enzymes (such as troponin, brain natriuretic peptide (BNP) and creatinine kinase), or evidence of right-heart dysfunction on either echocardiography or CTPA, have a worse short-term survival rate than those without these findings.<sup>21,23-26</sup> There are also studies pointing to the role of plasmin degradation products, such as D-Dimer concentration, in the risk stratification of patients with PE.<sup>10,27</sup> More recently, a prospective management study showed that out of hospital treatment is safe in hemodynamically stable PE-patients with low NT-proBNP level (<500 pg/ml).<sup>10</sup> Future prospective management studies are required to assess if the use of biomarkers can improve stratification of patients with PE and optimize the number of patients with PE that can be safely treated as outpatients.

In a recent publication, Aujeskey et al. showed that emergency physicians in the United States are reluctant to discharge patients with PE for outpatient treatment due to insufficient data supporting the effectiveness and safety of the outpatient management of PE.<sup>27</sup> However, safe outpatient management of patients with PE may lead to: 1) a decrease in unnecessary hospitalizations; 2) decrease in hospital acquired

infections and death; 3) improvement in health-related quality of life; and 4) reduction in health care costs.<sup>27-30</sup> Our results suggest that outpatient treatment is feasible and safe in selected patients with PE.

It is important to note the limitations of our study. First, this is a retrospective cohort study and as such, our findings may be subject to bias, incomplete information or misdiagnosis. We tried to minimize selection bias by including all consecutive patients with confirmed PE on CTPA or V/Q scan over a defined time period and by adjudicating all outcome events (two independent reviewers). Complete information about follow up was only missing in 5.1% of the sample. We performed a worse-case-scenario analysis for all patients who were lost to follow-up. Assuming that all of these patients died at their end of follow-up, the overall mortality for the outpatients would have been 8 (2.9%) within the first 14 days and 25 (9.1%) at 3 months follow-up. Second, as previously stated, the decision to admit or discharge the patient was left to the discretion of the treating physician. Hence, it is possible that some admitted patients could have been safely managed as outpatients. Nonetheless, our results are conservative as they suggest already that a majority of the patients can be treated as outpatient with low risk of adverse events. Future prospective management studies are required to validate this approach. Finally, all patients with PE treated as outpatients were seen within 24 to 48 hours in our thrombosis clinic and followed up after 7 days. Close follow-up of patients managed as outpatients in a specialized thrombosis clinic might not be possible in all settings and therefore rates of major bleeding episodes and recurrent VTE may differ if patients are followed by other health care professionals.

In conclusion, a majority of patients with acute PE at the Ottawa Hospital were treated as outpatient with a low risk of mortality, recurrent VTE and major bleeding episodes. Out of hospital treatment for PE should be considered as a feasible and safe treatment in uncomplicated patients and can contribute to a substantial reduction in health care costs.

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# Chapter 7

**Does the Pulmonary Embolism Severity Index accurately identify low risk patients eligible for outpatient treatment?**

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*Thrombosis Research 2011;129: 710-714*

## Abstract

### **Background**

The pulmonary embolism severity index (PESI) and the recently derived simplified PESI prognostic model have been developed to estimate the risk of 30-day mortality in patients with acute PE. We sought to assess if the PESI and simplified PESI prognostic models can accurately identify adverse events and to determine the rates of events in patients treated as outpatients.

### **Methods**

A retrospective cohort study of patients with acute pulmonary embolism (PE) presenting at the Ottawa Hospital (Canada) was conducted between 1 January 2007 and 31 December 2008.

### **Results**

Two hundred and forty three patients were included. A total of 118 (48.6%) and 81 (33.3%) were classified as low risk patients using the original and simplified PESI prognostic models respectively. None of the low risk patients died within the 3 months of follow-up. One hundred and fifteen (47.3%) patients were safely treated as outpatients with no deaths or bleeding episodes and only 1 recurrent event within the first 14 days or after 30 days of follow-up. Thirty four (29.6%) of these outpatients were classified as high risk patients according to the original PESI and 54 (47.0%) to the simplified PESI prognostic model.

### **Conclusion**

Both PESI strategies accurately identify patients with acute PE who are at low risk and high risk for short-term adverse events. However, 30 to 47% of patients with acute PE and a high risk PESI score were safely managed as outpatients. Future research should be directed at developing tools that predict which patients would benefit from inpatient management.

## Introduction

The mortality and morbidity of pulmonary embolism (PE) may vary considerably depending on the severity of the event and co-morbidities. Predicting patient outcomes may enable different management strategies and may inform the clinician which patients can be treated as outpatients.<sup>1,2</sup>

Over the last decade, several studies have suggested that outpatient treatment in a selected group of hemodynamically stable patients with acute PE is safe<sup>3-7</sup>. Benefits include: 1) cost savings from a decrease in hospitalizations; 2) fewer patients at risk for hospital acquired infections; and 3) an improvement in quality of life, increased physical activity and social functioning.<sup>3,8-11</sup> However, physicians are reluctant to treat patients with PE at home due to uncertainty on how to safely identify patients who are at low risk for short-term adverse events<sup>8</sup>, irrespective of whether the adverse events could be averted by hospitalization.

Prognostic models that will accurately predict short-term adverse outcomes may help identify patients with acute PE at low-risk of adverse events that can be safely treated as outpatients. Several prognostic models have been developed to assess the risk of death, recurrent venous thromboembolism (VTE) or major bleeding in patients with acute PE.<sup>12</sup> The most extensively validated prognostic models are the Geneva Prognostic Score (GPS) and the Pulmonary Embolism Severity Index (PESI).<sup>12</sup> The GPS predicts the combined adverse outcomes of death, recurrent VTE and major bleeding episodes during the first three months following the index PE. However, the GPS prognostic model is not frequently used since it requires the use of ultrasound variables and arterial blood gas which decrease feasibility. Moreover, a comparison of GPS low-risk patients with PESI low-risk patients in a cohort of 599 consecutive patients with acute symptomatic PE showed that the PESI low-risk patients had a significantly lower mortality.<sup>13</sup>

The PESI prognostic model stratifies patients in five risk classes with increasing risk of all cause short term mortality without any need for ultrasonography or laboratory studies.<sup>14</sup> The use of the PESI prognostic model requires computation of a score based on 11 variables each with a different weight (Table 7.1). Recently, a PESI-derived simplified model with a less complex scoring system has been proposed and seems to have a similar prognostic accuracy as the original PESI (Table 7.1).<sup>15</sup>

We sought to evaluate if the original and the simplified PESI prognostic models could identify patients with acute PE at low risk of short term adverse outcome who can be safely managed as outpatients.



Table 7.1 Pulmonary Embolism Severity Index (PESI).<sup>15</sup>

Predictors	Original score*	Simplified score <sup>¶</sup>
<i>Demographic characteristics</i>		
Age >80 years	Age, in years	1
Male sex	+10	
<i>Comorbid illnesses</i>		
Cancer <sup>†</sup>	+30	1
Heart failure	+10	—
Chronic lung disease	+10	—   1**
<i>Clinical findings</i>		
Pulse ≥110/min	+20	1
Systolic blood pressure <100 mmHg	+30	1
Respiratory rate ≥30/min	+20	
Temperature <36°C	+20	
Altered mental status <sup>‡</sup>	+60	
Arterial oxygen saturation <90% <sup>§</sup>	+20	1

\* A total point score for a given patient is obtained by summing the patient's age in years and the points for each predictor when present. The score corresponds with the following risk classes: <65, class I; 66–85, class II; 86–105, class III; 106–125, class IV; and ≥125, class V. Patients in risk class I and II are defined as being at low risk. <sup>†</sup> Cancer defined as a history of cancer or active cancer; <sup>‡</sup> Defined as disorientation, lethargy, stupor or coma; <sup>§</sup> With and without the administration of supplemental oxygen. <sup>¶</sup> A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥ 1, high risk. Empty cells indicate that the variable was not included. \*\* The variables were combined into a single category of chronic cardiopulmonary disease.

## Methods

### Study population

We performed a retrospective cohort study including consecutive patients with high risk and non-high risk acute PE<sup>16,17</sup> presenting at the Ottawa Hospital between 1 January 2007 and 31 December 2008.<sup>4</sup> PE was defined as an intraluminal filling defect on CTPA or a high probability V/Q scan. Patients diagnosed with PE during hospitalization, patients with chronic PE and patients in whom anticoagulation was not initiated (e.g. palliative care patients, small clinical non-significant PE) were excluded from the analyses. Patients were also excluded if they were followed-up by a health care professional out of the Ottawa Hospital.<sup>4</sup> Patients were considered for outpatient management if they were hemodynamically stable, did not require supplemental oxygenation and had no contraindications to Low Molecular Weight Heparin (LMWH) or significant comorbidities. The decision to manage the patients as an outpatient or an inpatient was ultimately left to the discretion of the emergency room physician. Outpatients were followed in the Outpatient Thrombosis Assessment and Treatment Unit within 24–48 hours of diagnosis, then again at 7 days and 3 months. Admitted patients were followed in the Thrombosis Unit after discharge.

## Risk-prognostic models

The original PESI prognostic model stratifies patients into five severity classes of increasing risk of mortality within 30 days after the diagnosis PE [16]. The model includes 11 routinely available clinical parameters at the time of presentation: age, male sex, cancer, heart failure, chronic lung disease, pulse  $\geq 110$  beats/min, systolic blood pressure less than 100 mmHg, respiratory rate  $30 \geq$  breaths/min, temperature  $< 36^\circ\text{C}$ , altered mental status and arterial oxygen saturation  $< 90\%$ . The model assigns points for each applicable characteristic and calculates a total point score by summing these points and the patient's age in years (Table 7.1). Point assignments correspond with the following risk classes: 65 or less, class I, very low risk; 66–85, class II, low risk; 86–105, class III, intermediate risk; 106–125, class IV, high risk; greater than 125, class V, very high risk.<sup>18</sup>

The simplified PESI prognostic model consists of 6 variables: one demographic variable (age  $> 80$  years), two comorbid conditions (cancer, chronic pulmonary disease), and three physical examination findings (pulse  $\geq 110$  beats/min, systolic blood pressure  $< 100$  mmHg and arterial oxygen saturation  $< 90\%$ ) (Table 7.1). Patients with none of these factors were defined as being at low risk.<sup>15</sup>

## Outcomes

Charts of all included patients were reviewed to extract the data necessary for computation of the original PESI and the simplified PESI prognostic models. All included patients were followed for 3 months.

The following variables were also specified prior to data collection: i) patient demographics; ii) reasons for hospitalization; iii) recurrent VTE and bleeding episodes; and iv) death (date and cause). Data were extracted from paper charts at the emergency department, hospital discharge reports and consultation notes from the Thrombosis Assessment and Treatment Unit. All outcomes were reviewed independently by two reviewers. Disagreements on the variables were resolved by consensus or retrieving further information from other medical records.

The primary outcomes used to validate the risk-prediction models were overall mortality and fatal PE. The cause of death was identified by discharge summaries or other medical records. Secondary outcomes included recurrent VTE and major hemorrhage. Recurrent PE was defined as a new arterial filling defect on CTPA or high probability V/Q-scan and recurrent DVT was defined as a new non-compressible venous segment on an ultrasound of the extremities. Major hemorrhage was defined according to the definition of the Control of Anticoagulation Subcommittees (ISTH SSC 2004).<sup>19</sup>

## Statistical analysis

Descriptive statistics were used to describe the patient characteristics and outcomes. Ninety-five percent confidence intervals (95% CI) and p-values were calculated for each event rate by using Fisher's exact test. The statistical analyses were performed using the Statistical Package for the Social Sciences software (version 17; SPSS; Chicago, IL, USA).

## Results

A total of 243 patients presenting at the Ottawa Hospital with confirmed PE were included in this study. One hundred and fifteen (47.3%) patients were directly discharged from the Emergency Department and were treated out of the hospital, while 128 (52.7%) patients were admitted. According to the original PESI prognostic model, 118 (48.6%; 95% CI 42.1–55.0) patients were classified as low risk (class I and II) and 125 (51.4%; 95% CI 45.0–58.0) were classified as high risk (class III to V). According to the simplified PESI prognostic model, 81 (33.3%; 27.4–39.6) patients were classified as low risk patients and 162 (66.7%; 60.4–72.6) were classified as high risk patients.

Baseline characteristics of patients in different PESI risk groups are shown in Table 7.2. High risk patients were older than low risk patients. High risk patients were more likely to have had a previous diagnosis of cancer, heart failure or chronic obstructive pulmonary disease (COPD) whereas low risk patients were more likely to have presented with chest pain and hemoptysis. Most low risk patients were treated with LMWH, while 16% to 22% of the high risk patients were treated with unfractionated heparin (UFH). Two (0.8%; 95% CI 0.1–2.9) patients were treated with thrombolysis.

### Overall mortality and fatal PE

No low risk patients, in either group, died within 14 days, 30 days or 3 months (Table 7.3). In the original PESI high risk group, 7 (5.6%; 95% CI 2.3–11.2) patients died within 14 days, 10 (8%; 95% CI 3.9–14.2) within 30 days and 32 (25.6%; 95% CI 18.2–34.2) patients died within 3 months. The overall mortality in the simplified PESI high risk group was 7 (4.3%; 95% CI 1.8–8.7) within 14 days, 10 (5.5%; 95% CI 2.7–9.9) within 30 days and 32 (19.8%; 95% CI 13.9–26.8) within 3 months (Table 7.3). None of the patients died from PE. The majority (84.4%; 95% CI 67.2–94.7) of the patients died from disease progression of an underlying cancer.

Table 7.2 Demographic and clinical characteristics of the patients in the cohort.

	Original PESI Low Risk* (n=118)	Original PESI High Risk† (n=125)	Simplified PESI Low risk‡ (n=81)	Simplified PESI High risk§ (n=162)	
	n (%; 95%CI)	n (%; 95%CI)	n (%; 95%CI)	n (%; 95%CI)	p-value
<b>Demographics</b>					
Male, n (%)	57 (48.3%)	59 (47.2%)	46 (56.8%)	70 (43.2%)	
Age, mean years (SD)	45.9 (17.0)	68.1 (11.7)	48.6 (17.0)	61.7 (17.3)	
	n (%; 95%CI)	n (%; 95%CI)	n (%; 95%CI)	n (%; 95%CI)	p-value
<b>Risk factors for VTE</b>					
Immobilization(≥3 days)	21 (17.8%; 11.4-25.9)	18 (14.4%; 8.8-21.8)	15 (18.5%; 10.8-27.7)	24 (14.8%; 9.7-21.2)	NS
Recent surgery (≤4 weeks)	18 (15.3%; 9.3-23.0)	15 (12%; 6.9-19.0)	14 (17.3%; 9.8-27.3)	19 (11.7%; 7.2-17.7)	NS
VTE in history	25 (21.2%; 14.2-29.7)	15 (12%; 6.9-19.0)	16 (19.8%; 11.7-30.1)	24 (14.8%; 9.7-21.2)	NS
<b>Comorbidity</b>					
Cancer¶	12 (10.2%; 5.4-17.1)	91 (72.8%; 64.1-80.4)	0 (0%; 0.0-4.5)	103 (63.6%; 55.7-71.0)	0.000
Heart Failure	1 (0.8%; 0.0-4.6)	12 (9.6%; 5.1-16.2)	0 (0%; 0.0-4.5)	13 (8.0%; 4.3-13.3)	0.006
COPD	3 (2.5%; 0.5-7.3)	13 (10.4%; 5.7-17.1)	0 (0%; 0.0-4.5)	16 (9.9%; 5.8-15.5)	0.002
CAD	7 (5.9%; 2.4-11.8)	17 (13.6%; 8.1-20.9)	4 (4.9%; 1.4-12.2)	20 (12.3%; 7.7-18.4)	NS
Stroke	3 (2.5%; 0.5-7.3)	9 (7.2%; 3.3-13.2)	2 (2.5%; 0.3-8.6)	10 (6.2%; 3.0-11.1)	NS
Altered mental status**	0 (0%; 0.0-3.1)	5 (4%; 1.3-9.1)	1 (1.2%; 0.0-6.7)	4 (2.5%; 0.7-6.2)	NS
<b>Clinical presentation</b>					
Dyspnea	90 (76.3%; 67.6-83.6)	102 (81.6%; 73.7-88.0)	60 (74.1%; 63.1-83.2)	132 (81.5%; 74.6-87.1)	NS
Chest pain	89 (75.4%; 66.7-82.9)	56 (44.8%; 35.9-54.0)	63 (77.8%; 67.2-86.3)	82 (50.6%; 42.7-58.6)	0.000
Hemoptysis	10 (8.5%; 4.1-15.0)	4 (3.2%; 0.9-8.0)	9 (11.1%; 5.2-20.1)	5 (3.1%; 1.0-7.1)	0.018
Syncope	3 (2.5%; 0.5-7.3)	4 (3.2%; 0.9-8.0)	1 (1.2%; 0.0-6.7)	6 (3.7%; 1.4-7.9)	NS
Heart rate ≥110 b/min	17 (14.4%; 8.6-22.1)	40 (32%; 23.9-40.9)	0 (0%; 0.0-4.5)	57 (35.2%; 27.9-43.1)	0.000
SBP < 100 mmHg	4 (3.4%; 0.9-8.5)	11 (8.8%; 4.5-15.2)	0 (0%; 0.0-4.5)	15 (9.3%; 5.3-14.8)	0.003
Arterial oxygen saturation <90% ††	5 (4.2%; 1.4-9.6)	29 (23.2%; 16.1-31.6)	0 (0%; 0.0-4.5)	34 (21.0%; 15.0-28.1)	0.000
Respiratory rate ≥30/min	4 (3.4%; 0.9-8.5)	12 (9.6%; 5.1-16.2)	2 (2.5%; 0.3-8.6)	14 (8.6%; 4.8-14.1)	NS
Temperature <36°C	0 (0%; 0.0-3.1)	11 (8.8%; 4.5-15.2)	3 (3.7%; 0.8-10.4)	8 (4.9%; 2.2-9.5)	NS
<b>Initial treatment</b>					
LMWH	112 (94.9%; 89.3-98.1)	97 (77.6%; 69.3-84.6)	75 (92.6%; 84.6-97.2)	134 (82.7%; 76.0-88.2)	NS
UFH	5 (4.2%; 1.4-9.6)	27 (21.6%; 14.7-29.9)	6 (7.4%; 2.8-15.4)	26 (16.0%; 10.8-22.6)	
Other treatment‡‡	1 (0.8%; 0.0-4.6)	1 (0.8%; 0.0-4.4)	0 (0%; 0.0-4.5)	2 (1.2%; 0.1-4.4)	

VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; LMWH, low molecular weight heparin; UFH, unfractionated heparin. \* Original PESI Class I-II; † Original PESI Class III-V; ‡ Simplified PESI no risk factors; § Simplified PESI ≥1 risk factor; ¶ Cancer defined as a history of cancer or active cancer. \*\* Defined as disorientation, lethargy, stupor or coma; †† Saturation assessed with and without the administration of supplemental oxygen. ‡‡ Patients with thrombolysis.

