Assessment of Prognostic Models for Patients with Acute Pulmonary Embolism



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Kellogg College

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ABSTRACT

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Background: Acute pulmonary embolism (PE) is a life-threatening condition. This thesis presents my research into the role of prognostic models and strategies for assessing the severity of acute PE, how these compare with recommendations in clinical guidelines and the role of physician's clinical judgment for improving patient management.

Methods: Methods used in each element in the research were appropriate to the relevant objectives: systematic reviews for assessing prognostic markers and prognostic models; sensitivity analysis using the net benefit decision-analytic measure across a range of threshold values for low-risk PE categories in direct comparisons; survey of clinical practice; development and assessment of a case-ascertainment strategy to detect PE patients in one hospital and to explore selection bias; and development of a study protocol for a future comparative study.

Findings: Individual prognostic markers are insufficient on their own to accurately predict outcome. Prognostic models are more successful, with the PE severity index (PESI) and simplified PESI (sPESI) models being the most validated. They provided a low event rate in patients identified as low-risk, which was similar to that obtained with other, less validated, strategies, such as the Hestia hospital checklist. High-risk groups were best identified using PESI or other models at high cut-off levels or by adding clinical vital signs, biomarkers and imaging-based markers of right ventricular dysfunction/ myocardial ischemia. The net benefit analysis confirmed the superiority of PESI and sPESI over original competing models, and the incremental value of adding prognostic markers. The survey showed that emergency physicians still rely mostly on their own clinical judgment when deciding about early discharge or complete outpatient management and the case-ascertainment study showed that if case-ascertainment is incomplete, selection bias may mean that event rates and prognosis will be underestimated, prognostic models will be overoptimistic and the results of different studies cannot be compared, contrasted or combined reliably.

Conclusions: Based on current evidence, the PESI models are the most appropriate strategies for deciding on early discharge and outpatient management for patients presenting to hospital with acute PE. Future research, with complete case-ascertainment, needs to compare these models with Hestia and clinical judgement to assess their value for decisions about the management of non-selected PE patients.

QUOTATION

"... a model is a tool to help us understand the complexities of the universe, and never a substitute for the universe itself".

"Distinguishing the signal from the noise requires both scientific knowledge and self-knowledge: the serenity to accept the things we cannot predict, the courage to predict the things we can, and the wisdom to know the difference."

Nate Silver[1].

[1] *The Signal and the Noise: Why So Many Predictions Fail - But Some Don't. New York, NY: Penguin Press; 2012.*

DEDICATION

It is with great emotion and love that I would like to dedicate this thesis to my family: to Marie for her love and support throughout all these years of common life at home and at work, to Mike and Marc for their encouragement and their patience while completing my thesis, and to Jen, Marion, Lily, Emma and Juliette.

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[2] INNOVTE (INvestigation Network On Venous ThromboEmbolism) - EuSEM (European Society for Emergency Medicine) - SFMU (French Society for Emergency Medicine)

STATEMENT OF CONTRIBUTION

"The thesis I am submitting is entirely my own work except where otherwise indicated. It has not been submitted, either partially or in full, either for this Honour School or qualification or for another Honour School or qualification of this University, or for a qualification at any other institution. I have clearly indicated the presence of all material I have quoted from other sources, including any diagrams, charts, tables or graphs. I have clearly indicated the presence of all paraphrased material with appropriate references. I have acknowledged appropriately any assistance I have received in addition to that provided by my supervisors. I have not copied from the work of any other candidate. I have not used the services of any agency providing specimen, model or ghostwritten work in the preparation of this thesis"[3].

As the author, I contributed to all aspects of the thesis (concept, design, conduct, analysis, interpretation and reporting of the studies) in all the chapters.

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PUBLICATIONS

At the time of submission, the chapter 4 was published.

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Two manuscripts are currently in development to publish the chapter 6 and the chapter 7.

Most of the thesis chapters will be submitted to peer-reviewed journals.

[3] Declaration of authorship, University of Oxford

ABBREVIATION AND DEFINITION TERMS

ACS: acute coronary syndrome
AE: adverse event
APACHE II: Acute Physiology and Chronic Health Evaluation II
Angio: angiography
BMI: body mass index
BNP: brain natriuretic peptides
BID: bis in diem (twice a day)
CAD: coronary artery disease
CCI: Charlson's comorbidity index
CHF: congestive heart failure
CI: confidence interval
Clin prob: clinical probability
CRNM: clinically relevant non-major (bleeding)
COPD: chronic obstructive pulmonary disease
CPD: chronic pulmonary disease
CPK: creatin phosphokinase
CPR: cardiopulmonary resuscitation
CR: cardiorespiratory
CRA: clinical research assistant
CRF: case report from
CT: computed tomography
CT-RVD: computed tomography right ventricular dysfunction
CT-PA: CT pulmonary angiography
CT-V: CT venography
CTEPH: chronic thrombo-embolic pulmonary hypertension
cTnT: cardiac troponin T
cTnI: cardiac troponin I
DOAC: direct oral anticoagulant
DVT: deep vein thrombosis
Echocardio: echocardiography
ED: emergency department
EMEP: Estudo Multicentrico di Embolia Pulmonar
EMPEROR: Emergency Medicine Pulmonary Embolism in the Real World Registry
ESC: European society of cardiology (2008/ 2014 ESC: 2008/ 2014 European Society of Cardiology guidelines)
FAST score: H-FABP, Syncope, Tachycardia
FEU: fibrinogen equivalent unit FU: follow-up
GCP: good clinical practice
GCS: Glascow coma scale
GFR: glomerular filtration rate
GP: general practitioner
GPS: Geneva prognostic score
GRACE: Global Registry of Acute Coronary Events
HR: heart rate
hscTnT: high sensitive cardiac troponin T
H-FABP: heart fatty acid binding protein
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICF: informed consent form
ICOPER: International Cooperative Pulmonary Embolism Registry
IQR: inter quartile range
IHD: ischemic heart disease
IPER: The Italian Pulmonary Embolism Registry
IVC: inferior vena cava
LE: life expectancy
LL: lower limb
LMWH: low molecular weight heparin
MDCT: multi-detector computed tomographic (angiography)
MRA: magnetic resonance angiography
MI: myocardial infarction
MPV: mean platelet volume
NA: not applicable
NLR: neutrophil to Lymphocyte ratio
NOAC(s): Non-vitamin K-dependent new oral anticoagulant(s)
NR: not reported
NT-proBNP: N terminal pro-BNP
OAC: oral anticoagulant
o.d.: omni die (every day)
OR: odds ratio
OTPE: outpatient treatment of pulmonary embolism study
PA: pulmonary angiography
P2: pulmonic component of second heart sound
Pd: P wave dispersion
PE: pulmonary embolism
PEITHO: Pulmonary EmbolIsm THrOmbolysis trial
PESI: pulmonary embolism severity index (original version)
PI: primary investigator
PIL : participant/ patient information leaflet
PIOPED: prospective investigation on pulmonary embolism
PREP: facteurs PRonostiques dans l'Embolie Pulmonaire
QD: once a day
QID: four times a day
QTcd : corrected QT interval dispersion
RCT: randomised controlled trial
REC: research ethics committee
RGS: Revised Geneva Score
RIETE: Registro Informatizado de la Enfermedad ThromboEmbolica venosa
RR: relative risk
RV: right ventricle/ ventricular
RVD: right ventricular dysfunction
SAE: serious adverse event
SBP: systolic blood pressure
SD: standard deviation
SGS: Simplified Geneva Score
SI: shock index (=HR/SBP)
SIRS: systemic inflammatory response syndrome
SOP: standard operating procedure
SPAP: systolic pulmonary artery pressure
sPESI: simplified PESI
SWIVTER: The SWIss Venous ThromboEmbolism Registry
TELOS: Thrombo-embolism lactate outcome study
TID: three times a day
TL: thrombolytics
TTE: transthoracic echocardiography
TTE-RVD: transthoracic echocardiography right ventricular dysfunction
UH: unfractionated heparin
UPS: Utrecht Prediction Score
US: ultrasound
V/Q: ventilation-perfusion scan/ scintigraphy
VOI: Vascular Obstruction Index (on CT angiography)
VKA: vitamin K antagonists
VTE: venous thromboembolism
WBC: White Blood Cells

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Chapter 1 - Introduction

CONTEXT OF THE THESIS

In my workplace, I take care of patients presenting with acute pulmonary embolism (PE), a common and potentially life-threatening vascular condition. I have a particular interest in the assessment of the "short-term" prognosis of these patients because adequate assessment of prognosis is essential for guiding management and treatment that will improve patient outcome.

When I started my DPhil research in January 2010, most physicians relied on their clinical intuition or judgment to assess prognosis in routine practice, although multiple prognostic markers and prognostic models or strategies had been developed to try to standardise the assessment of prognosis in acute PE. Like many physicians, I wanted to base my clinical practice on the most accurate and adequate model or strategy for patient prognosis so that I could use the predicted prognosis for each individual patient in order to select the appropriate management for him/her. My research question and area of clinical uncertainty related to the incorporation or not of a prediction model into the care pathway. In the years since then, the nature of the evidence in this area has changed. For example, in 2014, the European Society of Cardiology (ESC) launched new guidelines[1] that recommend the use of the original and the simplified versions of the PE severity index model (PESI and sPESI, respectively) as part of the risk stratification of patients with confirmed acute PE. The aim is to identify patients at low-risk, who could then be managed as outpatients. Subsequently, novel and updated models have emerged with the aim of improving risk prediction and management for both low-risk and high-risk acute PE patients. The availability of these models raises new clinical questions about their role in current practice, as compared to PESI and sPESI models and the recommendations in the 2014 ESC guidelines in general, and what they might add to the role of clinical intuition in decision-making.

Given the 2014 ESC guidelines, my research questions are now: (1) How do prognostic models compare with PESI and sPESI for the identification of acute PE patients at low-risk of adverse outcomes, and how do they compare with the 2014 ESC guidelines for the identification of patients at higher risk, (2) what part does physician's clinical intuition play in decision making and (3) what further research is needed for the development of prognostic models?

OVERALL AIM OF THE THESIS

The overall aim of this thesis is to use a variety of sources of evidence to show how prognostic models compare with the PESI and sPESI models and the recommendations in the 2014 ESC guidelines, to show the role of physician's clinical intuition and to discuss whether there is a need to improve prognostic risk assessment by adding clinical intuition to existing models. Achieving this aim will allow the identification of the prognostic models or strategies which are the most useful for predicting outcomes and informing decisions for acute PE patients about, for example, early discharge or complete outpatient management, admission to a medical ward or monitoring unit, and the use of more aggressive therapy such as thrombolysis? The research findings will also provide the evidence base for the protocol for a new study to assess the value of combining a prognostic model with clinical intuition in patients presenting with acute PE.

OBJECTIVES OF THE THESIS

The thesis is guided by the need to answer three main ***questions***, with the first two addressed by substantial pieces of new research and the third by drawing together the lessons learned from that research to design a new study:

1/ what is the evidence base for the use of prognostic models in acute PE and how do the models compare in terms of performance? Specifically, how do the models or strategies compare with PESI and sPESI for predicting patient outcome and improving decision-making?

2/ how is prognosis assessed in routine practice? How often do physicians use these models or strategies in routine practice in comparison to clinical intuition?

3/ what future research is needed in the development of prognostic models in acute PE?

Specific objectives for the first question about "***Evidence***" are:

. To review and summarise the existing literature about prognosis and prognosis markers in patients with acute PE, and to review the methodology for critically appraising studies about prognosis and prognostic models in this context. This is essential for informing readers of this thesis about the status of these topics at the time the thesis was written.

. To undertake a systematic review and meta-analysis of studies of prognostic models in acute PE

. To assess the performances of prognostic models in acute PE based on studies that have directly compared them and with reference to the PESI and sPESI models.

The specific objective for the second question about "***Clinical Practice***" is to conduct a survey about the use of prognostic models, strategies and clinical intuition in the management of acute PE.

Finally, specific objectives for the third question about "***Development Methods***" relative to prognosis assessment are:

. To develop a case-ascertainment strategy that would support the recruitment of all eligible patients in new studies and minimise selection bias, and to compare this case-ascertainment strategy versus usual recruitment methods on patient typology and prognosis profile in my hospital.

. To develop a protocol for a new study to assess the value of combining information based on clinical intuition with data from an effective prognostic model for the management of patients with acute PE.

STRUCTURE OF THE THESIS

Chapter 1 - Introduction: This chapter introduces the aim and objectives of my research and provides the rationale for the thesis.

Chapter 2 - Clinical Background and Literature Review on Prognosis: This chapter seeks to meet the objective of providing a summary of prognosis assessment in acute PE at the time that the research was done. It reviews recent developments in the epidemiology, diagnosis and management of acute PE, the clinical course in patients with acute PE and the accuracy of individual prognostic markers for predicting outcome. This shows the prediction power or strength for each prognostic marker, and highlights which markers might be added to available and effective prognostic models or strategies.

Chapter 3 - Methodology Background: This chapter provides an introduction to terminology and methods regarding prognosis assessment and performance measures tools that will be studied in the thesis. It describes the key elements in critical appraisal of studies about prognosis and prognostic models at different phases of their development and its application to acute PE, showing how this can provide better understanding of the potential biases and their influence on individual studies and systematic reviews. It uses existing research to provide a comprehensive account of the biases related to study design, conduct and analysis; methods of selection of the population, patient and setting; prognostic information about outcome and time-point and prognostic variables or models, and measures of performance. This shows how the existing evidence was used to develop a data extraction form which was used for the systematic review of prognostic models in acute PE (chapter 4) and could be used for other systematic reviews of

prognostic models and how appropriate measures were selected for assessing and comparing the performance of prognostic models.

Chapter 4 - Systematic Review and Meta-analysis of Prognostic Models in Acute Pulmonary Embolism: The next and major step in my research programme was to conduct a systematic review and synthesis of the evidence about prognostic models in acute PE, using current guidelines for searching, selection criteria, data extraction, study quality assessment, data analysis and synthesis. This chapter synthesizes the evidence that would help physicians who are deciding whether prognostic accuracy and other simple measures of performance (such as event rate and proportion of patients in different risk groups) are clinically relevant when choosing between models, so that they can select the most appropriate in terms of predictive performance (from validation studies) and utility (from impact studies), as well as considering their ease of use in clinical practice. This research, using the extensive review and meta-analyses, provides summary data for event rates in populations as a whole (prevalence) and in risk groups for different prognostic models, outcomes and time-points.

Chapter 5 - Net Benefit of Prognostic Models in Acute Pulmonary Embolism in Direct Comparison Studies: This chapter uses paired-data analysis (i.e. direct, head-to-head comparisons between models that share the same cohort) to compare the performance of different models. I used the individual studies identified in my systematic review. I used a decision-analytic approach and performed sensitivity analyses by varying decision threshold probability values. This approach is more clinically meaningful and assesses the clinical consequences for a decision because it accounts for both sensitivity and specificity and assigns a weight for false positive against true positive results. The difference in performance between two models can be reported as difference (or gain) in net benefit. I defined threshold values for one of the most important treatment decisions for physicians: early discharge versus in-hospital management for patients considered at low-risk by the prognostic model. I obtained these values through another element

in my research programme, which is reported in chapter 6: surveys among emergency and expert physicians and among physicians from the departments of Cardiology and Vascular Medicine in my workplace.

Chapter 6 - Opinion and Practice Survey about the Use of Prognostic Models in Acute Pulmonary Embolism: Alongside the theoretical and statistical properties of prognostic models, it is essential to know how they work in clinical practice if one wants to decide on their use in routine health care. The next element in my research programme investigated this, through a survey on the use of prognostic models among emergency department and expert physicians from different countries, who treat patients with acute PE. This is the first such study to determine attitudes toward the use of these models and the barriers to their uptake, and I also used it to investigate clinical opinion on prognosis and management of acute PE patients from this wide range of physicians who treat patients with acute PE.

Chapter 7 - Development and Assessment of Ascertainment Strategy: My systematic review identified wide variability in the event rates in study populations as a whole and within risk groups across studies, even with similar populations and for the same models. This suggests a potential for selection bias, such that patients in prognosis studies may be not representative of all hospital cases and differences between selected and non-selected patients may influence clinical outcomes (death and recurrence) in these studies. The patient risk profile in a study may depend on the type of recruitment services and the case-identification method used. Another element in my research programme investigates this and is reported in this chapter: my specific study to develop a case-ascertainment strategy in my hospital and assess the impact of case-ascertainment and recruitment methods on patient typology, including case-mix (demographic, clinical, biological and other patient characteristics), risk-classification according to existing prognostic models, and clinical outcomes. This study assesses the feasibility and quality for

obtaining prognostic information, as well as the role of case ascertainment in a large general hospital where many patients with PE are seen.

Chapter 8 - Development of a Study Protocol on Physician's Clinical Judgment: My research highlighted gaps in the existing knowledge about the prognosis of patients with acute PE and in how prognostic information should be used in decision making for this life threatening condition. The final element in my research programme builds on this knowledge to design a protocol for a new study. This will address the uncertainty around how physician's clinical judgment and the additional information that it may provide for assessing prognosis and choosing whether outpatient management of patients with acute PE is appropriate. This chapter proposes a study to explore the circumstances in which clinical intuition might override a prediction or prognostic model. The conduct of such a study is beyond the scope of this DPhil but its design brings together my various research elements and it would help identify limitations in the sPESI model and ways in which it might be improved.

Chapter 9 - Discussion and Conclusions: Finally, this chapter provides a summary and general discussion of the importance of this thesis. It places my findings in the context of the existing literature, and discusses the implications of my research for clinical practice and for clinical research.

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1. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. European heart journal 2014;**35**(43):3033-69, 69a-69k.

Chapter 2 - Clinical Background and Review on Prognosis

OBJECTIVES

This chapter introduces the topic for my research, describing recent developments in the epidemiology, diagnosis and management of acute PE, and reviewing the literature about the accuracy of individual prognostic markers for predicting outcome in patients with acute PE. This research investigates the prediction power and strength of individual prognostic markers and their potential value as additions to existing prognostic models or strategies.

CLINICAL BACKGROUND

Defining the context

A pulmonary embolism is anatomically defined as a partial or complete obstruction of the main pulmonary artery or of its branches by a blood clot that developed in the veins of the lower limbs (vein thrombosis) and has migrated through the bloodstream and the right-heart cavities to the lung vessels. As a consequence of the vascular obstruction, the disturbances in blood gas exchange (hypoxemia) and the neurohumorally mediated pulmonary vasoconstriction may lead to an increase in the peripheral pulmonary vascular resistance and the pulmonary artery pressure and to a right ventricle overload. This may result in right ventricular dysfunction and lowering of systemic blood pressure, clinical deterioration and haemodynamic collapse[1].