Table 7.3 Main outcomes within risk strata derived from the original PESI and simplified PESI.

	Original PESI Low Risk* (n=118) n (%; 95%CI)	Original PESI High Risk† (n=125) n (%; 95%CI)	p-value	Simplified PESI Low risk‡ (n=81) n (%; 95%CI)	Simplified PESI High risk§ (n=162) n (%; 95%CI)	p-value
<b>14 days follow up</b>						
Overall mortality	0 (0%; 0.0-3.1)	7 (5.6%; 2.3-11.2)	0.015	0 (0%; 0.0-4.5)	7 (4.3%; 1.8-8.7)	0.099
Fatal PE	0 (0%; 0.0-3.1)	0 (0%; 0.0-2.9)	-	0 (0%; 0.0-4.5)	0 (0%; 0.0-2.3)	-
Recurrent VTE	0 (0%; 0.0-3.1)	3 (2.4%; 0.5-6.9)	0.248	0 (0%; 0.0-4.5)	3 (1.9%; 0.4-5.3)	0.553
Major bleeding	0 (0%; 0.0-3.1)	8 (6.4%; 2.8-12.2)	0.007	0 (0%; 0.0-4.5)	8 (4.9%; 2.2-9.5)	0.055
Any adverse outcome	0 (0%; 0.0-3.1)	17 (13.6%; 8.1-20.9)	0.000	0 (0%; 0.0-4.5)	17 (10.5%; 6.2-16.3)	0.001
<b>30 days follow up</b>						
Overall mortality	0 (0%; 0.0-3.1)	10 (8%; 3.9-14.2)	0.002	0 (0%; 0.0-4.5)	10 (6.2%; 3.0-11.1)	0.033
Fatal PE	0 (0%; 0.0-3.1)	0 (0%; 0.0-2.9)	-	0 (0%; 0.0-4.5)	0 (0%; 0.0-2.3)	-
Recurrent VTE	0 (0%; 0.0-3.1)	4 (3.2%; 0.9-8.0)	0.123	0 (0%; 0.0-4.5)	4 (2.5%; 0.7-6.2)	0.304
Major bleeding	1 (0.8%; 0.0-4.6)	9 (7.2%; 3.3-13.2)	0.019	0 (0%; 0.0-4.5)	10 (6.2%; 3.0-11.1)	0.033
Any adverse outcome	1 (0.8%; 0.0-4.6)	21 (16.8%; 10.7-24.5)	0.000	0 (0%; 0.0-4.5)	22 (13.6%; 8.7-19.8)	0.000
<b>3 months follow up</b>						
Overall mortality	0 (0%; 0.0-3.1)	32 (25.6%; 18.2-34.2)	0.000	0 (0%; 0.0-4.5)	32 (19.8%; 13.9-26.8)	0.000
Fatal PE	0 (0%; 0.0-3.1)	0 (0%; 0.0-2.9)	-	0 (0%; 0.0-4.5)	0 (0%; 0.0-2.3)	-
Recurrent VTE	5 (4.2%; 1.4-9.6)	5 (4%; 1.3-9.1)	1.000	2 (2.5%; 0.3-8.6)	8 (4.9%; 2.2-9.5)	0.503
Major bleeding	2 (1.7%; 0.2-6.0)	10 (8%; 3.9-14.2)	0.035	0 (0%; 0.0-4.5)	12 (7.4%; 3.9-12.6)	0.010
Any adverse outcome	7 (5.9%; 2.4-11.8)	41 (32.8%; 24.7-41.7)	0.000	2 (2.5%; 0.3-8.6)	46 (28.4%; 21.6-36.0)	0.000

\* Original PESI Class I-II; † Original PESI Class III-V; ‡ Simplified PESI no risk factors; § Simplified PESI ≥1 risk factor.

## Recurrent VTE and major bleeding episodes

None of the low risk patients, in either group, had a recurrent event within 14 days (Table 7.3). At 3 months follow-up, 5 (4.2%; 95% CI 1.4–9.6) and 2 (2.5%; 95% CI 0.3–8.6) low risk patients from the original PESI and simplified PESI prognostic models developed recurrent VTE respectively. The rates of recurrent VTE in the high risk groups at 14 days and 3 months follow-up were 3 (2.4%; 95% CI 0.5–6.9) and 5 (4%; 95% CI 1.3–9.1) in the original PESI and 3 (1.9%; 0.4–5.3) and 8 (4.9%; 2.2–9.5) in the simplified PESI prognostic model (Table 7.3). The incidence of recurrent events did not differ significantly between the low and high risk groups at 14 days and 3 months (original PESI  $P=0.248$  and  $1.000$ , simplified PESI  $P=0.553$  and  $0.503$ ).

There were no major hemorrhages in the low risk groups within 14 days (Table 7.3). At 3 months follow-up 2 (1.7%; 95% CI 0.2–6.0) patients in the original PESI low risk group had a major hemorrhage, while no (0%; 95% CI 0.0–4.5) patients in the simplified PESI low risk group had a major bleed. The rates of major bleeding in the high risk groups were 8 (6.4%; 95% CI 2.8–12.2) at 14 days and 10 (8%; 95% CI 3.9–14.2) at 3 months follow-up using the original PESI prognostic model and 8 (4.9%; 95% CI 2.2–9.5) at 14 days and 12 (7.4%; 95% CI 3.9–12.6) at 3 month follow-up within the simplified PESI prognostic group (Table 7.3).

## Any adverse outcome

None of the low risk patients had any adverse outcome within the first 14 days after the index PE (Table 7.3). The difference in adverse events between the low risk and high risk patients at 14 days and 3 months follow-up were statistically significant (original PESI  $P=0.000$  and  $0.000$ , simplified PESI  $P=0.001$  and  $0.000$ )

## Outpatients versus inpatients

In our sample of 243 patients, 115 (47.3%; 95% CI 40.9–53.8) patients were safely treated out of the hospital with no deaths or bleeding episodes and only 1 recurrent event within the first 14 days or 30 days of follow-up. Thirty four (29.6%) of these outpatients were classified as high risk patients according to the original PESI (19 patients in class III, 13 in class IV and 2 patients in class V) and 54 (47.0%) were classified as high risk patients according to the simplified PESI prognostic model. In the majority of these patients (74.5%) a malignancy contributed to the high PESI scores. On the contrary, thirty seven (28.9%) out of the 128 admitted patients were classified as low risk patients according to the original PESI (19 patients in class I and 18 in class II) and 20 (15.6%) were classified as low risk patients according to the simplified PESI prognostic model. The most frequent reasons for admission of these 37 low risk patients were: extensive PE (22.0%) such as saddle PE, hypoxia (22.0%) and severe comorbidities (22.0%) such as pneumonia, transaminitis, advanced cancer, stroke and

coronary artery disease. Other reasons for admission were pain management, renal dysfunction, syncope and hypotension. Eight of these patients were treated with intravenous unfractionated heparin and 1 patient received thrombolysis. None of these 37 patients suffered from any adverse event during the first 14 days. There is 1 (2.7%; 95%CI 0.1–14.2) recurrent event and 1 (2.7%; 95% CI 0.1–14.2) major bleeding during the 3 months follow-up.

## Discussion

The results of our study suggest that both PESI prognostic models accurately identify patients with acute PE who are at low risk for short-term adverse events, including death, recurrent venous thromboembolism and major hemorrhage. None of the low risk patients died or had any adverse event within the first 14 days. Both PESI prognostic models also seem to identify patients with acute PE at low risk of adverse outcome who can be safely managed as outpatients.

Our results are consistent with previously published studies validating the original and simplified PESI.<sup>14,15,20-22</sup> The 3 months overall mortality in the low risk groups according to the original PESI model has been reported to be between 0% and 1.2%.<sup>14,20,21</sup> The overall mortality in the low risk group of our study was 0% (95% CI 0.0–3.1). The overall mortality in our high risk group was 25.6% (95% CI 18.2–34.2). Although this is consistent with two large validation studies<sup>14,20</sup>, a recent cohort reported an overall mortality of 9% in the risk classes IV and V in the first 3 months. This discrepancy might be explained by the exclusion of patients with terminal illness, such as metastatic cancer, in that particular study.<sup>21</sup> There is only one derivation and one validation study using the simplified PESI.<sup>15,23</sup> Their 30-day overall mortality of approximately 1% in the low risk groups correspond to our 30-day overall mortality of 0% (95% CI 0–4.5). To our knowledge, our study is the first external validation study reporting a shorter term follow-up of 14 days. Besides overall and PE-related mortality we also report recurrent VTE and major bleeding episodes. In order to select patients for outpatient treatment, clinicians require risk estimates of any adverse event in a short-term follow-up.

The overall proportion of patients classified into the low-risk category according to both PESI-scores and our own criteria for outpatient treatment was similar. However, in the current study 53% of patients were hospitalized following the diagnosis of the acute PE. Sixteen to 29% of these patients had a low risk PESI score. None of these admitted patients developed an adverse event during the first 14 days. However, some of these patients needed to be admitted to the hospital because of large PE (one patient with a saddle PE, severe tachycardia and tachypnea required thrombolysis), hypoxia or other severe comorbidities (e.g. advanced cancer). These features likely influenced the clinical judgment of the treating physician to hospitalize these patients. This emphasizes that the clinical judgment of the treating physician

may overrule a suggested decision by the PESI. On the contrary, 30 to 47% of patients with acute PE and a high risk PESI score were safely treated as outpatients. An underlying malignancy contributed to the high PESI scores in 75% of these cases. This suggests that a proportion of patients with high risk PESI scores might be safely treated as outpatients. Although, cancer patients have a high risk of death, it does not seem to be associated with worse short term adverse events in these patients with acute PE who were treated out of the hospital ( $P=0.339$  for any adverse event during 14 and 30-days follow-up). Future research is needed to identify patients with a low risk of short term adverse events who do not need hospitalization especially in those with significant other comorbidities.

Our study is limited by the small number of patients. The confidence intervals are large as a consequence of the small sample size and therefore our results and conclusions should be further investigated in larger studies. Secondary, the study is also limited by its retrospective design. However, we tried to minimize bias by reviewing patients' paper charts completed at the emergency department and all other patient data in our hospital database in duplicates. Furthermore, it is important to acknowledge possible selection bias by the exclusion of patients not followed at the Ottawa Hospital ( $n=21$ ). None of the included patients were lost to follow-up and no patients with PE were missed since we reviewed all VQs and CTPAs during the study period.

In conclusion, the original PESI as well as the simplified PESI prognostic models accurately identify patients with acute PE who are at low risk for short-term adverse events, such as death, fatal PE, recurrent VTE and major bleeding episodes. However, many high risk patients according to the PESI prognostic model were safely treated as outpatients. Further research using different prognostic models is required to better stratify patients according to their risk of short term adverse event and optimize outpatient management of patients with acute PE.



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# Chapter 8

## **Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis**

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*Plos One 2012;7:e42269*

## Abstract

### Background

The percentage of time within the target INR range 2.0 to 3.0 (TTR) in patients treated with vitamin K antagonists varies considerably among efficacy-studies of novel anticoagulants. In order to properly assess the quality of anticoagulant control in upcoming cost-effectiveness studies and real life registries this systematic review reports a benchmark of TTR for different treatment durations in patients with venous thromboembolism and discusses ways to calculate TTR. This review aims to inform clinicians on the benchmark of TTR and to discuss properly TTR assessments

### Methods

Medline and Embase were searched for studies published between January 1990 and May 2012. Randomized controlled trials and cohort studies reporting the TTR in patients with objectively confirmed venous thromboembolism treated with vitamin K antagonists (VKA) were eligible. Duplicate reports, studies only reporting INR during initial treatment or with VKA treatment less than 3 months were excluded. Three authors assessed trials for inclusion and extracted data independently. Discrepancies were resolved by discussion between the reviewers. A meta-analysis was performed by calculating a weighted mean, based on the number of participants in each included study, for each time-period in which the TTR was measured since the confirmation of the diagnosis of VTE.

### Results

Forty studies were included (26064 patients). The weighted means of TTR were 54.0% in the first month since the start of treatment, 55.6% in months 1 to 3, 60.0% in months 2 to 3, 60.0% in the months 1 to 6+ and 75.2% in months 4 to 12+. Five studies reported TTR in classes. The INR in these studies was  $\geq 67\%$  of time in therapeutic range in 72.0% of the patients.

### Conclusion

Reported quality of VKA treatment is highly dependent on the time-period since the start of treatment, with TTR ranging from approximately 56% in studies including the 1<sup>st</sup> month to 75% in studies excluding the first 3 months.

## Introduction

Traditionally, patients with venous thromboembolism (VTE) are treated with low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) such as warfarin, acenocoumarol or phenprocoumon.<sup>1,2</sup> As with any medical treatment, the weighing of risks and benefits must be carefully balanced. The effect of VKA therapy depends on many factors including variation in dose response between patients, individual variation in pharmacokinetics and pharmacodynamic response, multiple interactions with food, co-medication and finally also by variation in adherence.<sup>3,4</sup> VKA have a narrow therapeutic index, which needs to be monitored carefully in order to reduce the risk of thromboembolic events as well as bleeding complications.<sup>5</sup> With the large scale clinical testing of novel, direct acting oral anticoagulants, including the thrombin and factor Xa inhibitors dabigatran and rivaroxaban, a new era has been heralded. The main advantage of these new anticoagulants is the lack of a need for laboratory monitoring and dose adjustment due to more stable pharmacokinetics.<sup>6</sup> Several recent large randomized controlled trials have shown non-inferiority in effectiveness and safety of the new anticoagulants compared to VKA treatment.<sup>7-11</sup> However, the percentage of time within therapeutic range in the VKA-group, representing the quality of the control group, appears to vary considerably among these studies.

The International Normalized Ratio (INR), the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the International Sensitivity Index (ISI) value, is established by the World Health Organization (WHO) and the International Committee on Thrombosis and Hemostasis for monitoring the effects of VKA. A target INR range of 2.0 to 3.0 is recommended for the treatment of VTE.<sup>3</sup> The most recognized way to measure the therapeutic effectiveness of VKA over time is to measure the percentage of time in the therapeutic range (TTR). TTR has been shown to strongly correlate with the clinical outcomes of hemorrhage or thrombosis and, thus, TTR is a reliable measure of the quality of anticoagulation management.<sup>12</sup>

Dabigatran and rivaroxaban have been recently approved in many countries including the USA, Canada and also in Europe. This development will cause major changes in thrombosis management in the near future. Cost-effectiveness studies and real life registries will be the next step in the implementation of new oral anticoagulants. In order to adequately compare all treatment options, including novel anticoagulants and VKA, and to interpret the relative efficacy and safety of these novel anticoagulants, it is important to properly assess the quality of anticoagulant control, i.e. TTR, in the VKA group. This systematic review tries to provide a benchmark of TTR in patients with VTE receiving VKA and discusses the pros and cons of various ways to calculate TTR. Finally, it emphasizes the need to standardize TTR reporting, thereby contributing to a meaningful comparison among treatment options in studies evaluating novel anticoagulants.

## Materials and methods

### Data sources and searches

A systematic search was performed to identify randomized controlled trials and cohort studies reporting the TTR in patients treated with VKA for deep vein thrombosis (DVT) confirmed by a non-compressible venous segment on an ultrasound of the extremities, or pulmonary embolism (PE) confirmed by an arterial filling defect on Computed Tomographic Pulmonary Angiography (CTPA) or a high probability ventilation/perfusion (V/Q) scan, or both (VTE). We searched Medline and Embase for articles in English, French, German, Dutch, Polish, Swedish, Danish, Italian and Spanish. Since the World Health Organization introduced the INR in 1983<sup>13</sup> and the first studies reporting TTR in VKA in patients with VTE were published in the nineties, we searched for publications between January 1990 and May 2012. See [www.plosone.org](http://www.plosone.org) for detailed information about the search strategy and key words.