The first clinical manifestation of PE ranges from an absence of symptoms (incidental PE) to the worst clinical deterioration and death. The outcome in patients with PE may depend upon early and accurate diagnosis, the haemodynamic status as a result of the magnitude of lung vessel

obstruction and associated comorbidities, the underlying disease that caused PE and the persistence of risk factors for PE and deep vein thrombosis (DVT), and the type of management. Despite dramatic improvements in outcomes because of anticoagulant treatment, the clinical course in patients with PE may still be complicated by death, recurrence and anticoagulant-related bleeding. Assessing prognosis may help to predict the outcome and choose the type of management that an individual patient may need.

The assessment of prognosis in this thesis will focus on outcomes during the "active treatment" phase[2], that is event occurrence within the first 3 months after the diagnosis and start of treatment referred to as either "short-term"[3] or "long-term"[4 5] treatment phase. This time-period is critical as most of the events occur within the first three months, mainly within the first week and the first month[6 7] i.e. the "initial treatment" phase[4 5]. Indefinite treatment refers to an extended treatment beyond the first 3 months[5].

The assessment of prognosis in this thesis will not concern patients who present with shock or hypotension (unstable PE) defined by the European Society of Cardiology (ESC) guidelines[1] "as systolic blood pressure < 90 mm Hg or a systolic pressure drop by ≥40 mm Hg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis". This presentation is relatively uncommon, with less than 5% of patients with acute PE being haemodynamically unstable at presentation[8 9], but they are at such high-risk of PE-related in-hospital or 30-day mortality that they need a prompt and different therapeutic management to those patients who present without shock or hypotension.

Epidemiology

Disease burden of venous thromboembolism (VTE)

Venous thromboembolism (VTE), including PE and DVT, is a common and potentially fatal disorder that is associated with substantial health-care costs and a high rate of recurrence[10]. In this

respect, it is a major public health and medical problem. Overall VTE incidence is similar to that of stroke[10] and PE is the third most common cause of death from cardiovascular disease after heart attack and stroke[11].

Outcome from population-based data studies

From population-based data studies, Cohen et al[12] (VTE Impact Assessment Group in Europe: VITAE) estimated that there are more than one million VTE events or deaths per annum in six EU countries examined. In an incidence-based modeling study that included both hospital- and community-acquired incident and recurrent VTE events, an estimated 600,000 non-fatal VTE events (370,000 DVT and 270,000 PE) occurred in the USA in 2005[10 13]. In a French population[14], the annual incidence of VTE was reported to be 0.183% (95% CI: 0.169-0.198), with 0.124% (95% CI: 0.112-0.136) for DVT and 0.06% (95% CI: 0.052-0.069) for PE. The incidence of PE rises to nearly 1% per year in patients over 75 years of age. The reported 30-day case-fatality rate[15] in patients with PE is high (9.7% [95% CI: 6.1 – 13.3] overall), particularly in those with cancer: risk ratio of 3.8 (95% CI 1.6-9.2) for cancer compared to non-cancer patients.

Outcome from hospital-based data studies – The clinical course

The main adverse outcomes in hospital-based data studies in patients with acute PE are death and VTE events. If left untreated, PE has been found to be fatal in 26-30% of patients[16-18] and a study published in 1960 found 26% suffered recurrent events [17]. More recent studies[19 20] provide a lower estimate of adverse outcome (death or recurrence) of around 5% in untreated patients. Anticoagulant treatment has considerably improved the short term outcome in patients with acute PE. However, short term complication rates vary considerably across studies[21-30] (Table 2.1). This might be due to differences in population and treatment, as well as study design and study quality. Mortality rate ranges have been reported as 1.2 - 1.4% at the end of heparin treatment[31], 4.7% - 6.1% at 3 months in a meta-analysis of randomised controlled trials (RCT) of low molecular weight heparin (LMWH) versus unfractionated heparin(UFH)[31] and 15.3-17.4% at 3

months in the International Cooperative Pulmonary Embolism Register (ICOPER)[23]. A patient's outcome may also depend on whether she/he is clinically stable or in cardiogenic shock. In the Germany-based Management Strategy and Prognosis of Pulmonary Embolism Register (MAPPET)[22] that included 1001 patients with acute PE, in-hospital mortality was 8.1% for hemodynamically stable patients versus 25% for those presenting with cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation**.** In prospective cohorts, the reported 3-month mortality under treatment varies between 8.2 and 10.6%. The 3-month recurrence rate is around 2.8 - 3%. For example, the TROMSO prospective study published in 2017 (see supplemental material of publication) reported on patients with first lifetime unselected DVT/PE recruited from the general population (covering both the community and a unique hospital setting). It found all-cause mortality to be high starting from the first days (3.1% on the first day, 4.2% within the first week), reaching 8.6% at 1 month and 16.2% at 3 months (Table 2.1). Heit et al[10] have reported even higher rates in population-based studies: 33.2% at 1 month and 37.2% at 3 months.

Another complication in PE is related to the side effects of treatment. The estimated risk of major or clinically relevant bleeding under anticoagulant at 3 months is around 3.5% in prospective cohort studies (Table 2.1). Major bleeding rate rises to 9.2-11.7% in registers (Table 2.1).

In the long-term[32] [33] PE may lead to late recurrences, chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome. These last two outcomes can be severely disabling, but although these outcomes deserve special attention by clinicians, they are beyond the scope of this thesis.

Risk factors for VTE

VTE may be related to numerous environmental and genetic predisposing factors[1] and may be a consequence of interactions between temporary or major reversible risk factors related to specific circumstances (such as surgery, trauma, immobilisation, hospitalisation for acute medical illness, pregnancy, oral contraceptive use or hormone replacement therapy), and permanent or

persistent risk factors related to the patient[1]. VTE is considered unprovoked if it occurs when no major predisposing risk factor, no active cancer, no family history or known thrombophilia is present. In patients with unprovoked VTE and in those with persistent or permanent risk factors (e.g. cancer) the high-risk of recurrent events in the long term is a key element for the decision to extend the duration of anticoagulant treatment beyond the first 3-6 months.

Modifiable risk factors might be accounted for with prevention strategies in surgical patients and acute medical conditions. However, some risk factors like age and cancer may alter the clinical course of patients with PE/ DVT, and in this respect are considered as prognostic factors (see prognosis section).

Table 2.1: Death, recurrence and bleeding rates from hospital-based data in prognostic studies of acute PE (search performed via Google Scholar and PubMed through EndNote reference manager).

Author (Year) Reference	Study design	N Patients	Treatment	Outcome		
				Death (%)	Recurrence (%)	Bleeding (%)
Carson et al (1992)[21]	Prospective cohort (PIOPED cohort)	396	UFH, VKA, IVC interruption Thrombolysis, Embolectomy	1-year All-cause : 23.8 PE-related: 2.5 Cancer-related: 8.3	1-year: 8.3	NR
Kasper W et al (1997)[22]	Prospective register (MAPPETT register - Germany)	1001 (patients with RVD, hypotension, cardiogenic shock or circulatory collapse)	Heparin, VKA IVC interruption Thrombolysis (48%), Embolectomy, Catheter thrombus fragmentation	In-hospital Stable PE: 8.1 Shock: 25 CPR: 65	In-hospital PE: 17	In-hospital Major bleeding: 9.2 (cerebral: 0.5)
Goldhaber SZ et al (1999)[34]	Prospective register (ICOPER register – Europe and North America)	2454	Heparin, VKA, IVC interruption, Thrombolysis, Embolectomy, Catheter embolectomy	3-month All-cause: 15.3 to 17.4 (+necropsy) PE-related: 7.8 Cancer-related: 3.1 (stable 15.1, unstable 58.3)	3-month PE: 7.9	3-month Major bleeding: 10.5
Arcelus JI et al (2003)[24]	Prospective register (RIETE register - Spain)	VTE 4011 PE : 900 PE and DVT : 588	UFH, LMWH, VKA, IVC interruption, Thrombolysis, Embolectomy	FU (156 ± 95) All-cause: 14.8	FU (156 ± 95): 5.2	FU (156 ± 95): 11.7
Nijkeuter et al (2007)[25]	Prospective cohort (The Netherlands)	673 (stable only PE)	UFH, LMWH, VKA	3-month All-cause: 8.2 PE-related: 1.6 Cancer-related: 2.5	3-month VTE: 3 (PE: 2.1)	3-month Major bleeding: 1.9 (Fatal: 0.3) CRNMB: 1.5