### Study selection

To be eligible for inclusion, studies had to fulfill the following criteria:

1. Study population consisted of consecutive adult patients with objectively confirmed DVT or PE.
2. Patients were treated with VKA for a minimum of three months.

Studies were excluded if they only reported the TTR in the initial treatment period while patients were still on parental medication such as low molecular weight heparin and unfractionated heparin.

### Data extraction and management

Three reviewers (PE, HTC, MP) operating in pairs of two extracted independently the following characteristics from each included study: study design, type of study (e.g. evaluation of a new drug, dose-finding, evaluation of duration of anticoagulation), characteristics of the study population (e.g. number of patients treated with VKA, country, inclusion criteria, proportion of patients with a malignancy), initial treatment, type of VKA (e.g. warfarin, acenocoumarol, phenprocoumon or other), initial dose of VKA, treatment duration, INR-monitoring by thrombosis service or self-management, percentage of time below therapeutic range (INR <2), percentage of time within therapeutic range (INR 2.0–3.0), percentage of time above therapeutic range (INR >3), method of calculation TTR, adverse events (e.g. recurrent VTE, major bleeding and mortality), period of follow-up and percentage lost to follow-up. The quality of the included studies was assessed by addressing the following issues: a) were consecutive patients included in the study?, b) did the authors report reasons for exclusion?, c) were incomplete data adequately addressed?, d) did the authors address potential sources of bias?, e) what was the duration of follow-up?, f) how many patients

(percentage) were lost to follow-up?. Discrepancies were resolved by discussion. If agreement could not be reached a third reviewer was consulted.

### Data synthesis and analysis

A meta-analysis was performed by calculating a weighted mean, based on the number of participants in each included study, for each time-period in which the TTR was measured since the confirmation of the diagnosis of VTE.

## Results

### Results of the search

The systematic search yielded 3636 citations. The results were screened and after reading titles and abstracts 3154 articles were excluded. Of the remaining 482 publications the full text was assessed. (Figure 8.1)

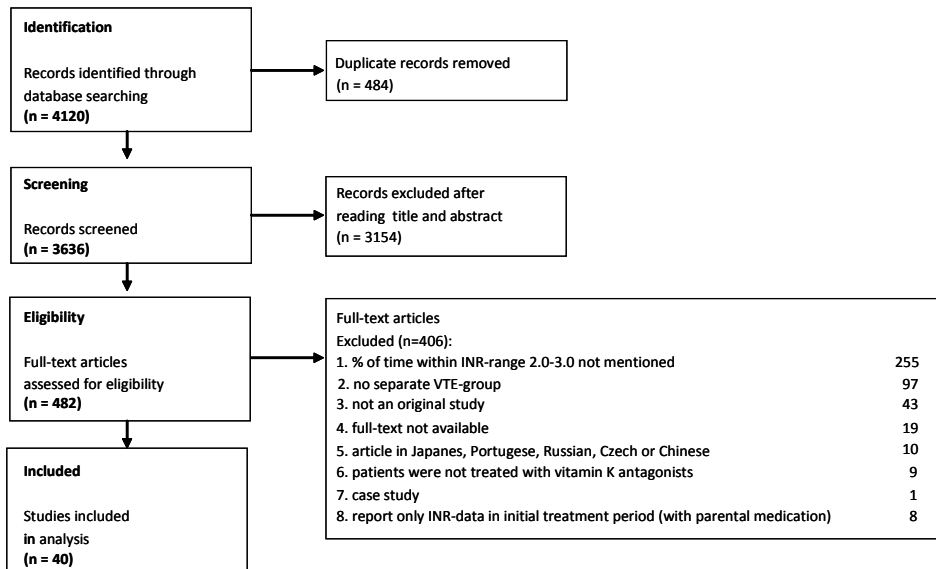


Figure 8.1 Flow diagram of literature search.

### Included studies

In total, 40 studies<sup>8,9,14-51</sup> reporting the TTR in 26064 patients treated with VKA for VTE were included in the analyses. Most studies included patients with DVT as well as PE.



Fifteen studies<sup>9,14,16,19-22,25,31-33,36,39,42,47</sup> reported the results from patients with only DVT and eight studies<sup>15,18,38,47-51</sup> reported the results from patients with only PE. The percentage of cancer ranged from 0% to 100%. The study characteristics of the included studies are presented in Table 8.1a. The quality assessment of each study is available at [www.plosone.org](http://www.plosone.org).

### Methods of calculating TTR

Five studies<sup>24,39,42,43,45</sup> reported TTR in classes ranging from <33% to ≥75% of time spent within INR-range 2.0 to 3.0. (e.g. 57% of all patients spent 70% of time within therapeutic range). All other TTRs were reported in percentages over time. Two studies<sup>9,20</sup> reported the TTR in the first month since the start of treatment, thirteen studies<sup>14,18,19,21,25,29,31,34,36,40,46,48,49</sup> reported the TTR measured in months 1 to 3, four studies<sup>20,28,32,44</sup> measured the TTR in months 2 to 3, fifteen studies<sup>8,9,17,22,23,26,33,35,37,38,41,45,47,50,51</sup> in months 1 to a minimum of 6 months and four studies<sup>15,16,27,31</sup> reported the TTR in months 4 to at least 12 months since the start of treatment. Twenty (50%) studies<sup>15-19,25,27-31,33,35,37,41,45,47-50</sup> reported that they calculated the TTR by using linear interpolation.<sup>52</sup> The method used for calculating TTR was not mentioned in 12 (30.0%) studies<sup>8,14,20-23,32,34,36,38,44,46</sup> (Table 8.1).

### Percentage of time in therapeutic range

Table 8.2 presents the percentage of time below, within and above the therapeutic INR range of 2.0 to 3.0 of the individual studies. A histogram with the TTR in each individual study is given in Figure 8.2.

Table 8.3 details the weighted means for different time-periods since objective confirmation of the diagnosis VTE. The reported quality of VKA treatment is highly dependent on the time-period. In the first month the reported TTR is 54.0%. The TTR is 55.6% during the months 1 to 3 and 60.0% during a treatment of at least 6 months including the INRs in the first month. In studies reporting TTR without INRs in the first month, the TTR was 60.0% in months 2 to 3 since the start of treatment and 75.2% in the months 4 to 12 or longer.

Table 8.1 Study characteristics of included studies.

First author and year	Study design / Type of study	n	% with cancer	Included patients	Treatment	Definition TR	Method measurement TTR
Research Committee of British Thoracic Society, 1992	RCT / duration OAC	358	3.6%	VTE	UFH and Warfarin (4 weeks treatment)	INR 2.0 - 3.0	Classes of %TTR
Agnelli, 2001	RCT / duration OAC	267	0%	DVT	LMWH and Warfarin / Acenocoumarol	INR 2.0 - 3.0	Linear interpolation
Agnelli, 2003	RCT / duration OAC	326	0%	PE	LMWH and Warfarin / Acenocoumarol	INR 2.0 - 3.0	Linear interpolation
Agnelli, 2007	RCT / dose-finding	126	<3%	DVT	LMWH and Warfarin / Acenocoumarol	INR 2.0 - 3.0	NR
		172	1%		LMWH and VKA local practice (outpatient treatment)		
Aujesky, 2011	RCT / outpatients vs. inpatients	172	2%	PE	LMWH and VKA local practice (inpatient treatment)	INR 2.0 - 3.0	Linear interpolation
Van Bladel, 2010	Cohort of PE patients	86	14%	PE	LMWH and Acenocoumarol	INR 2.0 - 3.5	Linear interpolation
Bona, 2000	Cohort with and without cancer	208	0%	VTE	Warfarin	INR 2.0 - 3.0	Linear interpolation
Büller, 2003	RCT / medication trial	1103	10.2%	PE	Fondaparinux and VKA local practice	INR 2.0 - 3.0	Linear interpolation
Büller, 2008	RCT / dose-finding	137	7.3%	DVT	LMWH / UFH and Warfarin / Acenocoumarol / Phenprocoumon / Fludione	INR 2.0 - 3.0	Linear interpolation
Caprini, 1999	Cohort / INR and DVT resolution	33	22.7%	DVT	UFH and Warfarin	INR 2.0 - 3.0	NR
Cassiopea Investigators, 2012	RCT / medication trial	1603	6%	PE	LMWH and Warfarin	INR 2.0 - 3.0	Linear interpolation
Columbus Investigators, 1997	RCT / medication trial	510	23.3%	VTE	LMWH and coumarin derivative	INR 2.0 - 3.0	NR
Das, 1996	RCT / medication trial	55	22.1%	DVT	UFH and coumarin derivative	INR 2.0 - 3.0	NR
Daskopoulos, 2005	RCT / medication trial	52	5.5%	DVT	LMWH and Warfarin	INR 2.0 - 3.0	NR
Einstein Investigators, 2010	RCT / medication trial	1718	15.4%	DVT	UFH and Acenocoumarol	INR 2.0 - 3.0	NR
Einstein Investigators, 2012	RCT / medication trial	2413	5.2%	DVT	LMWH and Warfarin / Acenocoumarol	INR 2.0 - 3.0	after discontinuation LMWH until end of treatment, including interruptions
Fiesinger, 2005	RCT / medication trial	1249	4.5%	PE	LMWH and Warfarin / Acenocoumarol	INR 2.0 - 3.0	after discontinuation LMWH until end of treatment, corrected for interruptions
		360	13.5%	VTE	LMWH (Enoxaparin) and Warfarin	INR 2.0 - 3.0	NR
			22.2%		UFH and Warfarin		

First author and year	Study design / Type of study	n	% with cancer	Included patients	Treatment	Definition TR	Method measurement TTR
Gallie Investigators, 2004	RCT / medication trial	360	21.1%	VTE	LMWH and Warfarin	INR 2.0 - 3.0	Classes of %TTR
Van Gogh Investigators, 2007	RCT / medication trial	1452	9.5%	DVT			
Gonzalez-Fajardo, 1999	RCT / medication trial	1120	8.4%	PE	LMWH / UFH and Warfarin / Acenocoumarol	INR 2.0 - 3.0	Linear Interpolation
Heidinger, 2000	Cohort / self-management OAC	80	10%	DVT	UFH and Coumarin	INR 2.0 - 3.0	Linear Interpolation
Kearon, 1999	RCT / duration OAC	622	NR	VTE	VKA according to local practice	INR 2.0 - 3.0	Last 12 values
Kearon, 2003	RCT / dose-finding	162	0%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 3.0	Linear Interpolation
Kearon, 2004	RCT / duration of OAC	369	0%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 3.0	Linear Interpolation
		165	0%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 3.0	Linear Interpolation
		355	16.6%	VTE	UFH and Warfarin		
Kearon, 2006	RCT / medication trial	353	15.0%	VTE	LMWH and Warfarin	INR 2.0 - 3.0	Linear Interpolation
		198	18.2%	VTE	UFH and VKA local practice		
Koopman, 1996	RCT / medication trial	202	16.8%	DVT	LMWH and VKA local practice	INR 2.0 - 3.0	Linear Interpolation
Levine, 1995	RCT / duration OAC	109	21.1%	DVT	UFH and Warfarin	INR 2.0 - 3.0	NR
López-Beret, 2001	RCT / medication trial	77	23.3%	DVT	LMWH (Nadroparin) and Acenocoumarol	INR 2.0 - 3.0	Linear Interpolation
Meyer, 2002	RCT / medication trial	75	100%	VTE	LMWH and Warfarin	INR 2.0 - 3.0	NR
Monreal, 1998	Cohort of VTE patients	244	13.5%	VTE	LMWH (Dalteparin) and Coumarin	INR 2.0 - 3.0	Linear Interpolation
Nielsen, 1993	RCT / medication trial	46	8.7%	DVT	UFH / Phenprocouman	INR 2.0 - 3.0	NR
		733	0%	VTE			
Palareti, 2000	Cohort with and without cancer	95	100%	VTE	Warfarin / Acenocoumarol	INR 2.0 - 3.0	Linear Interpolation
Pérez-de-Llano, 2010	RCT / medication trial	50	6%	PE	LMWH (Tinzaparin) and Acenocoumarol	INR 2.0 - 3.0	NR
Pini, 1994	RCT / medication trial	94	24.5%	DVT	Heparin and Warfarin	INR 2.0 - 3.0	Classes of %TTR
		1560	NR	VTE	VKA local practice (Manual dosage)		
Pouller, 2008	dosage vs medical staff	1649	NR	VTE	VKA local practice (Computer-assisted dosage)	INR 2.0 - 3.0	Linear Interpolation
Poli, 2007	Cohort of VTE patients	182	0%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 3.0	Median % of time
		90	16.7%	VTE	LMWH / UFH and VKA local practice (stockings)		
		90	11.1%	DVT	LMWH / UFH and VKA local practice (no stockings)	INR 2.0 - 3.0	Classes of %TTR
Prandoni, 2004	RCT / intervention stockings	90	11.1%	DVT	stockings	INR 2.0 - 3.0	Classes of %TTR
Santamaria, 2006	Cohort / cost-effectiveness	116	17.2%	VTE	Acenocoumarol / Warfarin	INR 2.0 - 3.0	NR
		1124	0%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 2.85	Linear Interpolation
Schulman, 1994	RCT / duration of OAC	1124	0%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 3.0	Classes of %TTR
Schulman, 2009	RCT / medication trial	1265	4.5%	VTE	LMWH / UFH and Warfarin	INR 2.0 - 3.0	NR

RCT= randomized controlled trial; OAC= oral anticoagulation; UFH= unfractionated heparin; LMWH= low molecular weight heparin; VTE= venous thromboembolism; DVT= deep vein thrombosis; PE= pulmonary embolism; TR= therapeutic range; INR= international normalized ratio; NR= not reported.

Table 8.2 Percentage of time below, within and above the Therapeutic Range of the individual studies.

First author and year	n	Time-Period TTR since diagnosis	% below TR	TTR % within TR	% above TR
Research Committee of The British Thoracic Society, 1992	358	Month 1	NR	37.4% (>67% TTR)	NR
Agnelli, 2001	267	Months 1 to 3	NR	35.2% (>67% TTR)	NR
Agnelli, 2003	326	Months 4 to 12+	NR	81%	NR
Agnelli, 2007	126	Months 4 to 12+	NR	83%	NR
Aujeskey, 2011	172	Months 1 to 3	NR	60%	NR
	172	Months 1 to 3	34.7%	51.8%	13.5%
Van Bladel	86	Months 1 to 3	32%	52.5%	15.6%
	104	Months 1 to 3	12.1%	76%	11.8%
Bona, 2000	208	Months 1 to 6+	NR	47.5%	NR
	1103	Months 1 to 6+	NR	56%	NR
Büller, 2003	1110	Months 1 to 3	28%	53%	19%
Büller, 2008	137	Months 1 to 3	28%	52%	20%
		Months 1 to 3	29%	50.3%	20.7%
		At 1 month	42.4%	48.5%	12.1%
		At 3 months	63.6%	39.4%	3%
Caprini, 1999	33	At 6 months	48.5%	45.5%	9.1%
Cassiopea Investigators, 2012	1603	Months 1 to 6+	25.6%	55.9%	18.5%
	510	Months 1 to 6+	22%	57%	21%
The Columbus Investigators, 1997	511	Months 1 to 3	24%	57%	21%
Das, 1996	55	Months 1 to 3	NR	68.8%	NR
Daskopoulos, 2005	52	Months 1 to 6+	19.1%	67.2%	13.6%
		Month 1	NR	54.1%	NR
The Einstein Investigators, 2010	1718	Months 1 to 6+	24.4%	57.7%	16.2%
The Einstein Investigators, 2012	2413	Months 1 to 6+	21.8%	62.7%	15.5%
Fiesinger, 2005	1249	Months 1 to 6+	NR	61%	NR
	360	Months 1 to 3	NR	72.7% ( $\geq 70\%$ TTR)	NR
The Galilei Investigators, 2004	360	Months 1 to 3	NR	70% ( $\geq 70\%$ TTR)	NR
	1452	Months 1 to 6+	26.2%	54.4%	19.4%
The van Gogh Investigators, 2007	1120	Months 1 to 6+	26.9%	54.8%	18.3%
Gonzalez-Fajardo, 1999	80	Months 1 to 3	15%	64%	21%
Heidinger, 2000	622	on average at 4.5 months	22.7%	69.2%	8.1%

First author and year	N	Time-Period TTR since diagnosis	% below TR	TTR % within TR	% above TR
Kearon, 1999	162	Months 4 to 12+	22%	64%	14%
Kearon, 2003	369	Months 4 to 12+	20%	69%	11%
Kearon, 2004	165	Months 2 to 3	29%	63%	8%
	355		28%	55%	17%
Kearon, 2006	353	Months 1 to 3	25%	56%	19%
	198		18%	56%	26%
Koopman, 1996	202	Months 1 to 3	16%	62%	22%
Levine, 1995	109	Months 2 to 3	29.6%	60.7%	9.7%
López-Beret, 2001	77	Months 1 to 6+	22.8%	67.8%	9.4%
Meyer, 2002	75	Months 1 to 3	NR	41%	NR
Monreal, 1998	244	Months 1 to 6+	25.5%	56.9%	17.6%
Nielsen, 1993	46	Months 1 to 3	NR	70%	NR
	733		22.5%	63.6%	13.9%
Palareti, 2000	95	Months 1 to 6+	23.3%	58.9%	17.8%
Pérez-de-Llano, 2010	50	Months 1 to 6+	41.5%	51.7%	6.8%
Pini, 1994	94	Months 1 to 3+	NR	38% ( $\geq 67\%$ TTR)	NR
	1560		NR	64.9%	NR
Poller, 2008	1649	Months 1 to 6+	NR	66%	NR
Poli, 2007	182	Months 1 to 3	18.8%	69.7%	11.5%
	90		NR	70% ( $> 70\%$ TTR)	NR
Prandoni, 2004	90	Months 1 to 3+	NR	72.2% ( $> 70\%$ TTR)	NR
Santamaria, 2006	116	At 3 months	NR	61.1%	NR
		At 12 months	NR	63% ( $\geq 75\%$ TTR)	NR
Schulman, 1994	1124	Months 1 to 6+	25%	58%	17%
Schulman, 2009	1265	Months 1 to 6+	21%	60%	19%

TTR= time in therapeutic range; TR= therapeutic range; INR= international normalized ratio; NR= not reported.

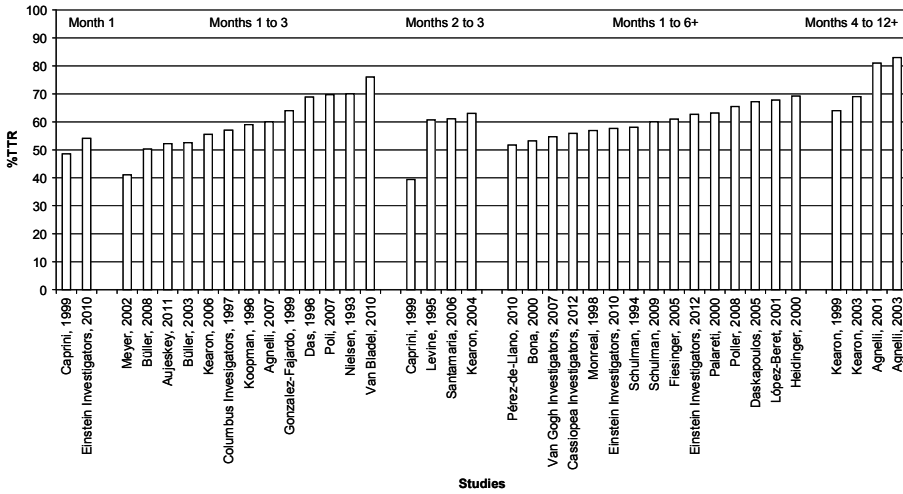


Figure 8.2 Time in therapeutic range in individual studies. (A weighted mean is calculated if a study reported more than 1 group; studies that only presented classes of %TTR are not represented here).

Table 8.3 Weighted mean % of time below, within and above Therapeutic Range INR 2.0–3.0.

Time-period TTR INR 2.0-3.0 Since diagnosis	% below TR Weighted mean	% TTR Weighted mean	% above TR Weighted mean
Month 1 (n studies=2, n patients=1751)	42.4%	54.0%	12.1%
Months 1 to 3 (n studies=13, n patients=5473)	35.0%	55.6%	19.2%
Months 2 to 3 (n studies=4, n patients=423)	32.9%	60.0%	8.1%
Months 1 to 6+ (n studies=13, n patients=17338)	24.1%	60.0%	16.7%
Months 4 to 12+ (n studies=4, n patients=1124)	20.6%	75.2%	11.9%

TTR= time in therapeutic range; INR= international normalized ratio; TR= therapeutic rang.

## Discussion

A strong relationship between TTR and bleeding or thromboembolic rates has been observed across a large number of studies with different patient populations.<sup>53</sup> Since under-anticoagulation gives inadequate protection against thromboembolic events and over-anticoagulation increases the bleeding risk, it is important to report the quality of VKA treatment by using the TTR.<sup>54</sup> The evidence for non-inferiority of new

anticoagulants depends on the quality of the VKA control group. The present review provides a benchmark of TTR in patients with VTE receiving VKA and discusses the pros and cons of various ways to calculate TTR.

We included 40 studies with more than 26000 participants and the results indicate that the achieved TTR ranges from approximately 56% to 75%.

The reported quality of VKA treatment was highly dependent on the time-period since the start of treatment. A statistically significant lower TTR was seen in studies reporting a TTR that covers all INRs, including the first month, compared to studies reporting the TTR without the first month. This difference is to be expected because of the difficulty to reach the therapeutic range in the initial treatment period and improvement in TTR during continuation of VKA treatment. Another explanation of the high TTR during longterm treatments is a selection-to-continue bias. Patients with stable INRs are more likely to continue their treatment with VKA than patients who experience problems in reaching the therapeutic range.<sup>55</sup> However, even after 4 to 12 months of treatment with VKA, patients spent 25% of their time outside of the therapeutic range.

Our review has some limitations that have to be mentioned. First, methods used to calculate TTR differed across the included studies. Fifty percent of the studies used linear interpolation, a few studies reported the percentage of time in a certain TTR class and 30% of the studies did not report the method of TTR calculation at all. Due to missing information about the exact calculation of TTR, we were unable to compare the different methods in a meaningful way. In literature, several methods to assess therapeutic control are described: e.g. the assessment of the number of INR measurements within the target range expressed as a percentage of the total number of INRs obtained, the cross-section-of-the-files technique (the fraction of patients in range at one point in time compared to the total number of patients who had an INR at that point in time), equidivision, linear interpolation and the hybrid method.<sup>52,56,57</sup> Each approach has its advantages and disadvantages. A disadvantage of the first two methods is that they do not incorporate time and therefore cannot be used to calculate incidence rates of recurrences at different INR levels.<sup>54</sup> Time is incorporated in the method of equidivision, which assumes that the change between two consecutive INR measurements occurred halfway the interval.<sup>[56]</sup> The time spent in INR ranges can also be estimated by linear interpolation, which assumes that the INR between two measurements varies linearly from the first INR to the second INR.<sup>52</sup> A disadvantage of these last two methods is that extreme out of range INR values may bias overall results.<sup>58</sup> The hybrid method, in addition, takes effects of dosage modifications into account.<sup>54</sup> The results of all of these methods depend on whether an exact (INR 2.0–3.0) or an expanded therapeutic range is used, whether VKA-naïve patients (those just beginning therapy) are included or only patients already on established therapy, whether INRs obtained during invasive procedures when VKA therapy might be interrupted are excluded, and whether different oral anticoagulant preparations (e.g. warfarin or acenocoumarol) are allowed.<sup>53</sup> In a comparison of the

equidivision, linear interpolation and hybrid methods, linear interpolation has been suggested as the preferred method as it shows a high validity and reproducibility.<sup>54</sup> We suggest that drug trials and real life registries with a VKA control group report the TTR in a uniform manner, to allow adequate comparison of data. Since linear interpolation has a high validity and was the most common method used to calculate TTR in the present review, we recommend to use linear interpolation in future studies covering the INRs from each patient from the discontinuation of heparin until the end of treatment. In order to avoid complex calculations, we believe that including time-periods with interruptions in VKA treatment in the TTR are acceptable. However, for calculating the relationship between TTR and adverse events, such as major bleeding episodes and thromboembolic events, we would suggest to exclude bridging periods, since the TTR will not represent the quality of anticoagulant treatment during these periods when most patients receive LMWH (Figure 8.3).

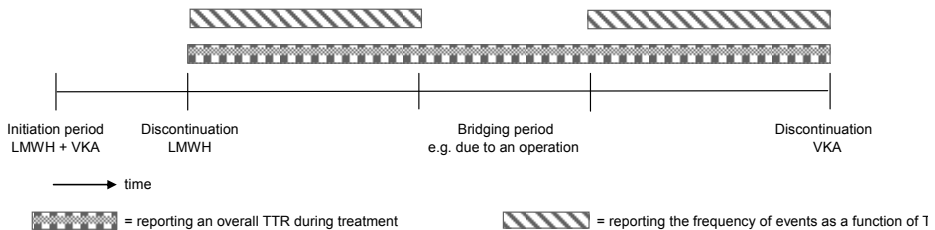


Figure 8.3 Suggestions for calculating TTR.

A second important limitation of the present review is that we were not able to investigate the association between TTR and clinical endpoints. Several studies in literature show a strong relationship between TTR and bleeding or thromboembolic events.<sup>53</sup> Unfortunately, data on such clinical endpoints related to TTR was not provided in the included studies.

Additionally, some other interesting sub-analyses were difficult due to small subgroups and the absence of detailed data. Hutten et al. indicated that the therapeutic quality of treatment was decreased when patients were treated with acenocoumarol rather than with warfarin.<sup>59</sup> This might implicate that the use of warfarin is preferable. However, since it is not clear whether these results might be influenced by factors such as frequency of monitoring and comorbidities, we need to be careful with drawing a conclusion. Furthermore, Hutten et al. showed that TTR was decreased in the presence of cancer and in the presence of a pulmonary embolism.<sup>59</sup> The same subgroup analyses in the present review did not show statistically significant results (data not shown). This might be explained by the fact that we did not have individual patient data (IPD). An IPD meta-analysis may give more detailed



information for investigating such associations and may be interesting. Hutten et al. also showed a decrease in the therapeutic quality of VKA treatment when more than four changes in co-medication occurred.<sup>59</sup> Unfortunately such data was not available for our review.

The main conclusion of our systematic review is that the reported quality of VKA treatment is highly dependent on the time-period since the start of treatment, with the TTR ranging from approximately 56% in studies including the first month to 75% in studies excluding the first 3 months. The clinical consequences of our findings are not straightforward. However, it needs to be emphasized that the reported quality of VKA treatment should be taken into consideration while interpreting results from trials with new anticoagulants. Assuming an average treatment duration of 6 months, the mean TTR is approximately 60%. We recommend to calculate the TTR by using linear interpolation covering the INRs from each patient from discontinuation of heparin until the end of treatment. Furthermore, TTR is predictive of thromboembolic and bleeding complications for patients on VKA<sup>53</sup>; therefore a proper calculation of TTR in the VKA group is of importance in assessing the adequacy and quality of novel anticoagulants.

Oral anticoagulants are also effective in preventing stroke<sup>60-64</sup> and prolonging survival rates in patients with atrial fibrillation (AF).<sup>65</sup> It may be interesting to investigate a benchmark of the TTR in patients treated with VKA in AF in the near future. However, since patients with AF are usually on long-term VKA treatment, selection-to-continue bias will be more evident than in patients with VTE and should be taken into consideration in an analysis in AF patients.<sup>55</sup>

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# Chapter 9

## General discussion



## General discussion

In this general discussion the overall methodological considerations of the studies in this dissertation will be discussed and practical implications of the results, new developments in the field and recommendations for further research will be outlined. In line with the structure of this thesis, these items will be addressed in two parts: 'diagnosing pulmonary embolism in primary care' and 'treatment of pulmonary embolism in secondary care'.

### Diagnosing pulmonary embolism in primary care

#### *Methodological considerations*

The diagnostic part of this thesis comprises research findings obtained from 598 adult patients with suspected PE enrolled in a prospective multicenter diagnostic cohort by primary care physicians between July 2007 and December 2010 (AMUSE-2). In chapter 4 we show that none of the clinical decision rules in secondary care is sensitive enough to exclude PE on its own.<sup>1</sup> Therefore, we validated the use of the Wells clinical decision rule for PE combined with D-dimer testing for excluding PE in primary care. In primary care, physicians are frequently confronted with situations where quantitative laboratory based D-dimer tests are not readily available. To ensure that the AMUSE-2 diagnostic strategy was accessible for all primary care physicians we chose to use a qualitative point-of-care D-dimer test.

Since this was a validation study to investigate the safety of excluding PE in primary care, we chose to refer all included patients to the hospital for further diagnostic work-up. In secondary care, the diagnostic strategy was based on current guidelines and routine care protocols. In the Netherlands, this commonly is a combination of probability estimation by a clinical decision rule and quantitative laboratory based D-dimer testing, followed by CT-scanning if indicated. To guarantee independence and thereby avoiding that physicians in secondary care would base their decision for imaging on the results of the Wells rule and point-of-care D-dimer test in primary care, secondary care physicians were not informed by the referring primary care physician that the particular patient was a study patient and thus they were not aware of the risk-score in primary care.

PE was confirmed or refuted based on a composite reference, including spiral CT and 3 months of follow-up. There is convincing evidence from large diagnostic studies that a low probability of PE according to a clinical decision rule combined with D-dimer testing safely excludes PE in secondary care.<sup>2,3</sup> Therefore, spiral CT-scanning deemed to be unethical in patients with a low probability of PE in secondary care. In low-risk patients PE was excluded if an alternative diagnosis was found that completely explained the symptoms of the included patient and no thromboembolic event occurred during 3 months of follow-up. An independent adjudication committee



evaluated all patients with a diagnosis of PE despite a negative Wells PE rule and a negative point-of-care D-dimer test in primary care.

Information about the investigations done in the hospital and the final diagnosis were retrieved from hospital discharge letters or from the 3 months follow-up form filled out by the primary care physician. In 30% of clinically serious alternative diagnoses of PE, i.e. patients who needed immediate medical treatment, it was not clear if objective testing was performed to confirm these diagnoses. These alternative diagnoses may be mainly based on clinical features. Since this also occurs in daily clinical practice, we think that our study still is a good representation of daily practice. There was some missing data in a few patients. Missing data seldom occurs completely at random. We compared the values of several variables from the patients without to the patients with missing information. The missing data turned out to be rather selective. For example, missing values were less frequently observed in patients with a positive point-of-care D-dimer test. Deleting subjects with a missing value would therefore not only lead to a loss of statistical power but also to biased results. To minimize the effect of selective missing we chose to impute the missing values of the most important variables using multiple imputation techniques. The imputation technique was based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects.<sup>4,5</sup>

### *Practical implications*

AMUSE-2 demonstrated that a diagnostic approach of a Wells score  $\leq 4$  combined with D-dimer testing would rule out PE in 4 to 5 out of 10 primary care patients with an acceptably low failure rate of less than 2%.<sup>6</sup> This implies that probably more than 40% of the patients with suspected PE do not need to be referred to secondary care for further diagnostic work-up to exclude PE. These results are comparable to the efficiency and failure rate of clinical decision rules combined with D-dimer testing in secondary care as seen in chapter 4, which justifies the use of the AMUSE-2 diagnostic strategy in a future management study.

The most common alternative diagnoses of PE in primary care are thoracic pain/dyspnoea e.c.i., pneumonia and myalgia. We found that a low probability of PE according to the Wells rule and point-of-care D-dimer testing in primary care, may not only exclude PE but also other serious diseases. Patients with a high probability of PE often have a clinically serious diagnosis and need immediate medical treatment, while patients with a low probability of PE are often diagnosed with a less serious disease. This emphasizes the usefulness of the Wells rule and point-of-care D-dimer testing in the differentiation between high and low risk patients for clinically serious diseases in primary care and further justifies referral to secondary care in high risk patients.<sup>7</sup>

Do these findings imply that in case of suspected PE a primary care physician should have the Wells clinical decision rule and a point-of-care D-dimer test readily available at his office or in his briefcase? Before implementing this diagnostic strategy in daily practice it may be prudent first to evaluate the safety of withholding anticoagulant

therapy in primary care patients with a low suspicion of PE in a management study. Further research will be discussed in the next paragraph.

*Developments and recommendations for further research*

Before moving on to management and implementation studies it might be informative to investigate whether the use of the Wells rule for PE combined with D-dimer testing in primary care will be cost-effective. In a cost-effectiveness study we can evaluate whether the Amuse-2 strategy will reduce health care costs while increasing the quality of life of patients suspected of PE.

In a health economics evaluation we are currently modeling different scenarios of the diagnostic strategy used in AMUSE-2. Modeling allows us to synthesize all relevant data and information from multiple sources of evidence, including the results of the AMUSE-2 study and results in literature.<sup>5,8</sup>

The following Markov model represents the complex process of health states and events following suspicion of PE (Figure 9.1).

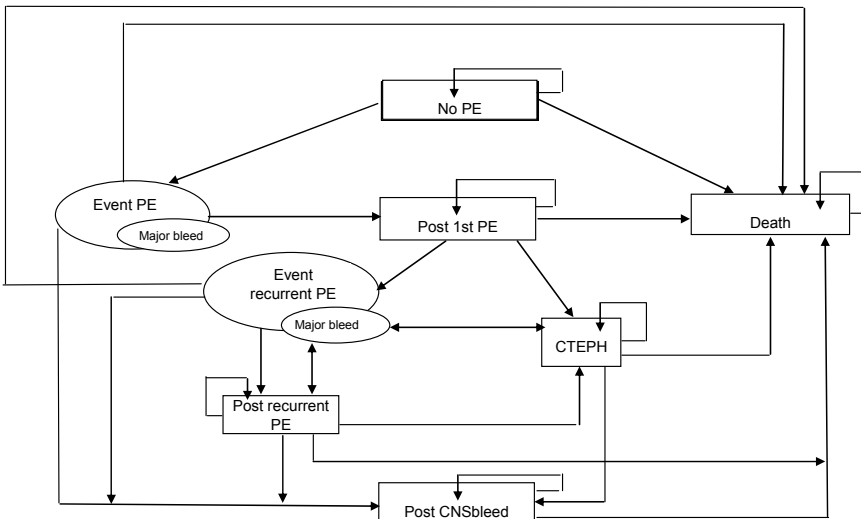


Figure 9.1 Markov model AMUSE-2. PE= pulmonary embolism; CTEPH= chronic thromboembolic pulmonary hypertension; CNS= central nervous system.