Conget et al (2008) [26]	Prospective cohort (Spain)	1338	UFH, LMWH, VKA Thrombolysis	1-week All-cause: 2.7 PE-related: 1.6 3-month All-cause: 10.6 PE-related: 3	1-week VTE: 0 3-month VTE: 2.8	1- week Major bleeding: 1.6 3-month Major bleeding: 3.6
Laporte et al (2008)[27]	Prospective register (RIETE register - Europe)	15 520 (DVT: 58%, Stable PE: 40.4%, Unstable PE: 1.6%)	UFH, LMWH, VKA, IVC interruption, Thrombolysis, Embolectomy	3-month All-cause Whole sample: 8.65 PE-related in stable PE: 2.99 in unstable PE: 9.27	Not reported	Not reported
Palla et al (2009) [28]	Prospective cohort (Italy)	497	UFH, LMWH, VKA Thrombolysis	1-year All-cause: 27.4 PE-related: 7.2, Cancer-related:11.9	10-day PE: 7.8 1-year PE: 9.6	1-year Bleeding:3.4 (Major: 0.2)
Pollack et al (2011)[29]	Prospective register (EMPEROR register - USA - emergency departments)	1880	UFH, LMWH, VKA, IVC interruption, Thrombolysis	In-hospital All-cause: 3.4 PE-related: 1.1 30-day All-cause: 5.4	30-day PE: 2.6 DVT: 0.58	In-hospital Bleeding-related death:0.16 30-day Bleeding-related death:0.16
Casazza et al (2012)[35]	Prospective register (IPER register - Italy)	1716 (Unstable PE: 11.7%)	UFH, LMWH, VKA, IVC interruption, Thrombolysis, Embolectomy	In-hospital - whole sample All-cause: 6.7 PE-related: 3.9 Cancer-related: 0.3 In-hospital - unstable PE) All-cause: 31.8 PE-related: 23.3 Cancer-related: 1 In-hospital - stable PE	In-hospital PE events Whole sample: 1.3 unstable PE: 1 Stable PE: 1.4	In-hospital - whole sample Intracerebral bleeding-related death:0.3 In-hospital - unstable PE) Intracerebral bleeding-related death:0.5 In-hospital - stable

				All-cause: 3.4 PE-related: 1.4 Cancer-related:0.3		PE Intracerebral bleeding-related death:0.3
Verso et al (2012)[30]	Prospective register (MASTER register - Italy)	2119 DVT: 1541(72.7%) PE ± DVT: 578 (27.3%)	UFH, LMWH, VKA, IVC interruption, Thrombolysis	24-month Unprovoked VTE: 1.43%p-y Cancer- associated VTE: 20.32%p-y Provoked VTE: 1.73%p-y	24-month VTE: 3.63%p-y (3.84%p-y in patients with DVT alone, 3.09%p-y in patients with PE ± DVT)	24-month With Heparin: 1.7% With VKA: 2.7%
Arshad et al (2017)[36]	Prospective study (Community and unique hospital settings) TROMSO study	710 First lifetime VTE DVT: 415 (58.4%) PE: 295 (41.5%)	UFH, LMWH, VKA, IVC interruption, Thrombolysis, surgery	All-cause death 1-day: 3.1 (2.1-4.6) 7-day: 4.2 (2.9-6.0) 30-day: 8.6 (6.7-11.0) 3-month: 16.2 (13.6-19.1)	VTE 1-day: 0.2 (0.1-1.1) 7-day 0.8 (0.3-1.9) 30-day 1.7 (0.01-3.1) 3-month 2.7 (1.7-4.3)	Not applicable

Cohort studies dedicated to the assessment of individual prognostic factors or prognostic models, diagnostic studies and randomised controlled trials are not included.
PE: pulmonary embolism, DVT: deep vein thrombosis, VTE: venous thromboembolism, RVD: right ventricular dysfunction. UFH = unfractionated heparin, LMWH = Low Molecular Weight Heparin, VKA = Vitamine K Antagonists, IVC: inferior vena cava interruption. Shock is cardiogenic shock, CPR: cardiopulmonary resuscitation. FU: follow-up, CRNMB: clinically relevant non-major bleeding. “p-y”: person-year.

Diagnosis

Diagnosis of PE is difficult. The clinical presentation varies widely and is not specific. Because of the high risk of death and VTE events that may occur in undiagnosed and untreated PE, and the risk of death and major or clinically relevant bleeding due to treatment, an objective, accurate, reliable and cost-effective diagnostic management strategy is required. As well as being important to the patient and the physician, an accurate diagnosis is essential to researchers designing, conducting and analyzing diagnosis and prognosis studies, and for those doing and using clinical trials in VTE. A confirmed diagnosis is the basis for including patients with PE in a prognosis study and can be used as a reference for later comparison to assess VTE event outcomes during follow-up.

To review the ***diagnostic management strategies*** for patients with PE, I sought relevant studies by searching in Google Scholar and PubMed using terms related to the diagnosis of PE (pulmonary embolism, diagnosis, management, strategy, clinical prediction rule), and diagnostic tests (D-dimer, venous ultrasonography, helical CT, ventilation perfusion scan, pulmonary angiography, echocardiography and magnetic resonance angiography). Strategies that have proved accurate and clinically effective are displayed on Table 2.2. Validated diagnostic strategies integrating at least two different diagnostic modalities under various combinations most often include at first a clinical probability assessment, usually a clinical prediction rule. When they are negative, these strategies are safe and provide a low failure rate, i.e. a low VTE event rate at a 3-month follow-up after withholding anticoagulant therapy. The decrease in prevalence of objectively confirmed diagnosis of PE from around 35% to 20-25% and even less (9-10%) in some studies (Table 2.2) makes it possible to safely rule out the diagnosis without additional imaging in patients with a non-high clinical probability (PE unlikely) and a negative D-dimer testing that can be now age-adjusted[37]. In other situations, PE can be ruled out on the basis of a normal ventilation perfusion

scan, or a normal high quality CT angiography. On the contrary, the diagnosis of PE is established on the basis of a positive CT pulmonary angiography, a high probability ventilation perfusion scan or a non-conclusive one when associated with a proximal DVT on ultrasound.

To sum-up, an ***appropriate diagnostic management strategy*** is useful for patient safety[38] and avoids unnecessary imaging. In patients who are haemodynamically stable, the recommendations are to use a strategy that follows a sequential testing approach, which includes a clinical prediction or decision rule, D-dimer testing (if PE is unlikely) and CT pulmonary angiography if necessary (i.e. PE unlikely and D-dimer positive, or PE likely without D-dimer testing)[1]. In patients who are haemodynamically unstable, the diagnostic approach is different and needs an immediate diagnostic imaging test (including echocardiography and CT) and simultaneous therapeutic management[1].

Statements provided by guidelines[1 39 40] about diagnosis criteria and diagnostic value for each individual test, and about diagnostic management (see Chapter 3. Methodology Background) either for a first episode of pulmonary embolism or for a recurrent VTE event (PE or DVT) are used in this thesis to critically appraise study quality in my systematic review (Chapter 4), for designing my study of a new case ascertainment strategy (Chapter 7) and to develop my protocol for a new study (Chapter 8).

Table 2.2: Diagnostic management strategies in patients with clinically suspected pulmonary embolism.

Author (year)	Diagnostic strategy	PE Prevalence (%)	Patients: N (type)	VTE events* % [95% CI]
Hull et al. (1994)[41]	V/Q, repeated IPG	9.6	627 (in-patients and out-patients)	1.9 (1.0-3.2)
Perrier et al. (1999)[42]	Clin, Ddi, USl, V/Q, PA	23.4	321 (out-patients)	0.9 (0.2-2.7)
Wells et al. (2001)[43]	Clin, Ddi, V/Q, repeated USl, PA	8.7	849 (out-patients)	0.6 (0.2-1.4)
Kruip et al. (2002)[44]	Clin, Ddi, USl, PA	22	234 (in-patients and out-patients)	0.5 (0.1-3.0)
Musset et al. (2002)[45]	Clin-USl-HCT, V/Q, PA	34.6	507 (in-patients and out-patients)	1.8 (0.8-3.3)
Leclercq et al. (2003)[46]	Clin, Ddi, Thorax/V/Q, USl, PA	29	202 (in-patients and out-patients)	0.0 (0.0-2.8)
Van Strijen et al. (2003)[47]	CTPA, USl	25.3	376 (in-patients and out-patients)	0.8 (0.2-2.3)
Perrier et al. (2004)[48]	Clin, Ddi, USl, CTPA, PA	23	965 (out-patients)	1.0 (0.5-2.1)
ten Wolde et al. (2004)[49]	Clin, Ddi, V/Q, USl	20	631 (in-patients and out-patients)	1.3 (0.6-2.8)
Anderson et al. (2005)[50]	Clin, Ddi, CTPA, USl, PA	10	858 (out-patients)	0.2 (0.1-0.8)
Elias et al. (2005)[51]	Clin-Ddi-USc, CTPA	40	274 (out-patients)	0.6 (0.1-3.4)
Ghanima et al. (2005)[52]	Ddi, Clin, CTPA	.24	432 (out-patients)	0.6 (0.2-2.2)
Perrier et al. (2005)[53]	Clin, Ddi, CTPA, USl, PA	26	756 (out-patients)	1.0 (0.4-2.2)
Van Belle et al. (2006)[54]	Clin, Ddi, CTPA	20	3 306 (in-patients and out-patients)	0.9 (0.6-1.4)
Anderson et al. (2007)[55]	Clin, Ddi, V/Q, repeated USl	14	712 (in-patients and out-patients)	1.0 (0.5-2.1)
Anderson et al. (2007)[55]	Clin, Ddi, CTPA, repeated USl	19	694 (in-patients and out-patients)	0.4 (0.1-1.3)
Righini et al. (2008)[56]	Clin, Ddi, USl, CTPA	21	855 (out-patients)	0.3 (0.1-1.1)
Righini et al. (2008)[56]	Clin, Ddi, CTPA	21	838 (out-patients)	0.3 (0.1-1.2)

* VTE events in patients with a negative diagnostic strategy. V/Q: ventilation Perfusion scan, IPG: Impedance plethysmography, Clin: assessment of clinical probability, Ddi: D-dimer, USl: ultrasound limited to the popliteal and femoral veins, USc: complete ultrasound of the whole venous system of the lower limbs, PA: pulmonary angiography, CT: computed tomography, CTPA: CT-based pulmonary angiography. "," indicates sequential testing, "-" indicates combined testing

Management

Treatment is initiated as soon as the diagnosis of PE is confirmed and sometimes before this point pending the diagnostic confirmation in patients with high or intermediate clinical suspicion[57]. Several therapeutic modalities are available for patients with acute PE: parenteral anticoagulants and vitamin-k antagonist anticoagulants, direct oral anticoagulants, thrombolytic therapy, surgical embolectomy and endovascular treatment, and venous filter insertion.