This Markov model is divided into 6 mutually exclusive health states: no PE, post 1<sup>st</sup> PE, post recurrent PE, chronic thromboembolic pulmonary hypertension, post central nervous system bleed and death. Use of the Wells clinical decision rule and D-Dimer

test in primary care may have consequences for all health states and outcomes related to PE. Each health state has its own quality of life and costs. In order to investigate the cost-effectiveness of using the Wells rule and point-of-care D-dimer testing in primary care, the costs and health effects of each health state and event have to be taken into account.

A cost-effectiveness study can also help in deciding whether further research will be necessary. If the Amuse-2 strategy is more cost-effective than care as usual, a management study should be the next step. Since implementation of a method on a larger scale remains difficult, a management study may be combined with implementation research to promote the uptake of our research findings and to close the gap between science and clinical practice.

If the Amuse-2 strategy turns out not to be cost-effective further research should be focused on optimizing the diagnostic strategy. In AMUSE-2 we used a qualitative point-of-care D-dimer test (Simplify, Clearview, Inverness Medical, Bedford, UK).<sup>9</sup> A review of point-of-care D-dimer testing showed that the user-friendly quantitative tests Cardiac and Triage also have good diagnostic accuracy.<sup>10</sup> This is important since it is known that the specificity of a D-dimer test decreases with age, whereas the risk of PE increases with aging.<sup>11-14</sup> The lower specificity makes D-dimer testing less useful to exclude PE in older patients. It has recently been shown that an age-adjusted cut-off of the D-dimer (patient's age multiplied by 10) in combination with an unlikely clinical decision rule increases the number of patients above 50 years in whom PE could safely be excluded.<sup>15,16</sup> It may be interesting to validate the use of the Wells rule combined with age-adjusted quantitative point-of-care D-dimer testing for excluding PE. A limitation of the available quantitative D-Dimer tests, however, is that, because of their size, the primary care physician will not be able to use them out of the office. Therefore, the qualitative point-of care test still will be needed for excluding PE during home visits.

## Treatment of pulmonary embolism in secondary care

### *Methodological considerations*

PE is usually treated with anticoagulant therapy. There is considerable evidence on the effectiveness of the traditional treatment of heparin and vitamin K antagonists (VKA). In a systematic clinical review we pooled all available data on the efficacy of the initial heparin treatment and compared intravenous unfractionated heparin to subcutaneous low molecular weight heparin (LMWH).<sup>17</sup>

The use of fixed-dose subcutaneous LMWH makes it possible to treat patients out of the hospital. In most countries in Europe, including the Netherlands, patients with DVT are managed as outpatients, whereas patients with PE are usually admitted to the hospital for at least a few days. This differs from the situation in Canada and the United States where a lot of patients with acute PE receive outpatient treatment.

Therefore, Canada seemed to be the right place to investigate the safety of outpatient treatment in PE.

Generally, randomized controlled trials evaluate efficacy and may be the first and preferred choice to investigate an intervention such as outpatient treatment. We, however, aimed for a pragmatic approach with a retrospective cohort study, since outpatient treatment of PE is everyday clinical practice in Canada. To minimize selection bias we included all consecutive patients with confirmed PE on CTPA or V/Q scan over a predefined time period and adjudicated all outcome events by two independent reviewers.

In our study all patients who did not have a systolic blood pressure of 100 mmHg or less, who had an oxygen saturation of 92% or more and did not require supplemental oxygen, who did not have contraindications for the use of LMWH and who did not need hospitalization for other co-morbidities, were managed as outpatients. However, the final decision to admit the patient or not was left to the discretion of the treating physician. Sharper inclusion criteria for outpatient treatment might help physicians to decide whether a patient can be treated out of the hospital. Therefore, we decided to perform an additional analysis in chapter 7 to investigate whether a widely validated prognostic model, the Pulmonary Embolism Severity Index, could help in identifying appropriate patients for outpatient treatment.

Recently, novel oral anticoagulants have been introduced and approved in many countries worldwide. To be able to properly assess the quality of anticoagulant control in the VKA control group in upcoming cost-effectiveness studies and real life registries of novel anticoagulants, we decided to conclude this dissertation with an evaluation of the international quality of VKA therapy and report a benchmark for time in therapeutic range in the meta-analysis in chapter 8.

### *Practical implications*

Our review on the initial heparin treatment of venous thromboembolism (VTE) showed that subcutaneous LMWH is more effective and safer than intravenous unfractionated heparin.<sup>17</sup> Adopting subcutaneous LMWH as the standard initial treatment enables outpatient treatment of patients with VTE.

The Canadian study suggests that outpatient treatment is safe and feasible in more than 50% of the patients with PE.<sup>18</sup> All patients treated as outpatients were seen within 24 to 48 hours in a specialized thrombosis clinic where they learned to administer the LMWH and were followed up after 7 days. Close follow-up of patients managed as outpatients in specialized thrombosis clinics might not be possible in all settings and therefore event rates of recurrent VTE and major bleeding episodes may differ if patients are followed-up in other health care settings. In the Netherlands anticoagulant monitoring is usually done by one of the many Thrombosis Services. Since the Thrombosis Service already is involved in anticoagulant treatment it may also be the right institution for the coordination of outpatient treatment.

Although several studies showed the safety of outpatient treatment, physicians are reluctant to treat patients with PE at home due to uncertainty on how to safely identify patients who are at low risk for short-term adverse events<sup>19</sup>, irrespective of whether the adverse events could be averted by hospitalization. In an additional analysis of the Canadian cohort we showed that the Pulmonary Embolism Severity Index accurately discriminates between patients who are at low versus patients who are high risk of adverse events.<sup>20</sup> A randomized controlled trial in Europe confirmed our findings that in low-risk patients, selected by the Pulmonary Embolism Severity Index, outpatient care can be safe and effective.<sup>21</sup> These results imply that outpatient treatment of PE should be considered in patients who are at low risk of adverse events.

The practical implications of our findings on the quality of anticoagulant treatment with VKA are not straightforward. The reported quality of VKA treatment, however, should be taken into consideration while interpreting results from trials with novel anticoagulants.

#### *Developments and recommendations for further research*

As addressed above PE is traditionally treated with LMWH and VKA. Although VKA are highly effective for the prevention and treatment of thrombosis, they carry a number of relevant limitations including the need for regular laboratory monitoring and dose adjustments. Recently a new era has been heralded with the large scale clinical testing and approval of novel, direct acting oral anticoagulants, including the thrombin and factor Xa inhibitors dabigatran and rivaroxaban, respectively. Several studies have shown that the efficacy of those new oral anticoagulants is non-inferior to VKA.<sup>22-25</sup> These new agents have been recently approved in many countries including the USA, Canada and several countries in Europe, including the Netherlands. However, trials studying the efficacy of the novel anticoagulants had in- and exclusion criteria that limit their ability to be generalized or at least raise questions with regard to how well they will perform in the real world of non-selected patients. The efficacy was investigated in study settings with a carefully selected, motivated study population. The effectiveness in real life may differ from the efficacy in trials due to other patient populations and medication adherence. With a recently acquired postdoctoral grant we will investigate the effectiveness of novel anticoagulants in everyday clinical practice mainly focusing on medication non-adherence.

The main advantage of the new agents is that regular follow-up and dose-adjustments will not be necessary anymore, due to more stable pharmacokinetics.<sup>26</sup> However, the frequent patient contacts served as a constant reminder of the necessity for medical treatment and allowed caregivers to observe problems that may hamper adequate medication intake at an early stage. It is known from experience with other chronic conditions, such as hypertension and hyperlipidemia, that medication use is not consistent over time and may be as low as 50% if left unmonitored.<sup>27,28</sup> This raises concerns with regard to medication adherence to the novel oral anticoagulants.

Proper medication adherence is extremely important to attain good clinical outcomes<sup>29,30</sup>, even more so because the new anticoagulants have a short half-life, necessitating daily intake to maintain an effective drug level. Lack of proper drug intake may also contribute to a higher bleeding risk; as antidotes are still lacking this poses an additional risk related to these novel anticoagulants. As a result of non-adherence it is expected that a substantial number of patients will not get the maximum benefit of anticoagulant treatment, resulting in thrombo-embolic events, major bleeding episodes, lower quality of life and increased health care costs. In our research project we will focus on predicting anticoagulant adherence by investigating associations between non-adherent behavior and patient, disease and treatment characteristics.

## Conclusion

The main findings of this dissertation are that PE can be safely ruled out in primary care by using the Wells clinical decision rule for PE combined by point-of-care D-dimer testing and that the majority of hemodynamic stable patients with confirmed acute PE can be safely treated out of the hospital. These findings may cause changes in the role of primary and secondary care in the management of PE. Although specialized care in the hospital still will be needed for complex situations, primary care physicians could play a much larger role in the management of PE in the near future. In case of suspected PE a primary care physician should have readily available the Wells clinical decision rule and a point-of-care D-dimer test. Furthermore, not all patients with confirmed PE need to be admitted to the hospital. Outpatient treatment should be considered in hemodynamic stable patients who do not need supplemental oxygenation. Treatment with novel anticoagulants may even facilitate treatment in primary care in the future. Further pragmatic research should follow the efficacy studies of novel anticoagulants in order to evaluate the safety and effectiveness of the new medication in daily clinical practice.

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## Summary



## Summary

### Chapter 1

Chapter 1 introduces the topic of the thesis. In this thesis we investigated the management of pulmonary embolism (PE) at the interface of community and hospital based health care.

The chapter first describes the definition and epidemiology of PE. PE is a blood clot that blocks the main artery of the lung or one of its branches. It is the third most common cause of death from cardiovascular disease and results from a combination of hereditary and acquired risk factors.

The chapter then discusses the historical developments in diagnosing PE. Diagnosis of PE is a major challenge because patients often present with non-specific symptoms. The invasive and labor intensive catheter guided pulmonary angiography has been the gold standard reference test for PE for many years. Nowadays, probability estimation by using a clinical decision rule and laboratory-based D-Dimer testing, followed by CT-scanning if indicated, is the routine protocol in patients suspected of PE in secondary care. The diagnostic strategy of assessing the probability of PE by a clinical decision rule and D-dimer testing seems also ideal for primary care to decide which patients suspected of PE need to be referred to secondary care for further diagnostic work-up. The chapter then goes on to report the rationale and aim of part I of this thesis 'Diagnosing pulmonary embolism in primary care'. In the Netherlands, the primary care physician is commonly the first to encounter outpatients suspected of PE. In the Amsterdam Maastricht Utrecht Study on thromboEmbolism (AMUSE-2) we investigated the accuracy and safety of the Wells clinical decision rule combined with point-of-care D-dimer testing for excluding PE in primary care.

The next section of the chapter starts with the historical developments in the treatment of PE. Patients with PE are usually treated with low molecular weight heparin for 5 to 10 days simultaneously with vitamin K antagonists (VKA). However, recently novel anticoagulant medication with a similar efficacy as VKA has been developed and approved in many countries worldwide. The guidelines of the American College of Chest Physicians recommend to treat patients with a first provoked PE for 3 months, patients with a first episode of idiopathic PE at least 6 to 12 months and patients with two or more objectively documented PE indefinitely. The chapter then describes the rationale and aim of the second part of this thesis 'Treatment of pulmonary embolism in secondary care'. The role of outpatient therapy in patients with PE is unclear and has been a matter of debate in literature. We investigated whether patients with hemodynamically stable PE could be safely treated out of the hospital and whether the Pulmonary Embolism Severity Index, a prognostic model for prediction of short-term adverse outcomes, could help in the identification of appropriate patients for outpatient management.

The chapter ends with an outline of the thesis.

## Part I: Diagnosis pulmonary embolism in primary care

### Chapter 2

Chapter 2 describes the Amsterdam Maastricht Utrecht Study on thromboEmbolism (AMUSE-2) in which we investigated the safety of using the Wells clinical decision rule for PE combined with point-of-care D-Dimer testing to exclude PE in primary care. We included 598 adult patients with suspected PE. After medical history and physical examination, primary care physicians scored the seven variables of the Wells PE-rule, and performed a point-of-care D-dimer test. All patients were referred to secondary care and diagnosed according to local protocols. PE was confirmed or refuted based on a composite reference standard, including spiral CT and 3 months of follow-up. The proportion of 'low-risk' patients and the number of missed PE cases in the low-risk category were calculated. PE was present in 73 patients (prevalence 12%). Using a threshold score  $\leq 4$  on the Wells PE rule and a negative point-of-care D-dimer test, 272 of these patients were classified as 'low-risk' (efficiency 45%). In these patients 4 PE cases were observed (false negative rate 1.5%). The sensitivity and specificity of this diagnostic approach were 94.5% and 51.0%.

### Chapter 3

This chapter aims to report the most common alternative diagnoses of PE in primary care patients suspected of PE and investigates whether the Wells rule combined with a point-of-care D-dimer test not only excludes PE but also other serious diagnoses. The chapter presents a secondary analysis of AMUSE-2. The most frequent alternative diagnoses after excluding PE were: nonspecific thoracic pain / dyspnoea (42.6%), pneumonia (13.0%), myalgia (11.8%), asthma / COPD (4.8%), panic disorder / hyperventilation (4.1%) and respiratory tract infection (2.3%). Patients with a Wells score of  $>4$  or a positive D-dimer test were significantly more often diagnosed with a clinically serious disease that needs immediate medical treatment. Therefore, a low probability of PE according to the Wells rule and point-of-care D-dimer testing may also help to exclude other serious diseases than PE.

### Chapter 4

Chapter 4 provides a frame of reference to interpret the results of the AMUSE-2 study. We performed a systematic review and meta-analysis to compare the sensitivity and specificity of different clinical decision rules used to exclude PE in adult patients suspected of PE. We searched Medline and Embase for articles in English, French, German, Italian, Spanish and Dutch, published between 1966 and June 2011. Three reviewers operating in pairs of two selected prospective studies conducted in

consecutive patients suspected of PE. The studies provided PE-probability estimate using gestalt or decision rule as compared to an appropriate reference standard. We extracted data on study characteristics, test performance and prevalence, constructed 2\*2-tables and assessed methodological quality. Fifty-two studies, including 55268 patients were selected. A meta-analysis was performed on studies investigating gestalt (n=15; sensitivity 0.85/specificity 0.51), Wells-rule at cut-off <2 (n=19; 0.84/0.58), Wells-rule at cut-off ≤4 (n=11; 0.60/0.80), Geneva-rule (n=5; 0.84/0.50) and revised Geneva-rule (n=4; 0.91/0.37). Increasing prevalence of PE was associated with higher sensitivity and lower specificity. Combining a decision rule or gestalt with a D-dimer test seemed safe for all strategies except for combining the less sensitive Wells4 with the less sensitive qualitative D-dimer.

## Part II: Treatment of pulmonary embolism in secondary care

### Chapter 5

In chapter 5 the literature is reviewed to determine the effect of LMWH compared with unfractionated heparin for the initial treatment of venous thromboembolism. Randomised controlled trials comparing fixed dose subcutaneous LMWH with adjusted dose intravenous or subcutaneous UFH in people with VTE were included. At least two reviewers assessed trials for inclusion and quality, and extracted data independently. Twenty-three studies were included (n=9587). Thrombotic complications occurred in 3.6% of the participants treated with LMWH, compared with 5.3% of the participants treated with UFH (odds ratio (OR) 0.70). Thrombus size was reduced in 53% of participants treated with LMWH and 45% treated with UFH (OR 0.69). Major haemorrhages occurred in 1.1% of the participants treated with LMWH, compared with 1.9% of the participants treated with UFH (OR 0.58). In nineteen trials, 4.3% of the participants treated with LMWH died, compared with 5.8% treated with UFH (OR 0.77). Nine studies (n=4451) examined proximal thrombosis; 2192 participants treated with LMWH and 2259 with UFH. A subgroup analysis showed statistically significant reductions favouring LMWH in thrombotic complications and major haemorrhage. By end of follow up, 3.6% of the participants treated with LMWH had thrombotic complications, compared with 6.3% of the participants treated with UFH (OR 0.57). Major haemorrhage occurred in 1.0% of the participants treated with LMWH, compared with 2.1% of the participants treated with UFH (OR 0.50). Nine studies showed a statistically significant reduction favouring LMWH with respect to mortality. By the end of follow up, 3.3% of the participants treated with LMWH had died, compared with 5.3% treated with UFH (OR 0.62). Our conclusion is that fixed dose LMWH is more effective and safer than adjusted dose UFH for the initial treatment of VTE. LMWH, compared to UFH, significantly reduces

the incidence of thrombotic complications, the occurrence of major haemorrhage during initial treatment and overall mortality at follow up.

## Chapter 6

In chapter 6 the safety of outpatient treatment in hemodynamically stable patients with acute PE is investigated. This is a retrospective cohort study of consecutive patients presenting at the Ottawa Hospital with acute PE diagnosed between January 1, 2007 and December 31, 2008. Patients were managed as outpatients if they were hemodynamically stable, did not require supplemental oxygenation and did not have contraindications to low molecular weight heparin therapy. In the cohort of 473 patients with acute PE, 260 (55.0%) were treated as outpatients and 213 (45.0%) were admitted to the hospital. The majority of the patients were admitted because of severe co-morbidities (45.5%) or hypoxia (22.1%). No outpatient died of fatal PE during the 3 month follow-up period. At the end of follow-up, the overall mortality was 5.0%. The rates of recurrent venous thromboembolism (VTE) in outpatients were 0.4% and 3.8% within 14 days and 3 months, respectively. The rates of major bleeding episodes were 0% and 1.5% within 14 days and 3 months, respectively. Four (1.5%) outpatients were admitted to the hospital within 14 days.