Parenteral anticoagulants and vitamin-k antagonist anticoagulants

Conventional care in the very early (initial) phase in stable PE usually involved treating the patient in hospital using parenteral anticoagulants (either UFH a dose-adjusted standard anticoagulant or a fixed dose LMWH[31 58-62], or a fixed dose specific inhibitor of factor Xa[62 63]) as bridging therapy[64] before using oral vitamin-K antagonist (VKA) anticoagulants. Anticoagulants in use are shown in table 2.3, and a systematic review of RCTs has shown that "fixed-dose" (weight-adjusted) LMWH treatment was as effective and safe as dose-adjusted intravenous UFH for the initial treatment of "non-massive" (stable) PE[31].

Direct oral anticoagulants (DOACs).

In recent care, usual practice for patients with acute PE has changed to the use of DOACs. These are new anticoagulants that are direct inhibitors of factor IIa (Dabigatran etexilate) or factor Xa (Rivaroxaban, Apixaban, and Edoxaban), have quick onset of effect and minimal food and drug interactions, and are administered orally once or twice daily (table 2.3) without laboratory monitoring of the anticoagulant effect and without dose adjustment to blood coagulation tests as opposed to VKA[65]. I identified 7 publications that compared DOACs to standard anticoagulant treatment (UFH/LMWH and VKA), with a systematic search through Google and PubMed using terms related to direct/new anticoagulants (with their specific names), "venous thromboembolism" or "vein thrombosis"/"pulmonary embolism", and "randomised controlled

trials". I did not include RCTs concerning extended treatment or "secondary prevention" (i.e. after the "active treatment" phase) because these are beyond the focus of this thesis on immediate care, but these do deserve attention by clinicians. The characteristics of the RCTs are displayed in table 2.4, and comparative effects of both types of treatment for different outcomes are shown in table 2.5.

In a systematic review of RCTs[66], DOACs and VKAs had similar efficacy in terms of VTE events in the treatment of acute symptomatic VTE. The non-inferior efficacy of the DOACs was consistent across subgroups (PE, DVT, a body weight ≥100 kg, moderate renal insufficiency, an age ≥75 years, and cancer) with possibly superior efficacy in the elderly and in cancer patients[66 67]. Treatment with a DOAC significantly reduces the risks of major bleeding as well as reducing clinically relevant non-major bleeding, intracranial bleeding and fatal bleeding but not gastrointestinal bleeding. This safety advantage of reduced major bleeding was consistent across the subgroups, except possibly in cancer patients[66 67].

A systematic review and indirect comparison in a network meta-analysis[68] has examined eight anticoagulation options for the treatment of acute VTE: UFH, LMWH or Fondaparinux with VKA; LMWH with Dabigatran or Edoxaban; Rivaroxaban, Apixaban and LMWH alone. There were no statistically significant differences in efficacy and safety for most treatment strategies compared with the LMWH–VKA combination, but the UFH–VKA combination was the least effective strategy, and Rivaroxaban and Apixaban were associated with the lowest risk for bleeding.

A more recent systematic review, which used both standard and network meta-analyses[69] and included cost-effectiveness analysis using discrete-time Markov models, found little evidence that DOACs offer an efficacy advantage over warfarin for acute treatment and secondary prevention of VTE. However, the risk of bleeding complications was lower for some DOACs than for warfarin. The phase III trials and those testing treatment of acute VTE were generally judged to be at low risk of bias for generation of the randomisation sequence, allocation concealment, blinding of

outcome assessment, blinding of participants and personnel (except for EINSTEIN DVT and PE studies which were open label studies), selective reporting, and completeness of data analysed. Although in all studies that assessed DOACs for the treatment of acute VTE, the comparator was the same (LMWH and VKA), it is difficult to draw any conclusion about the superiority of any DOAC over the others because of the lack of direct head-to-head comparison trials, and differences between studies in the population included (proportion of patients with PE, severity of PE, proportion of cancer patients, proportion of patients with a history of VTE, creatinine clearance, etc), outcomes used to assess efficacy and safety, treatment duration and follow-up, and the statistical analysis used (non-inferiority margin). The mean time (%) in therapeutic range (INR) in patients treated by Warfarin was similar across the studies and varied between 56.9% and 63.5%. No differences were found between DOACs for symptomatic VTE, PE, DVT or major CRNMB bleeding in the network meta-analysis.

In patients with acute VTE and no haemodynamic compromise, DOACs are equivalent in efficacy to LMWH-VKA treatment and improve patient safety outcomes. Intravenous UFH will still be indicated in patients who have an unstable haemodynamic status, who are at high-risk of bleeding, who have a creatinine clearance < 30 ml/min, or who have an extreme body weight (over-weight or under-weight). LMWH is mainly indicated in cancer-associated VTE (no direct comparison with DOACs) and in pregnancy (contra-indications for the use of DOACs). DOACs may be preferable to LMWH-VKA standard treatment for outpatient management because anticoagulant treatment is simplified as there is no bridging and no monitoring with DOACs.

Table 2.3: Anticoagulants in use and dose administration.

Anticoagulant	**Dose administration**
Unfractionated heparin **Intravenous infusion** (dose-adjusted to APTT and anti-Xa activity) **Subcutaneous injections (e**ither fixed dose or dose adjusted to APTT and anti-Xa activity)	 Bolus 80 U/kg then infusion 18U/kg/h Bolus 333 U/kg then 250 U/kg bid
Low molecular weight heaprin - Subcutaneous injections - Body-weight adjusted **<u>2 injections/ day</u>** Enoxaparin (Lovenox®) Nadroparin (Fraxiparine®) Dalteparin (Fragmine®) **<u>1 injection/ day</u>** Tinzaparin (Innohep®) Nadroparin (Fraxodi®) Daltéparin (Fragmine®)	 100 U/kg bid 85 U/kg bid 100 U/kg bid 175 U/kg qd [(1)] 170 U/kg qd 200 U/kg qd (1 month) then 150 U/kg qd [(2)]
Indirect inhibitor of factor Xa - 1 subcutaneous injection/ day Fondaparinux (Arixtra®)	 < 50 kg : 5 mg qd 50 – 100 kg : 7.5 mg qd > 100 Kg : 10 mg qd
Vitamin K antagonist dose-adjusted to INR Warfarin (Coumadine®) Acenocoumarol (Sintrom® and Minisintrom®) Fluindione (Previscan®)	INR target : 2-3
Direct oral anticoagulant - direct inhibitor of factor Xa Rivaroxaban (Xarelto®)	 15 mg bid x 21days, then 20 mg qd

Apixaban (Eliquis®) Edoxaban (Lixinia®)	10 mg bid x 7 days, then 5 mg bid [3] 60 mg qd (or 30 mg qd if Cockcroft 30 – 50 ml/min, body weight < 60 kg or P-gp inhibitor) after 5 days of UFH/ LMWH
Direct oral anticoagulant - direct inhibitor of factor IIa Dabigatran Etexilate (Pradaxa®) [4]	150 mg bid after 5days of UFH/ LMWH

APTT: activated partial thromboplastin time, INR: international normalized ratio. [1] Dose for patients with DVT/ PE with or without associated cancer. [2] Dose for patients with DVT/ PE with associated cancer. [3] Apixaban 2.5 mg bid for extended treatment beyond 3 – 6 months. [4] No marketing authorisation application for DVT/ PE. Precaution of use is not shown. All anticoagulants are contra-indicated if creatinine clearance is < 30 ml/ min except unfractionated heparin and vitamin K antagonists.

Table 2.4: Study design and characteristics of randomised controlled trials that compared direct oral anticoagulants to standard anticoagulant treatments during the first 3-12 months in patients with venous thromboembolism

Study (year)	Study design N patients	Population	DOAC treatment	Control treatment	Treatment duration	Efficacy outcome	Safety outcome
EISTEIN-DVT (2010) [70 71]	Open-label n= 3449	Symptomatic DVT	Rivaroxaban 15 mg bid during 21 days then 20 mg qd	Enoxaparin 1mg/Kg/12h – Warfarin	3, 6, 12 months	DVT, Non-fatal PE or Fatal PE	Major bleeding or CRNMB
EINSTEIN-PE (2012) [71 72]	Open-label n= 4832	Symptomatic PE	Rivaroxaban 15 mg bid during 21 days then 20 mg qd	Enoxaparin 1mg/Kg/12h - Warfarin	3, 6, 12 months	DVT, Non-fatal PE or Fatal PE	Major bleeding or CRNMB
AMPLIFY (2013)[73]	Double-blind, double-dummy n= 5395	Symptomatic DVT/PE	Apixaban 10 mg bid during 7 days then 5 mg bid	Enoxaparin 1mg/Kg/12h - Warfarin	6 months	DVT, Non-fatal PE or Fatal PE	Major bleeding
HOKUSAI-VTE (2013)[74]	Double-blind, double-dummy n= 8240	Symptomatic DVT/PE	UFH or LMWH ≥ 5 days then Edoxaban 60 mg od (30 mg od if ClCr 30-50 ml/mn, weight <60Kg or if P-Gp inhibitors)	UFH or LMWH + Warfarin	3 – 12 months	DVT, Non-fatal PE or Fatal PE	Major bleeding or CRNMB
RE-COVER and RE-COVER II (2014) [75 76]	Double-blind, double-dummy n= 5107	Symptomatic DVT/PE	UFH or LMWH ≥ 5 days then Dabigatran 150 mg bid	UFH or LMWH + Warfarin	6 months	DVT, Non-fatal PE or Fatal PE	Major bleeding

Table 2.5: Results from randomised controlled trials that compared direct oral anticoagulants to standard anticoagulant treatments during the first 3-12 months in patients with venous thromboembolism.

Study (year)	Treatment	VTE recurrence (including fatal PE) (%)	Fatal PE (%)	Major bleeding (including fatal bleeding) (%)	Major bleeding and CRNMB (%)	Intra-cranioal bleeding (%)	Gastro-intestinal bleeding (%)	Fatal bleeding (%)
EINSTEIN-DVT	Rivaroxaban	36/1731 (2.1)	1/1731 (<0.1)	14/1718 (0.8)	139/1718 (8.1)	2/1718 (0.1)	2/1718 (0.1)	1/1718 (<0.1)
(2010) [70 71]	Enoxaparin Warfarin	51/1718 (3.0)	0/1718	20/1711 (1.2)	138/1711 (8.1)	2/1711 (0.1)	0/1711	5/1711 (0.3)
EINSTEIN-PE	Rivaroxaban	50/2419 (2.1)	2/2419 (<0.1)	26/2412 (1.1)	249/2412 (10.3)	3/2412 (0.1)	0/2412	2/2412 (<0.1)
(2012)[71 72]	Enoxaparin Warfarin	44/2413 (1.8)	1/2413 (<0.1)	52/2405 (2.2)	274/2405 (11.4)	11/2405 (0.4)	0/2405	3/2405 (0.1)
AMPLIFY	Apixaban	59/2691 (2.3)	1/2691 (<0.1)	15/2676 (0.6)	115/2676 (4.3)	3/2676 (0.1)	7/2676 (0.3)	1/2676 (<0.1)
(2013)[73]	Enoxaparin Warfarin	71/2704 (2.7)	2/2704 (0.1)	49/2689 (1.8)	261/2689 (9.7)	6/2689 (0.2)	18/2689 (0.7)	2/2689 (0.1)
HOKUSAI-VTE	UFH/LMWH - Edoxaban	130/4118 (3.2)	4/4118 (0.1)	56/4118 (1.4)	349/4118 (8.5)	5/4118 (0.1)	1/4118 (<0.1)	2/4118 (<0.1)
(2013)[74]	UFH/LMWH + Warfarin	146/4122 (3.5)	3/4122 (0.1)	66/4122 (1.6)	423/4122 (10.3)	18/4122 (0.4)	2/4122 (<0.1)	10/4122 (0.2)
RE-COVER and	UFH/LMWH - Dabigatran	60/2553 (2.4)	2/2553 (<0.1)	37/2553 (1.4)	136/2553 (5.3)	2/2553 (<0.1)	48/2553 (1.9)	Not reported
RE-COVER II	UFH/LMWH + Warfarin	55/2554 (2.2)	3/2554 (0.1)	51/2554 (2.0)	217/2554 (8.5)	5/2554 (0.2)	33/2554 (1.3)	Not reported
(2014)[75 76]								

CRNMB: clinically relevant non-major bleeding.

Thrombolytic therapy

Thrombolytic therapy has the advantage of rapidly restoring pulmonary perfusion and improving patient's haemodynamic status but has the disadvantage of increasing bleeding risk[77-81]. Thrombolytic therapy is used in unstable PE but there is debate about its effectiveness in normotensive PE patients[82 83].

In patients with acute PE and unstable haemodynamic status (systolic BP <90 mm Hg), the 2014 ESC guidelines[1] and the American College of Chest Physicians (ACCP) 9th edition update guidelines (2016 ACCP) suggest that the clinical benefit outweighs the risk of bleeding and systemic thrombolytic therapy for patients who do not have a high bleeding risk[5]. According to the 2014 ESC guidelines, "most contra-indications to thrombolysis should be considered relative in patients with life-threatening, high-risk (unstable) PE[1]".

In patients with acute PE and stable haemodynamic status, there is still debate about the role of thrombolytic therapy. As most RCTs of thrombolytic therapy versus heparin did not select stable PE patients according to their risk profile, it is likely that most of the included patients were at low-risk[84] (and not only intermediate-risk). This may explain the lack of significant differences between thrombolytic therapy and heparin in death or for the composite outcome of death or recurrent PE in large-scale meta-analyses[78 81]. In the PEITHO study[85] that randomized 1,006 normotensive PE patients at "intermediate-high-risk" (i.e. with CT/TTE-based right-ventricular dysfunction and myocardial injury) to receive a fibrinolytic (Tenecteplase) or placebo, death or hemodynamic decompensation occurred in 13/506 patients (2.6%) in the tenecteplase group compared with 28/499 (5.6%) in the placebo group (OR, 0.44; 95% CI, 0.23–0.87; P = 0.02). Fibrinolytic therapy did not prevent in-hospital death (1.2% versus 1.8%) and increased the risk of major bleeding significantly (11.5% versus 2.4%) and increased stroke (2.4% versus 0.2%). In a meta-analysis that compared thrombolytic therapy with heparin in patients with intermediate-risk PE[86] thrombolytic therapy was associated with a non-significant reduction in overall mortality (OR:

0.42; 95% CI, 0.17–1.03), a significant reduction in PE-related death (OR: 0.17; 95% CI, 0.05–0.67), a non-significant reduction in PE recurrence (OR: 0.25; 95% CI, 0.06–1.03), but a significant increase in major bleeding (OR: 2.91; 95% CI: 1.95–4.36), and fatal or intracranial hemorrhage (OR: 3.18; 95% CI: 1.25– 8.11). Because the risk of major bleeding may outweigh the clinical benefit in intermediate-risk PE patients, both the 2014 ESC[1] and the 2016 ACCP[5] guidelines suggest systemic thrombolytic therapy in selected patients with acute PE who deteriorate after starting anticoagulant therapy and who have a low bleeding risk. To improve safety while maintaining efficacy, reduced doses of thrombolytic therapy[87-89] and catheter-directed treatment[90-93] have seemed promising in small and single-arm studies but still need to be assessed in large RCTs.

Surgical embolectomy and endovascular treatment

The 2016 ACCP guidelines[5] suggest catheter-assisted thrombus removal (mechanical interventions with or without catheter directed thrombolysis) "in patients with acute PE associated with hypotension and who have a high bleeding risk, failed systemic thrombolysis, or shock that is likely to cause death before systemic thrombolysis can take effect (within hours), if appropriate expertise and resources are available". The same recommendations are made by the 2014 ESC guidelines[1] for surgical pulmonary embolectomy, and as an alternative percutaneous catheter-directed treatment if thrombolysis is contra-indicated (high bleeding risk) or has failed.

Inferior vena cava filter insertion

Early and late complications related to IVC filters restrain the indication for their placement. In the "Prevention du Risque d'Embolie Pulmonaire par Interruption Cave" (PREPIC) randomised trial[94 95], a permanent inferior vena cava (IVC) filter reduced PE but increased DVT and post-thrombotic syndrome and did not influence mortality. In the PREPIC-2 randomised trial[96] including PE patients with at least one prognostic factor, an IVC filter for 3 months did not reduce recurrent PE, including fatal PE. The recommended indication[1 5] is absolute contra-indication to anticoagulant

treatment i.e. a high-risk of bleeding if patient is given an anticoagulant, together with a high-risk of VTE events related to PE or proximal DVT. Anticoagulant should be resumed as soon as the risk of bleeding is resolved.

Trends in the management and outcomes

Changes in the management of patients with VTE during the last decade may have an impact on medical and economic outcomes.

For example, in the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) large international register that included 23,858 patients with PE[97], trends in improvements in the initial treatment of PE (i.e. decrease in the use of UFH, increase in the use of LMWH, and in the use of thrombolysis and surgical embolectomy) were observed and were accompanied by significant reductions in length of hospital stay, as well as short-term all-cause and PE-specific mortality. The population-based Worcester VTE Study[98] also observed changes in VTE management and improved long-term outcomes, although rates of adverse events remained fairly high, implying the lack of prognostic assessment tools over the long term according to the study authors.

Economic evaluation

There is a need to assess how prognosis assessment and recent changes in management related to the use of DOACs, percutaneous catheter-directed treatment and other treatments impact on short- and long-term clinical outcomes, length of hospital stay, patient satisfaction and cost. Regarding DOAC impact, using a single-drug regimen (rivaroxaban) may reduce the VTE treatment burden for patients and healthcare systems[99]. Economic evaluations show cost savings ($3419) from reduction in length of hospital stay (median reduction 1 day, mean reduction 1.6 days) with rivaroxaban in hospitalized North American VTE patients[100]. Based on a Markov model and transition probabilities from EINSTEIN trials (and a 3-month cycle length, USA payer perspective

($2012), 5-year time horizon and a 3% annual discount), treatment with rivaroxaban was a dominant strategy compared to enoxaparin-VKA and resulted in lower cost, more QALYS (Quality-adjusted-life-years) gained in sensitivity analysis, reduction in hospitalised days related to VTE and bleeding, and shorter hospital stay[101]. The economic implications are important as "the reduction in inpatient utilization, recurrences, and major bleeding resulting from a 25% shift from standard therapy to rivaroxaban following acute VTE would conserve $860,475 for every 1 million commercial health plan enrolees[102]."