## Chapter 7

In chapter 7 we study whether the pulmonary embolism severity (PESI) index can help identifying patient with PE who are at low risk for short-term adverse events and can be treated out of the hospital. The PESI is a prognostic model that has been developed to estimate the risk of 30-day mortality in patients with acute PE. This chapter contains an additional analysis of the retrospective cohort study in chapter 6. Two hundred and forty three patients were included. A total of 118 (48.6%) and 81 (33.3%) were classified as low risk patients using the original and simplified PESI prognostic models respectively. None of the low risk patients died within the 3 months of follow-up. One hundred and fifteen (47.3%) patients were safely treated as outpatients with no deaths or bleeding episodes and only 1 recurrent event within the first 14 days or after 30 days of follow-up. Thirty four (29.6%) of these outpatients were classified as high risk patients according to the original PESI and 54 (47.0%) to the simplified PESI prognostic model. Both PESI strategies accurately identify patients with acute PE who are at low risk and high risk for short-term adverse events. However, 30 to 47% of patients with acute PE and a high risk PESI score were safely managed as outpatients.

## Chapter 8

Chapter 8 presents a benchmark for time in therapeutic range in the treatment of venous thromboembolism. The percentage of time within the target INR range 2.0 to 3.0 (Time in Therapeutic Range (TTR)) in patients treated with vitamin K antagonists

varies considerably among efficacy-studies of novel anticoagulants. In order to properly assess the quality of anticoagulant control in upcoming cost-effectiveness studies and real life registries this systematic review reports a benchmark of TTR for different treatment durations in patients with venous thromboembolism and discusses ways to calculate TTR. Medline and Embase were searched for studies published between January 1990 and May 2012. Randomized controlled trials and cohort studies reporting the TTR in patients with objectively confirmed venous thromboembolism treated with vitamin K antagonists (VKA) were eligible. Duplicate reports, studies only reporting INR during initial treatment or with VKA treatment less than 3 months were excluded. Three authors assessed trials for inclusion and extracted data independently. Discrepancies were resolved by discussion between the reviewers. A meta-analysis was performed by calculating a weighted mean, based on the number of participants in each included study, for each time-period in which the TTR was measured since the confirmation of the diagnosis of VTE. Reported quality of VKA treatment was highly dependent on the time-period since the start of treatment, with TTR ranging from approximately 56% in studies including the 1<sup>st</sup> month to 75% in studies excluding the first 3 months.

## Chapter 9

Chapter 9 discusses the overall methodological considerations of our studies and outlines practical implications of the results, new developments in the field and recommendations for further research. These items are addressed in two parts: 'diagnosing PE in primary care' and 'treatment of PE in secondary care'.

In the first part we discuss the composite reference standard in AMUSE-2 and the use of multiple imputation techniques to deal with missing data. The results of AMUSE-2 imply that a diagnostic approach of a Wells score  $\leq 4$  combined with D-dimer testing would rule out PE in 4 to 5 out of 10 primary care patients suspected of PE with an acceptably low failure rate. However, before moving on to a management or implementation study it might be informative to investigate whether the use of the Wells rule for PE combined with D-dimer testing in primary care will be cost-effective. Furthermore, research to optimize the diagnostic strategy by using an age-adjusted quantitative point-of-care D-dimer test may be interesting.

The second part discusses the retrospective character of our cohort to investigate the safety of outpatient treatment. This study suggests that outpatient treatment is safe and feasible in more than 50% of the patients with acute PE. The Pulmonary Embolism Severity Index can be used to discriminate between patients with PE who are at low risk and patients who are at high risk of adverse events.

Since recently novel anticoagulant medication has been developed and approved in many countries worldwide, future research investigating the treatment of PE should be focussed on the effectiveness of those novel anticoagulants. The efficacy of the new medication was investigated in a study setting with a carefully selected,



motivated study population. The effectiveness in real life, however, may differ from the efficacy in trials due to other patient populations and medication adherence. With a recently acquired postdoctoral grant we will investigate the effectiveness of novel anticoagulants in everyday clinical practice focussing on medication non-adherence. The chapter ends with our overall conclusion. The main findings of this dissertation are that PE can be safely ruled out in primary care by using the Wells clinical decision rule for PE combined by point-of-care D-dimer testing and that the majority of hemodynamic stable patients with confirmed acute PE can be safely treated out of the hospital. These findings stimulate a much larger role for primary care physicians in the management of PE in the near future.

## Samenvatting



# Samenvatting

## Hoofdstuk 1

Hoofdstuk 1 introduceert het onderwerp van de dissertatie. In deze dissertatie onderzoeken we het management van longembolie op het snijvlak van de huisarts en het ziekenhuis.

Het hoofdstuk beschrijft eerst de definitie en epidemiologie van longembolie. Een longembolie is een bloedstolsel dat de slagader of een vertakking daarvan blokkeert. Het is de derde meest voorkomende doodsoorzaak door hart- en vaatziekten en komt voort uit een combinatie van erfelijke en verworven risicofactoren.

Het hoofdstuk bespreekt vervolgens de historische ontwikkelingen in de diagnostiek van longembolie. Het stellen van de diagnose longembolie is een grote uitdaging, omdat patiënten zich vaak presenteren met aspecifieke symptomen. De invasieve en arbeidsintensieve methode waarbij via een catheter een pulmonalis angiografie wordt uitgevoerd, werd lang gezien als de gouden standaard. Tegenwoordig echter is de standaard procedure in het ziekenhuis dat de klinische waarschijnlijkheid van een longembolie wordt vastgesteld aan de hand van uitslagen van een klinische beslisregel en een D-dimeer bloedtest, eventueel gevolgd door een CT-scan. De diagnostische strategie om de waarschijnlijkheid van een longembolie vast te stellen door middel van een klinische beslisregel en een D-dimeer test lijkt ideaal voor gebruik in de eerste lijn en kan een huisarts helpen bij de beslissing om een patiënt met verdenking longembolie wel of niet te verwijzen naar het ziekenhuis. Vervolgens vermeldt het hoofdstuk de beweegredenen en het doel van het eerste deel van het proefschrift 'Diagnostiek van longembolie in de 1<sup>e</sup> lijn'. In Nederland is, buiten het ziekenhuis, de huisarts over het algemeen de eerste medicus met wie patiënten, die mogelijk longembolie hebben, contact hebben. In de Amsterdam Maastricht Utrecht studie naar trombo-embolie (Amuse-2) onderzochten we de nauwkeurigheid en veiligheid van het gebruik van de klinische beslisregel van Wells in combinatie met een point-of-care D-dimeer test voor het uitsluiten van longembolie in de eerste lijn.

De volgende paragraaf van het hoofdstuk begint met de historische ontwikkelingen in de behandeling van longembolie. Patiënten met een longembolie worden over het algemeen gedurende 5 tot 10 dagen behandeld met laag moleculair gewicht heparine waarna de behandeling wordt voortgezet met vitamine K-antagonisten (VKA). Onlangs zijn er echter een nieuwe antistollingsmiddelen ontwikkeld en goedgekeurd in vele landen wereldwijd, die even werkzaam zijn als de traditionele VKA. De richtlijn van het American College of Chest Physicians adviseert om een longembolie met een duidelijke oorzaak 3 maanden te behandelen, patiënten met een eerste episode van idiopatische longembolie minstens 6 tot 12 maanden te behandelen en patiënten met twee of meer objectief gedocumenteerde longembolieën levenslang te behandelen.

Het hoofdstuk vermeldt vervolgens de beweegredenen en het doel van het tweede deel van het proefschrift 'Behandeling van longembolie in de tweede lijn'. De rol van

mogelijke poliklinische behandeling van patiënten met een longembolie is onduidelijk en een discussiepunt in de literatuur. In dit proefschrift is onderzocht of patiënten met een hemodynamisch stabiele longembolie veilig poliklinisch kunnen worden behandeld. Ook is onderzocht of de 'Pulmonary Embolism Severity Index', een prognostisch model voor het inschatten van de kans op korte termijn complicaties, zou kunnen helpen bij de bepaling welke patiënten met een longembolie geschikt zijn voor een poliklinische behandeling.

Het hoofdstuk eindigt met een overzicht van het proefschrift.

## Deel I: Diagnostiek van longembolie in de eerste lijn

### Hoofdstuk 2

Hoofdstuk 2 beschrijft de Amsterdam Maastricht Utrecht Studie naar trombo-embolie (Amuse-2) waarin de veiligheid van het gebruik van de klinische beslisregel van Wells voor longembolie in combinatie met een point-of-care D-dimeer test onderzocht is om veilig longembolie uit te sluiten in de eerste lijn. We hebben 598 volwassen patiënten met verdenking longembolie geïnccludeerd in de studie. Na het afnemen van de medische voorgeschiedenis en het doen van een lichamelijk onderzoek, scoorde de huisarts de 7 items van de klinische beslisregel van Wells en voerde een point-of-care D-dimeer test uit. Alle patiënten werden daarna verwezen naar een ziekenhuis in de buurt, alwaar volgens de daar geldende protocollen een diagnose werd gesteld. Na 3 maanden werd beoordeeld of de patiënt een longembolie had of niet, door een onafhankelijke commissie. Bij 73 patiënten is een longembolie gediagnosticeerd (prevalentie 12%). Tweehonderdtweeënzeventig van de 598 patiënten (45%) hadden een lage klinische waarschijnlijkheid, dat wil zeggen een Wells-score van 4 of lager en een negatieve point-of-care D-dimeer test. Bij 4 van deze patiënten (1,5%) werd toch een longembolie gediagnosticeerd. De sensitiviteit en specificiteit van deze diagnostische strategie was 94,5% en 51,0%.

### Hoofdstuk 3

Dit hoofdstuk heeft tot doel het rapporteren van de meest voorkomende alternatieve diagnoses van longembolie in de eerste lijn bij patiënten bij wie eerst gedacht werd aan een longembolie. Ook onderzoeken we of de klinische beslisregel van Wells gecombineerd met een point-of-care D-dimeer test niet alleen longembolie, maar ook andere ernstige diagnoses kan uitsluiten. Het hoofdstuk is een secundaire analyse van Amuse-2. De meest voorkomende alternatieve diagnoses, na het uitsluiten van een longembolie, waren: aspecifieke thoracale pijnklachten / dyspnoe (42,6%), pneumonie (13,0%), myalgie (11,8%), astma / COPD (4,8%), paniekstoornis / hyperventilatie (4,1%) en een luchtweginfectie (2,3%). Patiënten met een Wells-score van meer dan 4

punten of een positieve D-dimeer test werden significant vaker gediagnosticeerd met een klinisch relevante diagnose waarbij onmiddellijke medische behandeling nodig is. Het lijkt erop dat een lage klinische waarschijnlijkheid op longembolie op basis van de klinische beslisregel van Wells en een point-of-care D-dimeer test niet alleen longembolie, maar ook andere klinisch relevante diagnoses kan uitsluiten.

## Hoofdstuk 4

Hoofdstuk 4 geeft een referentiekader om de resultaten van de Amuse-2 studie te interpreteren. In een systematische literatuurstudie en meta-analyse hebben we de sensitiviteit en specificiteit vergeleken van verschillende klinische beslisregels die gebruikt worden voor het uitsluiten van longembolie bij patiënten met verdenking longembolie in de tweede lijn. Medline en Embase zijn doorzocht voor wetenschappelijke artikelen in het Engels, Frans, Duits, Italiaans, Spaans en Nederlands, die gepubliceerd zijn tussen 1966 en juni 2011. Drie beoordelaars hebben prospectieve studies geselecteerd waarin de klinische waarschijnlijkheid van longembolie werd bepaald met behulp van Gestalt of een klinische beslisregel bij patiënten met verdenking longembolie. De studies dienden een geschikte referentiestandaard te gebruiken. De volgende gegevens werden genoteerd: de studie-karakteristieken, de accuraatheid van de test, de prevalentie van longembolie en de methodologische kwaliteit van het artikel. Tweeënvijftig studies met in totaal 55.268 patiënten werden geïncludeerd in de analyses. In de meta-analyse werden de volgende resultaten met betrekking tot de sensitiviteit en specificiteit van de beslisregels gevonden: Gestalt (n=15; sens 0,85 / spec 0,51), Wells-regel met afkappunt <2 (n=190; sens 0,84 / spec 0,58), Wells-regel met afkappunt ≤4 (n=11; sens 0,60 / spec 0,80), Geneva-regel (n=5; sens 0,84 / spec 0,50) en de gereviseerde Geneva-regel (n=4; sens 0,91 / spec 0,37). Een toenemende prevalentie van longembolie werd geassocieerd met een hogere sensitiviteit en lagere specificiteit. De combinatie van een beslisregel of Gestalt met een D-dimeer test leek bij alle strategieën veilig longembolie uit te sluiten, met uitzondering van de combinatie van de minder sensitieve Wells-regel met afkappunt 4 en de minder sensitieve kwalitatieve D-dimeer test.

## Deel II: Behandeling van longembolie in de tweede lijn

### Hoofdstuk 5

In hoofdstuk 5 is er een literatuuronderzoek gedaan om in de initiële behandeling van veneuze trombo-embolie de effectiviteit van laag moleculair gewicht heparine te vergelijken met niet-gefractioneerde heparine. In de analyses werden gerandomiseerde studies geïncludeerd die een vaste dosis subcutane laag moleculaire gewicht heparine (LMWH) vergeleken met een aangepaste dosis intraveneuze gefractioneerde

heparine (UFH) in de behandeling van patiënten met veneuze trombo-embolie. Tenminste 2 beoordelaars hebben onafhankelijk de geïncludeerde studies beoordeeld op kwaliteit en de benodigde gegevens geregistreerd. Drieëntwintig studies werden geïncludeerd (n=9587). Trombotische complicaties kwamen voor bij 3,6% van de patiënten behandeld met LMWH, in vergelijking met 5,3% van de patiënten behandeld met UFH (odds ratio (OR) 0,70). De grootte van de trombus was afgenomen in 53% van de patiënten behandeld met LMWH en in 45% van de patiënten behandeld met UFH (OR 0,69). Grote levensbedreigende bloedingen kwamen voor bij 1,1% van de patiënten behandeld met LMWH, in vergelijking met 1,9% van de patiënten behandeld met UFH (OR 0,58). In 19 studies werd de mortaliteit beschreven: 4,3% van de patiënten behandeld met LMWH stierf en 5,8% van de patiënten behandeld met UFH (OR 0,77). Negen studies hebben patiënten met proximale trombose geïncludeerd: 2192 deelnemers hiervan werden behandeld met LMWH en 2259 met UFH. Een subgroep analyse toonde bij deze patiënten een significante vermindering aan in trombotische complicaties en ernstige bloedingen ten gunste van LMWH-behandeling. Aan het einde van de follow-up had 3,6% van de patiënten behandeld met LMWH een trombotische complicatie in vergelijking met 6,3% van de patiënten behandeld met UFH (OR 0,57). Grote bloedingen traden op bij 1,0% van de patiënten behandeld met LMWH en bij 2,1% van de patiënten behandeld met UFH (OR 0,50). In negen studies werd aangetoond dat de mortaliteit significant lager was in de groep met LMWH. Aan het einde van de follow-up was 3,3% van de deelnemers met LMWH overleden, terwijl in groep met UFH 5,3% was overleden (OR 0,62). Uit deze bevindingen concluderen we dat LMWH effectiever en veiliger is voor initiële behandeling van veneuze trombo-embolie dan UFH. De incidentie van trombotische complicaties als ook van ernstige bloedingen tijdens de initiële behandeling en de totale sterfte bij follow-up zijn lager bij behandeling met LMWH dan met UFH.

## Hoofdstuk 6

In hoofdstuk 6 wordt de veiligheid van een poliklinische behandeling bij hemodynamisch stabiele patiënten met een longembolie onderzocht. Dit is een retrospectieve cohort studie met patiënten die tussen 1 januari 2007 en 31 december 2008 in het ziekenhuis in Ottawa, Canada, gediagnosticeerd zijn met een acute longembolie. Patiënten werden poliklinisch behandeld indien ze hemodynamisch stabiel waren, geen extra zuurstof nodig hadden, er geen contra-indicaties waren voor behandeling met laag moleculair gewicht heparine en er geen ernstige comorbiditeit was. Het cohort bestond uit 473 patiënten met een acute longembolie: 260 (55%) mensen werden poliklinisch behandeld en 213 (45,0%) werd opgenomen in het ziekenhuis. De meerderheid van de patiënten werd opgenomen vanwege een ernstige comorbiditeit (45,5%) of hypoxie (22,1%). Tijdens de 3 maanden follow-up is geen van de poliklinische patiënten overleden aan een fatale longembolie. Aan het einde van de follow-up was de totale mortaliteit 5,0%. Het percentage recidieven bij de

poliklinische behandeling was 0,4% en 3,8% binnen 14 dagen en 3 maanden, respectievelijk. Het percentage ernstige bloedingen was 0,0% en 1,5% binnen 14 en 3 maanden, respectievelijk. Vier (1,5%) poliklinische patiënten werden binnen 14 dagen alsnog opgenomen in het ziekenhuis.