REVIEW ON PROGNOSIS

Strategies to help predict a patient's outcome and to influence decisions about her/his management are essential in acute PE. Several prognostic tools have been suggested which use either individual prognostic markers or prognostic models (clinical prediction models without and with individual markers). Decision makers might also use clinical variables (for example, with a hospital checklist including prognostic, medical and social variables for hospitalisation or outpatient management) or physician's clinical judgment (so-called gestalt).

Population event rate

Population event rates for adverse outcomes depend on type of study, patient selection and recruitment (patient care pathway, geographic area, referral, setting, ascertainment strategy), eligibility criteria, diagnostic strategy for PE, patient typology and risk profile, type of treatment and management, duration of follow-up, type and methods of assessment of outcomes.

Before assessing prognosis, the diagnosis of PE must be confirmed using validated strategies. As noted above, methods for confirming the diagnosis are different in case of hypotension or shock, and diagnosis work-up and treatment are conducted simultaneously in this situation. When

comparing studies, the date of publication can also be a guide to differences between their results. In older studies, more invasive diagnostic methods were used resulting in a lack of diagnosis work-up completion and a high selection of patients in more serious conditions which, in combination with less effective treatments at that time, may have resulted in higher mortality rates.

The management that is used for the patient, such as their clinical pathway, local healthcare system and treatment, may also influence the outcome and bias findings about prognosis. Furthermore, because results are not consistent across studies even when they share the same characteristics, I assess population event rates more precisely in my systematic review (chapter 4) and case-ascertainment study (chapter 7).

In the following sections, I present my reviews of the evidence on the assessment of a patient's risk profile by individual prognostic markers, clinical judgment, hospital checklists and prognostic models.

Systematic review of systematic reviews of individual prognostic markers of right ventricular dysfunction or ischemia and thrombus burden

Short term prognosis in acute PE has been reported to depend on haemodynamic status, and underlying diseases including clinical context and co-morbidities. Several individual prognostic markers have been reported and are displayed in table 2.6. To be consistent with other publications[103], they may be classified as follows:

- clinical markers including demographic, comorbidities and haemodynamic status (vital signs) variables
- RVD strain assessed by echocardiography (TTE-RVD),
- CT angiography (CT-RVD), and serum biomarkers: brain natriuretic peptide (BNP) or N-terminal–proBNP (NT-proBNP),

- myocardial injury assessed by cardiac troponins (cTnI, cTnT, hs-cTnt, hs-cTnI) and heart-type fatty acid-binding protein (H-FABP)
- clot burden and hypercoagulable status (imaging studies, US-DVT, D-dimer)
- other serum biomarkers (sodium levels as a marker of neuro-hormonal activation, creatinine and glomerular filtration rate, serum lactate, white blood cell count, reduced circulating haptoglobin).
- Many of these markers may be helpful and are simple and easy to obtain in routine clinical practice. Some are already used for diagnosis and available on admission. But, uncertainties remain about the accuracy of these markers for predicting a specific outcome and the strength of association with short-term adverse events. It is also important to know if results are consistent across studies and systematic reviews, and the limitations of the markers.

Table 2.6: Main variables used to assess prognosis in patients with acute pulmonary embolism

Variable group	**Variables**
Demographic variables	Age, Sex
Clinical context and co-morbidities	Provoked VTE (cancer excluded) or unprovoked VTE episode Cancer Previous episode of VTE Heart failure (History of Heart failure) Chronic lung disease (History of COPD) Cerebrovascular disease Chronic renal failure
Vital signs	Temperature Heart rate Systolic Blood Pressure Respiratory rate Arterial oxygen saturation on room air (arterial blood gas analysis or pulse oximetry) Consciousness and altered mental status
Biological markers	Troponin (cTnI, cTnT, hs-cTnT, hs-cTnI), Brain Natriuretic Peptide (BNP/ N terminal-ProBNP), Heart-type Fatty Acid-Binding Protein (H-FABP), D-dimer and other coagulation parameters
Cardiovascular imaging testing	Venography/ Venous Ultrasound (proximal or distal, superficial or deep vein thrombosis) Echocardiography (right ventricular dysfunction, pulmonary arterial hypertension, right heart cavity thrombi) CT scan (thrombus burden, thrombus location and right ventricular dysfunction)
Other factors	ECG, Chest X ray Contraindication to anticoagulation therapy (active or recent bleeding, recent surgery, bleeding diathesis, recent neurologic event, platelet count < 100 000, associated antithrombotic or thrombolytic therapy). Creatinine clearance or glomerular filtration rate (GFR) (≥ 60 ml/ mn, 30 – 59 ml/ mn, < 30 ml/ mn) Sodium levels, White blood cell count Serum lactate Circulating haptoglobin Growth differentiation factor-15 (GDF-15) Copeptin

Methods

I performed a systematic review of systematic reviews to assess the prognostic value of RVD/ischemia and thrombus burden assessed by imaging and biomarkers, in keeping with the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement[104 105], and using methodology for a systematic review of systematic reviews of healthcare interventions reported by Smith et al [106].

Box 2.1 shows the search terms used and their combinations in databases. In general, I used "Pulmonary embolism" AND ("Systematic review" OR "Meta-analysis") in titles for PubMed, Ovid MEDLINE (not displayed) and Embase, in Title OR Abstract for PubMed, and in "Title, Abstract, Key-words" for all databases in the Cochrane Library. Searches were done from inception of the relevant source to January and March 2016. Additional searches were done by combining pulmonary embolism and each dedicated prognostic marker term in PubMed and Google Scholar, and by examining references in publications. I searched for "grey" and unpublished literature through conference abstracts in the meetings of the ESC and the ISTH (International Society on Thrombosis and Haemostasis).

Publications were selected if they were systematic reviews that included studies that assessed either "stable only" PE or "both unstable and stable PE", assessed a single prognostic indicator (whether this was a biomarker-based or imaging-based RVD/ischemia or thrombus burden) and provided results on clinical outcomes (i.e. all-cause mortality, PE-related mortality and serious "adverse events" or "adverse outcomes") within the first three months. "Adverse outcome" events were defined as a composite of death, recurrent pulmonary embolism or clinical deterioration requiring an escalation therapy[82] (need for rescue thrombolysis, endotracheal intubation, catecholamine infusion, cardiopulmonary resuscitation, emergency surgical embolectomy or catheter-directed thrombus removal). Reviews reporting on surrogate outcomes such as other RVD prognostic markers (i.e. CT-RVD or TTE-RVD) without clinical outcomes were

not included. Reviews not related to biomarker-based or imaging-based RVD/ischemia and thrombus burden were excluded. Study selection was not restricted to English language publications.

Two independent reviewers identified publications through titles and abstracts, then through full text articles when needed. Two independent reviewers also extracted data on review characteristics, quality and results (tables 7-10). Disagreements were resolved by discussion. Quality was assessed using AMSTAR [107-109] (http://amstar.ca/Amstar_Checklist.php), which is an 11-item measurement tool to assess the methodological quality of systematic reviews.

In order to compare the findings of the systematic reviews, we extracted the summary results for the proportion of patients in risk groups (efficiency) and event rates in risk groups (i.e. failure rate in low-risk group), the summary results of measures of classification (sensitivity, specificity) and measures of associations (odds ratio).

Results

The flow chart of search results is displayed in figure 2.1. Details on selection strategy and included publications are provided in table 2.7. In the Cochrane Library, the search of all databases led to 703 hits, but the search results for DARE (Database of Abstracts of Reviews of Effect) alone are presented because publications related to the topic were found only in this database in the Cochrane Library (figure 2.1). The search used "Title, Abstract, Key-words" in DARE, PubMed and Embase (figure 2.1). Search results from Ovid MEDLINE (n= 116 hits) are not presented as they provided the same results as PubMed.

Finally, 21 publications were included in the analysis: 18 identified from the titles (20 from titles or abstracts) in both PubMed and Embase, 11 identified in Cochrane and one found by the supplementary search only (figure 2.1 and table 2.7 with referenced publications for included and excluded publications).

Table 2.8 shows the conclusions of our *assessment of review quality*, with most reviews being of high quality.

The characteristics of each systematic review and their main conclusions (according to the original authors) are reported in table 2.9. Among 21 included systematic reviews (Table 2.9), 14 assessed studies that combined all (both stable and unstable) PE[110-123] and 15 assessed studies that reported separately on stable only PE[110 111 116-119 121 123-130] (7 reviews[124-130] reported only on stable only PE). For clarity, all terms in table 2.9 are presented and defined as reported in the original systematic reviews. A single term may express different outcomes and time-points (e.g. short-term) in the systematic reviews, and different terms may have been used for the same outcome (serious adverse events, adverse outcome events, adverse clinical events, PE-related complications or complicated clinical course). All RVD-related prognostic factors that were assessed (biomarkers, TTE-RVD, CT-RVD, D-dimer and DVT) show an association with the outcome events and seem to be useful for the management of patients identified as low-risk. However, because of the low prediction performance, the heterogeneity of the studies included in the systematic reviews, and the absence of studies of impact, they are suggested as potential additional tools to be combined with either other prognostic factors or with clinical prediction rules. For clinically stable patients identified as high-risk, it is difficult to rely on these single prognostic markers for selecting candidates for thrombolytic therapy or other aggressive therapies because they provide a low positive predictive value, due to the low specificity of the prognostic markers and the low prevalence (i.e. event rate in the whole population sample). The positive predictive value might be increased by combining them with other prognostic factors or prediction models. Among all biomarkers, H-FABP[114-116 126] and hs-cTnT[125] are presented in the most recent reviews as the most promising. There is a small association between TTE-RVD[127] or CT-RVD[120-122 128] and short-term all-cause and PE-related mortality, and adverse outcomes in hemodynamically stable patients with acute PE. Across all quantitative and qualitative parameters of CT severity that were assessed[120-122 128], the RV/LV diameter ratio on transverse CT sections has the strongest predictive value for

adverse clinical outcomes[122]. Lower extremity DVT[123] and D-dimer[118] levels were significantly associated with an increased risk of short-term mortality and both are potentially useful as a diagnostic as well as a prognostic tool.