## Hoofdstuk 7

In hoofdstuk 7 wordt bestudeerd of de Pulmonary Embolism Severity Index (PESI) gebruikt kan worden voor identificatie van patiënten met een longembolie met een laag risico voor complicaties op de korte termijn die veilig poliklinisch behandeld zouden kunnen worden. De PESI is een prognostisch model dat oorspronkelijk ontwikkeld is voor het voorspellen van de 30-dagen mortaliteit bij patiënten met een acute longembolie. Dit hoofdstuk beschrijft een secundaire analyse van het retrospectieve cohort uit hoofdstuk 6. Tweehonderdendrieënveertig patiënten werden in deze secundaire analyse geïnccludeerd. Het originele PESI model classificeerde 118 (48,6%) van deze patiënten in de laag risico groep, terwijl het vereenvoudigde PESI model 81 (33,3%) van de patiënten in de laag risico groep classificeerde. Geen van de laag risico patiënten stierf gedurende de 3 maanden follow-up. Honderdenvijftien (47,3%) patiënten werden veilig poliklinisch behandeld zonder overlijden en slechts 1 recidief binnen de 14 en 30 dagen follow-up. De originele PESI classificeerde 34 (29,6%) van deze poliklinische patiënten in de hoog risico groep en het vereenvoudigde PESI model classificeerde 54 (47,0%) van deze patiënten in de de hoog risico groep. Beide PESI-strategieën identificeren nauwkeurig longembolie-patiënten met een laag en hoog risico op korte termijn complicaties. Dertig tot 47% van de longembolie-patiënten in de hoog-risico groep werd echter veilig poliklinisch behandeld.

## Hoofdstuk 8

Hoofdstuk 8 geeft een benchmark voor de tijd doorgebracht in de therapeutische range bij de behandeling van veneuze-tromboembolie. Het percentage van de tijd dat de patiënten in de controlegroep behandeld met vitamine K-antagonisten (VKA) doorbrengt binnen de gewenste INR-range van 2,0 tot 3,0 (TTR) verschilt aanzienlijk tussen studies met nieuwe antistollingsmiddelen. Om goed de effectiviteit van de nieuwe antistollingsmiddelen te kunnen beoordelen in toekomstig onderzoek rapporteert dit hoofdstuk een benchmark van de TTR en worden manieren om de TTR te berekenen besproken. Medline en Embase werden onderzocht voor studies gepubliceerd tussen januari 1990 en mei 2012. In aanmerking voor inclusie kwamen gerandomiseerde trials en cohort studies die de TTR rapporteerden bij patiënten met veneuze trombo-embolie die behandeld werden met VKA. Geëxcludeerd werden duplicaten, studies die alleen de INR tijdens de initiële behandelperiode rapporteerden en studies met een VKA-behandeling van minder dan 3 maanden. Drie auteurs selecteerden onafhankelijk van elkaar studies voor inclusie en extraheerden



de data voor de analyses. Verschillen werden opgelost door overleg tussen de beoordelaars. In een meta-analyse werd een gewogen gemiddelde berekend gebaseerd op het aantal deelnemers per studie. De TTR werd berekend voor de verschillende lengten van de behandeling. De gerapporteerde kwaliteit van de VKA-behandeling was sterk afhankelijk van de duur van de behandeling. De TTR varieerde van ongeveer 56% in de 1<sup>e</sup> maand van de behandeling tot 72% vanaf 4 maanden behandeling.

## Hoofdstuk 9

Hoofdstuk 9 gaat in op de methodologische overwegingen van de studies en schetst de praktische implicaties van de resultaten, nieuwe ontwikkelingen in het vakgebied en aanbevelingen voor verder onderzoek. Dit wordt geadresseerd in twee delen: 'diagnostiek van longembolie in de eerste lijn' en 'behandeling van longembolie in de tweede lijn'.

In het eerste deel bespreken we de samengestelde referentiestandaard in de Amuse-2 studie. Ook wordt het gebruik van multiële imputatie als techniek voor het omgaan met missende variabelen besproken. De resultaten van Amuse-2 impliceren dat de klinische beslisregel van Wells voor longembolie met een afkappunt van  $\leq 4$  gecombineerd met een point-of-care D-dimeer test veilig longembolie kan uitsluiten in 4 tot 5 van de 10 patiënten in de eerste lijn met verdenking longembolie. Voor het uitvoeren van een management studie kan het echter informatief zijn om eerst een kosteneffectiviteitsstudie te doen naar het gebruik van de Wells-regel en D-dimeer test in de eerste lijn. Bovendien zou het interessant kunnen zijn om te onderzoeken of de diagnostische strategie geoptimaliseerd kan worden door gebruik te maken van een kwantitatieve point-of-care D-dimeer test met een leeftijdsafhankelijk afkappunt. Het tweede deel gaat in op het retrospectieve karakter van de cohort studie naar de veiligheid van een poliklinische behandeling bij longembolie. Deze studie laat zien dat een poliklinische behandeling veilig en haalbaar is in meer dan 50% van de patiënten met een acute longembolie. De Pulmonary Embolism Severity Index kan gebruikt worden om onderscheid te maken tussen patiënten met een laag risico en patiënten met een hoog risico op complicaties.

Sinds kort zijn er nieuwe antistollingsmiddelen ontwikkeld en goedgekeurd over de hele wereld. Verder onderzoek naar deze nieuwe middelen dient vooral de effectiviteit van deze nieuwe antistollingsmiddelen in de dagelijkse klinische praktijk te onderzoeken. De werkzaamheid van deze nieuwe middelen werd tot nu toe onderzocht in een zorgvuldig geselecteerde en gemotiveerde studiepoulatie. De werkzaamheid in de dagelijkse klinische praktijk kan echter anders zijn vanwege een andere samenstelling van de patiëntenpoulatie en vanwege die therapietrouw van patiënten. Met een onlangs verworven postdoctorale beurs zullen we de effectiviteit van de nieuwe antistollingsmiddelen onderzoeken en ons hierbij vooral richten op therapie-ontrouw.

Het hoofdstuk eindigt met een algemene conclusie. De belangrijkste bevindingen van dit proefschrift zijn dat longembolie op een veilige manier door de huisarts uitgesloten kan worden met behulp van de klinische beslisregel van Wells voor longembolie gecombineerd met een point-of-care D-dimeer test en dat de meerderheid van de hemodynamisch stabiele patiënten met een acute longembolie veilig poliklinisch behandeld kunnen worden. Deze bevindingen stimuleren een grotere rol voor huisartsen in de diagnostiek en behandeling van longembolie in de nabije toekomst.



# Appendix I

## Different clinical decision rules for pulmonary embolism



## Different clinical decision rules for PE

- **Wells rule:** Wells et al.<sup>1</sup> obtained data from a prospective cohort of 1239 patients suspected of PE to derive this clinical decision rule. Using logistic regression, seven variables from the patient history and physical examination were selected for inclusion in the final rule (Figure 1). Cut-off points were identified to classify patients as low (score <2), moderate (score 2-6) and high (score >6) probability for pulmonary embolism. Alternatively, the total score can be dichotomized into a pulmonary-embolism-unlikely (score ≤4) or a pulmonary embolism-likely (score >4) clinical probability. The rule was simplified<sup>2</sup> by assigning the same weight (one point) to each of the seven variables. The score was dichotomized in PE-unlikely (score ≤ 1) and PE-likely (score >1).

Figure 1 Wells rule.

Variable	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3-0
Alternative diagnosis less likely than PE	3-0
Heart rate > 100/min	1-5
Immobilization (>3days) or surgery in the previous 4 weeks	1-5
Previous PE or DVT	1-5
Haemoptysis	1-0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1-0
Clinical probability of PE:	
Unlikely	≤4 points
Likely	>4 points
Low	<2 points
Intermediate	2-6 points
High	>6 points

DVT= deep venous thrombosis; PE= pulmonary embolism.

- **Geneva rule:** Wicki et al.<sup>3</sup> combined clinical variables from the patient history and physical examination together with results of a chest x-ray, electro-cardiogram and arterial blood gas analysis in a cohort of 986 consecutive patients suspected of PE. Using logistic regression eight variables were selected (Figure 2). Subsequently a score was introduced to classify patients into groups of a low (score <5), moderate (score 5-8) or high (score >8) clinical probability.

Figure 2 Geneva rule.

.Variable	Score*
1. Previous pulmonary embolism or deep venous thrombosis	2
2. Heart rate >100 beats per minute	1
3. Recent surgery	3
4. Age (years):	
60–79	1
≥80	2
5. PaCO <sub>2</sub> :	
<4.8 kPa (36 mmHg)	2
4.8–5.19 kPa (36–38.9 mmHg)	1
6. PaO <sub>2</sub> :	
<6.5 kPa (<48.7 mmHg)	4
6.5–7.99 kPa (48.7–59.9 mmHg)	3
8–9.49 kPa (60–71.2 mmHg)	2
9.5–10.99 kPa (71.3–82.4 mmHg)	1
Chest radiograph:	
7. Platelike atelectasis	1
8. Elevated hemidiaphragm	1
PaCO <sub>2</sub> =partial pressure of carbon dioxide, arterial	
PaO <sub>2</sub> = partial pressure of oxygen, arterial.	
* Clinical probability:	
<5 points: low	
5-8 points: moderate	
>8 points: high	

In addition, a new rule, using only clinical variables, was derived by Le Gal et al.<sup>4</sup> (Figure 3, **the Revised Geneva rule**). In this rule, patients were classified as low (score <4), intermediate (score 4-10) or high (score >10) pre-test probability of PE. The score was dichotomized in PE-unlikely (score ≤5) and PE-likely (score>5)<sup>5,6</sup>. The rule was simplified<sup>5</sup> by assigning the same weight (one point) to each of the eight variables. Patients were classified into groups of low (score ≤1), intermediate (score 2-4) and high (score ≥5) clinical probability. The score was dichotomized in PE-unlikely (score ≤2) and PE-likely (score>2).

Figure 3 Revised Geneva.

Variable	Score
1. Age > 65 y	1
2. Previous DVT or PE	3
3. Surgery (under general anaesthesia) or fracture (of the lower limbs) within 1 month	2
4. Active malignant condition (solid or hematologic malignant condition, currently active or considered cured < 1 y)	2
5. Unilateral lower-limb pain	3
6. Haemoptysis	2
7. Heart rate	
75–94 beats/min	3
≥95 beats/min	5
8. Pain on lower-limb deep venous palpation and unilateral oedema	4
Clinical probability	
<4 points: low	
4-10 points: intermediate	
>10: high	

- **Pisa rule:** Miniati et al.<sup>7</sup> used logistic regression to construct a model of independent predictors associated with pulmonary embolism using data from a cohort of 1100 consecutive patients admitted to hospital with suspected pulmonary embolism. The final model comprises 15 variables of which ten are positively associated and five are negatively associated with pulmonary embolism (Figure 4). Patients were categorized as low ( $\leq 10\%$ ), intermediate ( $>10\%$ ,  $\leq 50\%$ ), moderately high ( $>50\%$ ,  $\leq 90\%$ ), or high ( $>90\%$ ) probability of pulmonary embolism. Because this model depends heavily on the interpretation of the chest radiograph, Miniati et al.<sup>8</sup> also developed a more simple model based only on variables from patient history, physical examination and the interpretation of the electrocardiogram (Figure 5, the **Revised Pisa rule**). Patients are categorized in the same way as in the original Pisa-rule.

Figure 4 Pisa-rule.

Factor	Regression Coefficient
1. Male sex	0.81
2. Age (years)	0.59
63–72	0.92
$\geq 73$	
Pre-existing disease:	
3. Cardiovascular	-0.56
4. Pulmonary	-0.97
5. Thrombophlebitis (ever)	0.69
Symptoms:	
6. Dyspnoea (sudden-onset)	1.29
7. Chest pain	0.64
8. Haemoptysis	0.89
9. Fever $>38^{\circ}\text{C}$	-1.17
10 ECG signs of acute right ventricular overload	1.53
Chest radiograph:	
11. Oligemia	3.86
12. Amputation of hilar artery	3.92
13. Consolidation (infarction)	3.55
14. Consolidation (no infarction)	-1.23
15. Pulmonary oedema	-2.83
Constant	-3.26
* To estimate the probability of pulmonary embolism, add all of the regression coefficients that apply to a particular patient to the constant (-3.26). The probability of pulmonary embolism then equals $1/(1+\exp(-\text{sum}))$ . For example, a 50-year-old woman with a history of thrombophlebitis (0.69), sudden-onset dyspnoea (1.29), and amputation of a hilar artery on chest radiograph (3.92), but no other characteristics, would have a sum of $0.69 + 1.29 + 3.92 - 3.26 = +2.64$ . Her probability of pulmonary embolism is $1/(1 + \exp(-2.64)) = 93.3\%$ .	
Clinical probability:	
0-10%:	low
11-50%:	intermediate
51-80%:	moderately
81-100%:	high



Figure 5 Revised Pisa.

Predictor	Coefficient
1. Age, yr	
57–67	0.80
68–74	0.87
≥75	1.14
2. Male sex	0.60
3. Immobilization	0.42
4. Deep venous thrombosis (ever)	0.64
Pre-existing diseases:	
5. Cardiovascular	-0.51
6. Pulmonary	-0.89
7. Dyspnoea (sudden onset)	2.00
8. Orthopnea	-1.51
9. Chest pain	1.01
10. Fainting or syncope	0.66
11. Haemoptysis	0.93
12. Leg swelling (unilateral)	0.80
13. Fever>38 C	-1.47
14. Wheezes	-1.20
15. Crackles	-0.61
16. Acute cor pulmonale on ECG*	1.96
Constant	-3.43
* One or more of the following abnormalities: S1Q3T3, S1S2S3, negative T waves in right precordial leads, transient right bundle branch block, pseudo infarction.	
Calculation of the clinical probability of pulmonary embolism: (1) Add all the coefficients that apply to a given patients and the constant (sum); (2) the probability of pulmonary embolism equals $1/[1 + \exp(- \text{sum})]$	
Clinical probability:	
0-10%:	low
11-50%:	intermediate
51-80%:	moderately high
81-100%:	high

- **PERC (Pulmonary Embolism Rule-out Criteria):** Kline et al.<sup>9</sup> derived this eight-factor decision rule from logistic regression analysis of 21 variables collected in 3148 emergency department patients evaluated for PE. The rule was developed to support the decision not to order subsequent diagnostic tests for PE in patients in whom the clinician had a low suspicion for PE. To be negative the PERC rule requires the clinician to answer ‘no’ to eight questions. (Figure 6)

Figure 6 PERC.

PERC negative requires the clinician to answer 'no' to the following eight questions:

1. Is the patient older than 49 years of age?
2. Is the pulse rate above 99 beats/ min?
3. Is the pulse oximetry reading <95% while the patient breathes room air?
4. Is there a present history of haemoptysis?
5. Is the patient taking exogenous oestrogen?
6. Does the patient have a prior diagnosis of venous thromboembolism (VTE)?
7. Has the patient had recent surgery or trauma? (Requiring endotracheal intubation or hospitalization in the previous four weeks.)
8. Does the patient have unilateral leg swelling? (Visual observation of asymmetry of the calves.)

- **Charlotte-rule:** Kline et al.<sup>10</sup> derived a six variable model using logistic regression from a database consisting of 934 emergency-department patients suspected of PE. This model combines two screening variables: patients younger than 50 years of age and with a shock-index (heart rate divided by systolic blood pressure) less than one are deemed "safe". The remaining patients are then further assessed using four variables. The rule classifies patients as safe (this is, eligible for D-dimer testing) and unsafe (requiring imaging). (Figure 7)

Figure 7 Charlotte rule.

This rule divides patients in safe (eligible for D-dimertesting) and unsafe.

- A. If the patient is 50 years of age or younger and the heart rate is less than or equal to the systolic blood pressure (ie, shock index  $\leq 1.0$ ), the patient is safe.
- B. If the patient is either older than 50 years or has a shock index of more than 1.0, the clinician should ask four sequential questions:
  1. Does the patient have unexplained hypoxemia?
  2. Does the patient have unilateral leg swelling?
  3. Has the patient had surgery requiring general anaesthesia in the past 4 weeks?
  4. Does the patient have haemoptysis?

If the answer to all four questions is "no," then the patient is safe.

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## Dankwoord



## Dankwoord

Het is misschien cliché, maar een promotieonderzoek doe je niet alleen. Er zijn veel mensen die belangrijk zijn geweest voor het tot stand komen van dit proefschrift, die ik hier graag wil bedanken.

Allereerst wil ik alle deelnemers, zowel huisartsen als patiënten, van het Amuse-2 project bedanken. Zonder deelnemers, geen onderzoek. Ondanks de drukte van de gemiddelde huisartsenpraktijk, hebben toch vele huisartsen de tijd genomen om patiënten te vragen voor deelname aan het Amuse-2 onderzoek.

Ten tweede mijn speciale dank aan het promotieteam. Van het sollicitatiegesprek kan ik me nog goed herinneren dat ik meteen een goed gevoel had. Mijn masterthesis bij epidemiologie moest nog afgerond worden, maar ik was al vastbesloten om verder te gaan in het wetenschappelijk onderzoek. Ik wilde graag werken aan praktisch onderzoek met een duidelijke klinische relevantie, het liefst in de cardiovasculaire richting gezien mijn ervaring als research-verpleegkundige op de afdeling cardiologie in het azM. Onderzoek naar de diagnostiek en behandeling van longembolie paste hier helemaal bij.

Beste dr. Stoffers, beste Jelle, jij was mijn dagelijks begeleider. Ik wil je ontzettend bedanken voor de vele gezamenlijke uurtjes overleg. Wij zijn allebei praktisch ingesteld en konden vaak redelijk snel een oplossing vinden voor de praktische problemen in de Amuse-2 studie. Ik heb jou leren kennen als iemand die hard werkt, veel op zich neemt en ook nog alles heel goed wil doen. Elke nieuwsbrief, flyer, artikel, presentatie en poster die ik jou liet zien voor feedback werd grondig van commentaar voorzien. Hier heb ik enorm veel van geleerd. Ik waardeer je directheid en betrokkenheid.

Beste Prof. dr. ten Cate, beste Hugo, met je warme persoonlijkheid en rustige uitstraling heb jij de rust weten te bewaren als ik wel eens zat te stressen over wat er nog allemaal moest gebeuren en of het allemaal wel goed ging. Je agenda zit overvol, maar toch kon ik altijd bij je terecht en reageer je snel op mails met vragen. Je hebt me veel ruimte gegeven en hebt altijd blij gegeven van je vertrouwen in mijn kunnen. Dit heb ik als heel prettig ervaren. Via jou werd ik opgenomen in de groep van het laboratorium voor klinische trombose en hemostase. Hier heb ik me altijd heel welkom gevoeld en veel geleerd van de dinsdagochtend-besprekingen. Dank ook dat ik via jouw netwerk heb mogen meewerken aan landelijke multicenter studies zoals de Prometheus studie.

Beste Prof. dr. Prins, beste Martin, jij verstaat de kunst om zo even uit je hoofd te brainstormen. Kennis over wat, wanneer, waar en door wie gepubliceerd is, heb jij altijd meteen paraat en de benodigde steekproefgrootte voor een studie reken je gewoon even op de achterkant van een kladje uit. Menigmaal heeft een brainstormsessie met jou ervoor gezorgd dat ik weer verder kon werken aan een artikel of onderzoeksvoorstel. Ook dank voor het delen van het internationale netwerk van jou en Hugo en dat jullie het mogelijk hebben gemaakt dat ik tijdens mijn

promotiestudie vele nationale en internationale congressen heb mogen bijwonen. Dit heeft mijn wetenschappelijk inzicht verruimd.

De leden van de beoordelingscommissie, Prof. dr. Geert-Jan Dinant, Prof. dr. Frank Buntinx, Prof. dr. Anna Falanga, Dr. Pieter Willem Kamphuisen en Prof. dr. Peter de Leeuw wil ik bedanken voor hun bereidheid mijn proefschrift te lezen en te beoordelen.

Een groot gedeelte van dit proefschrift komt voort uit het Amuse-2 project. Het Amuse-project is een samenwerkingsverband tussen 3 universiteiten: de universiteit van Amsterdam, de universiteit van Utrecht en universiteit Maastricht. Als eerste wil ik hier graag mijn medepromovendi uit Utrecht en Amsterdam bedanken: Geert-Jan Geersing en Wim Lucassen. Beste Geert-Jan, beste Wim, ik kwam pas bij de projectgroep toen jullie al een dik half jaar onderweg waren. Dank voor jullie hartelijke welkom en het mij wegwijs maken in de wereld van de huisarts en de wereld van de diagnostiek van longembolie. Dank voor de gezellige en leerzame overleggen. Ik heb onze samenwerking als zeer prettig ervaren. Ook wil ik de senior begeleiders uit Utrecht en Amsterdam bedanken: Prof. dr. Karel Moons, Prof. dr. Arno Hoes, Dr. Ruud Oudega, Prof. dr. Harry Büller en Prof. dr. Henk van Weert. Tot slot gaat hier speciale dank uit naar Marion de Mooij. Beste Marion, jouw hulp was onmisbaar in de dataverzameling van Amuse-2 in Zuidoost-Nederland. Dank voor het vele werk dat je verzet hebt. Jij hebt een belangrijke rol gespeeld in het enthousiasmeren van de huisartsen voor Amuse-2 en hebt voor een zo nauwkeurig mogelijke dataverzameling gezorgd. Ook dank voor de vele gezellige uurtjes die we samen doorgebracht hebben. We konden goed met elkaar praten en hebben heel fijn samengewerkt.

I also would like to thank dr. Carrier and dr. Wells for the opportunity to visit the Ottawa Hospital Research Institute and to investigate the safety of outpatient treatment in pulmonary embolism in Ottawa. I am grateful for your support. Dear dr. Wells, dear Phil, thank you for your enthusiastic response to my request to visit Ottawa and thank you for your help in arranging my stay. Dear dr. Carrier, dear Marc, thank you for your warm welcome when I arrived in Ottawa. I remember our first meeting at the airport. To make sure that I felt at home you brought some groceries. Also thanks for your supervision. Your input during our meetings and discussions helped me to conduct the research. Your comments on my articles helped me to be more focused and improved my writing skills. I hope we will continue to cooperate in the future. Finally, I would also like to thank Esteban Gandara. Dear Esteban, thank you for the critical comments on the research project and the pleasant dinners. It was nice sharing an office with you.

Ook wil ik hier Tiny Wouters en Charles Hilkens bedanken. Beste Tiny, hartelijk dank voor het verzorgen van de lay-out van mijn proefschrift. Beste Charles, jou wil ontzettend bedanken voor de het ontwerpen van de kaft. Zonder jullie bijdrage was het eindresultaat niet zo mooi geweest.

Ook wil ik Yvonne Leenders van het secretariaat van epidemiologie danken voor het regelen van praktische zaken omtrent het afronden van het proefschrift.

Daarnaast waren en ook allerlei mensen die niet direct bij het promotieproject betrokken waren, maar waar ik wel veel aan heb gehad.

Allereerst de mensen van het secretariaat van huisartsgeneeskunde. Bij jullie kon ik altijd terecht met praktische vragen. Met name Ine Siegelaer wil ik bedanken dat ze, naast de spil van de afdeling, ook iemand is die altijd voor iedereen een luisterend oor heeft. Vooral de laatste paar maanden heb ik hier gebruik van gemaakt. Ine, ik wil je laten weten dat het mij heel goed heeft gedaan om bij jou terecht te kunnen met mijn verhaal.

Met wie ik de afgelopen 4 jaar ook lief en leed heb gedeeld zijn de mede-promovendi van huisartsgeneeskunde. Sil, Janaica, Martine, Tineke, Mandy, Viola, Esther, Joris, Merijn, Luc, Eva en Eefje: dank voor de fijne tijd die wij samen hebben doorgebracht. Beste Sil, bijna 4 jaar lang hebben wij onze werkkamer met elkaar gedeeld. Ik had me geen beter kamergenootje kunnen voorstellen. Soms was het tijd om hard door te werken, maar we maakten ook regelmatig tijd vrij voor gezellige praatjes, diepgaande discussies of het luisteren naar muziek. Ik hoop dat we elkaar nog zo af en toe blijven zien en op de hoogte blijven van de belangrijke gebeurtenissen in elkaars leven. Beste Esther, sinds een jaar heb jij de werkplek van Sil ingenomen. Ik ben blij met jou als nieuw kamergenootje. Ook wij verzetten af en toe onze gedachten door gezellig te kletsen. Een apart woord wil ik ook nog richten tot Janaica Grispen. Lieve Janaica, jij was de sociale spil onder de promovendi van de tweede verdieping bij huisartsgeneeskunde. Wij hebben samen heel wat gezellige uurtjes doorgebracht. We hebben veel gelachen, maar ook samen gehuild. Het maakte niet uit hoe druk je was, je maakte altijd tijd vrij om me bij een kopje thee mijn verhaal te laten doen. De laatste tijd hebben we ons contact voortgezet in een gezellige gezamenlijke lunch af en toe. Ik hoop dat we dit nog lang blijven doen.

Ook wil ik graag de mensen van het laboratorium voor klinische trombose en hemostase bedanken. Zoals eerder gezegd heb ik veel geleerd van de dinsdagochtendbesprekingen. Door jullie ervaringen te delen hebben jullie mij een kijkje laten nemen in de keuken van basaal en biochemisch onderzoek op het gebied van trombose en hemostase. Ook wil ik jullie bedanken voor de gezelligheid tijdens de congresbezoeken in o.a. Boston, Kyoto en Liverpool. Het is fijn om met zo'n leuke groep mensen op pad te gaan.

De leden van Journal Club Maastricht wil ik graag bedanken voor de gezellige etentjes, leuke activiteiten en levendige discussies. Het is fijn om met jullie ook buiten werktijd over de wetenschap te filosoferen.

Tot slot wil ik graag een aantal dierbare mensen bedanken die mij gevormd hebben. Ik ben gezegend met aantal goede vriendschappen waar ik ontzettend dankbaar voor ben. Zonder anderen tekort te doen, wil ik een aantal mensen bedanken, die in het bijzonder hebben bijgedragen aan dit eindresultaat: Linda Dauwerse-Boersma, Suzanne van der Helm, Nicole Borghans-Laumen en Netty Beckers. Lieve Linda, wij



hebben eenzelfde carrièrepad gekozen en hebben elkaar daarin gesteund. Op de middelbare school kenden we elkaar wel, maar gingen nog niet zoveel met elkaar om. Onze vriendschap kwam pas tot stand in het propedeusejaar van Gezondheidswetenschappen op Universiteit Maastricht. Na de propedeuse behaald te hebben, hebben wij samen besloten dat we graag wat meer praktijkervaring wilden opdoen en zijn overgestapt naar hogeschool Zuyd voor de verpleegkunde-opleiding. Hier hebben we samen veel meegemaakt en ik weet zeker dat onze verpleegkundige achtergrond een belangrijke bijdrage heeft geleverd in onze vorming tot wetenschappers. Na de HBO-V zijn we samen de cursus methodologie en statistiek gaan volgen op Universiteit Maastricht om zo toegelaten te worden tot een master-opleiding. Jij koos voor zorgwetenschappen, ik heb gekozen voor epidemiologie. Nu we allebei aan het einde van ons promotieproject zijn, denk ik dat we met veel trots kunnen terugkijken op wat we bereikt hebben. Ook al zien we elkaar tegenwoordig niet meer zo heel vaak, ik hoop dat onze vriendschap nog lang blijft bestaan.

Lieve Suzanne, jij vertelt regelmatig dat je mij nog steeds als 6-jarig meisje ziet binnenkomen in het leslokaal van de muziekschool in Sittard. Een meisje met een rode strik in haar haren dat graag blokfluit wilde leren spelen. Jij hebt me echter veel meer geleerd dan het maken van muziek. Ik wil je graag bedanken dat je mij altijd aangemoedigd hebt om het beste uit mezelf te halen. Jij hebt een rotsvast vertrouwen in mijn kunnen en stimuleerde me om mijn eigen weg te kiezen. Ik heb bewondering voor hoe krachtig jij in het leven staat. Van mijn blokfluitlerares ben jij uitgegroeid tot een ware vriendin. Ik hoop dat we nog vaak samen zullen fluiten en kletsen.

Lieve Nicole, lieve Netty, jullie zijn mijn paranimfen. Twee betere vriendinnen dan jullie dan ik me niet wensen. Beiden zo verschillend, maar beiden zo belangrijk voor mij. Twee vriendschappen door dik en dun. Lieve Nicole, dank voor alle gezellige en mooie momenten samen. Wat is het fijn om zowel de kleine als grote gebeurtenissen in het leven te delen met iemand zoals jij. Ik zie al helemaal voor me hoe we over tig jaren als twee oude besjes elkaar verhalen vertellen over de middelbare schooltijd, onze reis naar Wenen en Budapest, hoe we beiden gingen studeren en op onszelf gingen wonen, de trouwdag van ieder, de wens om een gezin te stichten en misschien ook wel over hoe jij paranimf was bij de openbare verdediging van mijn proefschrift. Lieve Nicole, ik ben ontzettend dankbaar voor onze vriendschap en hoop dat zich de komende jaren nog maar meer zal verdiepen. Lieve Netty, ook wij hebben al veel samen meegemaakt. Vanaf dag 1 van de brugklas waren we onafscheidelijk. Wat hebben wij veel plezier gehad tijdens onze middelbare schooltijd, met name tijdens de muzieklessen en de repetities van het Serviam-koor. Later heeft onze vriendschap zich verdiept en nu vinden we onder het genot van een kopje thee een luisterend oor bij elkaar. Ik bewonder jouw krachtige persoonlijkheid. Jij laat je niet snel door iets of iemand van de wijs brengen. Lieve Netty, onze vriendschap is me ontzettend dierbaar en ik hoop dat we nog lang samen thee drinken!

Dan wil ik nog mijn familie en schoonfamilie bedanken voor de steun en fijne contacten de afgelopen jaren. Van beide kanten prijs ik me gelukkig met een fijne en hechte familie. Het is fijn te weten dat er zoveel mensen achter je staan. Een speciaal woord van dank wil ik richten tot ome Rein en tante Marie-José. Ik was nog maar net in de familie toen jullie mij vertelden graag een financiële bijdrage te willen leveren aan mijn proefschrift. Mijn dank hiervoor is groot. Tante Marie-José, het is jammer dat het niet zo heeft mogen zijn dat u deze bijzondere dag nog mag meemaken. Ik heb u leren kennen als een bijzondere en sterke vrouw met een grote interesse in alles en iedereen. Ik weet zeker dat u het heel fijn had gevonden hier samen met ons te zijn. Dat geldt ook voor opa. Lieve oma, ik weet dat u, nog meer dan ons allemaal, opa mist. Vooral op speciale gelegenheden zoals deze. Ik weet echter zeker dat opa het heel fijn vindt dat u nog even bij ons blijft en bijzondere gebeurtenissen van de kinderen, kleinkinderen en achterkleinkinderen kan meemaken.

Lieve schoonouders, het is nu ongeveer 4 jaar geleden dat jullie me een warm welkom gaven in jullie familie en ik me thuis mag voelen in Oirsbeek. Ik wil jullie bedanken voor alle steun die jullie mij en Frank geven. We weten dat we altijd bij u terecht kunnen.

Lieve mama en papa, jullie hebben mij de basis gegeven om uit te groeien tot de persoon die ik nu ben. Misschien is dit de juiste gelegenheid om jullie te laten weten dat ik me altijd ontzettend geliefd en thuis heb gevoeld bij jullie. Jullie hebben er alles aan gedaan om Ellen en mij groot te brengen tot verstandige en gelukkige vrouwen die stevig in hun schoenen staan. Jullie hebben ons geleerd bescheiden te zijn en klaar te staan voor andere mensen. Dat is een groot goed. Lieve papa en mama, dank voor alle kansen en mogelijkheden die jullie mij hebben gegeven.

Lieve Ellen, ik vind het moeilijk in woorden uit te drukken wat jij voor mij betekent. Jij bent niet alleen mijn grote zus, maar ook mijn vriendin, mijn sportmaatje en in veel opzichten mijn voorbeeld. Samen met Marcel, Sem en Cas vorm je een gelukkig gezin waar Frank en ik altijd welkom zijn. Ik kan bij veel mensen terecht, maar deel alles het liefste eerst met jou.

Lieve Frank, wij zeggen wel eens tegen elkaar “hadden we elkaar maar eerder ontmoet”. Dit zegt wellicht genoeg over hoe graag we bij elkaar zijn. Wij voelen ons bij elkaar thuis en geven elkaar de ruimte voor ontwikkeling. Lieve Frank, ik kan niet beschrijven hoe fijn ik het vind dat jij mijn man bent. Dank voor al je steun afgelopen tijd. Ik hoop dat we vele mooie jaren samen tegemoet gaan waarin we steeds dichter naar elkaar toegroeien.



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## Curriculum Vitae





## Curriculum Vitae

Petra Mathilda Gerardus Erkens was born on November 12, 1981 in Sittard, in the Netherlands. She completed secondary school (Gymnasium) at the Trevianum Scholengroep Sittard in 2000. In the same year she started her study Health Sciences at Maastricht University. After completing her first year of Health Sciences, she transferred to HBO-V (bachelor) where she graduated with distinction as a registered nurse (level 5). After het HBO-V, Petra spent six months as a volunteer nurse in a governmental hospital in Pretoria, South Africa. When she returned to the Netherlands, she began working as a research nurse at



the cardiology department of the academic hospital in Maastricht. At the same time, she was admitted to the Master of Epidemiology (Health Sciences) where she graduated in 2008. During this master, she fulfilled her internship at the department of Epidemiology of Maastricht University, resulting in the master-thesis "Clustering of metabolic factors and the risk of coronary heart disease: a prospective cohort study in the Netherlands." After graduating, Petra started working as a PhD student at the department of General Practice (School for Public Health and Primary Care (CAPHRI) and Cardiovascular Research Institute Maastricht (CARIM)) in June 2008 resulting in this thesis. Her PhD trajectory revolved around two main projects which were aimed at investigating the safety of diagnosing pulmonary embolism in primary care and the safety of outpatient treatment in patients with acute pulmonary embolism. From February until July 2010, she worked at the Ottawa Hospital Research Institute, Ontario, Canada. Recently, she was offered a post-doctoral position at CAPHRI. With the acquired postdoctoral grant she will investigate the effectiveness of novel anticoagulants in everyday clinical practice mainly focussing on medication non-adherence. Since September 2012 she is also employed at Hogeschool Zuyd as a teacher in nursing.

Petra is happily married to Frank Douven. Beyond her work she enjoys playing the recorder, reading and travelling.