Study characteristics of reviews and summary results from the meta-analyses are reported in table 2.10 for reviews combining "all PE" (stable and unstable PE) results and in table 2.11 for reviews assessing "stable only" PE.

In systematic reviews reporting on "all PE" results (table 2.10), none of the biomarkers (cTn, BNP, NT-proBNP, H-FABP, D-dimer), or markers for imaging-based RVD (TTE, CT) or thrombus burden (CT, US-DVT) consistently showed a low 30-day (or early) all-cause mortality in the low-risk group. The lowest reported 30-day all-cause mortality for a single marker in the low-risk groups was obtained with H-FABP (0.30%) in one review[115]. Although, a summary event rate was not available for hs-cTn, summary sensitivity was not high (92%, 95% CI 81 to 98). In the high-risk groups, all biomarkers were highly predictive for all-cause death (>10-15%), PE-related death (lower rates) and adverse outcomes (higher rates). The highest 30-day all-cause mortality rates were obtained with H-FABP (30-58%) and results were consistent across systematic reviews[114-116]. Results were less important (all-cause death <10%) for D-dimer, CT-RVD and for US-DVT. In a systematic review on TTE-RVD[119], no summary measure was reported because of heterogeneity among the included studies for the assessment criteria for RVD, patient characteristics and study quality.

In systematic reviews reporting on "stable only" PE results (table 2.11), none of the biomarkers consistently provided a low event-rate in the low-risk group when accounting for a sample size of more than 100, except BNP for in-hospital or short-term all-cause death (1.12% and 0.88%)[129 130]. These results have limited value because of moderate sample sizes. The lowest event rates were obtained with natriuretic peptides in general for short-term PE-death (0.2%)[126 130] and BNP for all-cause death (0.15%)[130]. In one review[128], CT-RVD using right to left ventricle ratio (RV/LV) criteria provided a 0.18% PE-death at the short-term. For the high-risk groups, results are inconsistent

across reviews. All-cause death rates with cTn were above 15% in some reviews[110 124] but lower (10.6%) in one review[125]. Natriuretic peptides provided various results for short-term all-cause death: 9.3%[126], 13.2%[130] (14.3% for NT-proBNP and 11.6% for BNP)[130], and so TTE-RVD[127 130] (< 15%), CT-RVD[121 128] (< 10%) and US-DVT(> 10%)[123].

In later chapters, I show how these systematic reviews may help to identify candidate markers to be used in addition to prognostic models in update studies (Chapters 4 and 5) and to design a study to assess the value of physician's clinical intuition (Chapter 8). This is because many of these prognostic factors are used in everyday clinical practice to help select patients who may be eligible for early discharge or complete outpatient management.

Box 2.1: Search terms used in databases and their combinations

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> (2016 March 25)
Search Strategy:
---
1 Pulmonary embolism.m_titl. (11923)
2 "Systematic review*".m_titl. (51263)
3 Meta-analysis.m_titl. (47462)
4 Metaanalysis.m_titl. (544)
5 2 or 3 or 4 (85049)
6 1 and 5 (116)

****

Database: PubMed
Present> (2016 March 25)
Search, Query, Items found
#12,"Search (#1 AND #9)",181
#11,"Search (#9 AND #10)",732
#10,"Search (#1 OR #2)",46226
#9,"Search ((#3 OR #4) OR (#5 OR #6) OR (#7 OR #8))",149647
#8,"Search Metaanalysis[Abstract]",41671
#7,"Search Metaanalysis[Title]",556
#6,"Search Meta-analysis[Abstract]",104981
#5,"Search Meta-analysis[Title]",49605
#4,"Search ""Systematic review*""[Abstract]",72534
#3,"Search ""Systematic review*""[Title]",51881
#2,"Search Pulmonary embolism[Abstract]",46226
#1,"Search Pulmonary embolism[Title]",12040

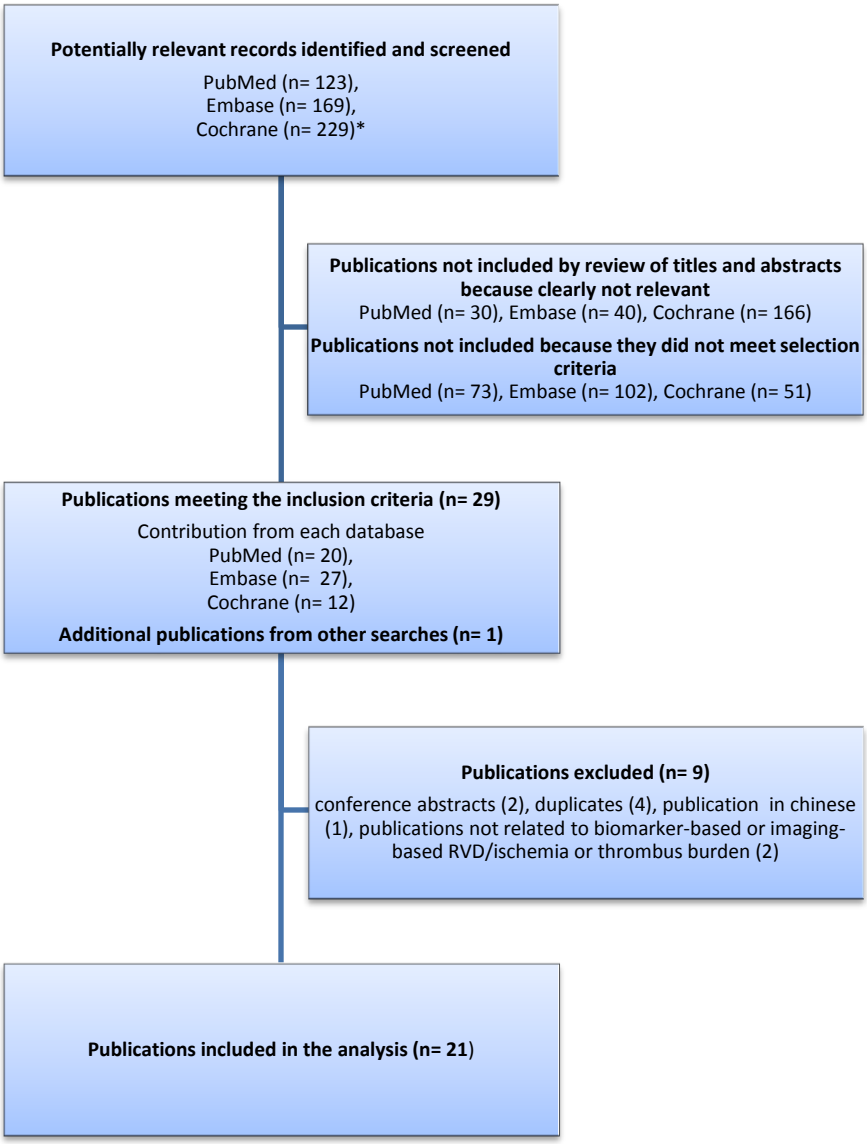
****

Database: Embase <1974 to 2016 March 25>
Search Strategy:
---
1 Pulmonary embolism.m_titl. (15604)
2 "Systematic review*".m_titl. (62722)
3 Meta-analysis.m_titl. (60536)
4 Metaanalysis.m_titl. (1264)
5 2 or 3 or 4 (106520)
6 1 and 5 (169)

****

Database: Cochrane since inception to 2016 January 16
Search strategy
#1: "Pulmonary Embolism" (2579)
#2: “Prognosis” (19935)
#3: Systematic Review (52754)
#4: "Meta Analysis as Topic" (662)
#5: #1 and #2 and (#3 or #4) (98)
#6: #1 and (#3 or #4) (703)

Figure 2.1: Flow-chart of search results



Search results displayed here were found in the "Title, Abstract, Key-words" with The Cochrane Library databases while they were found in the "Title" in PubMed and Embase databases which explains the difference in the number of hits. Only search results with DARE are presented* (see text).

Table 2.7: Search results for each database and other searches.

Systematic reviews	**Prognostic marker**	**PubMed**	**Embase**	**DARE***	**Only other searches**
Assessing all PE					
Becattini, Vedovati et al (2007)[110]	cTnT, cTnI, cTnT-cTnI	**yes**	**yes**	**yes**	
Cavallazzi, Nair et Al (2008)[111]	BNP, NT-proBNP	**yes**	**yes**	**yes**	
Coutance, Le Page et al (2008)[112]	BNP, NT-proBNP, NP	no	no	**yes**	
Klok, Mos et al (2008)[113]	BNP, NT-proBNP, NP	**yes**	**yes**	**yes**	
Lega, Lacasse et al (2009)[117]	BNP, NT-proBNP, NP, cTn-NP	**yes**	**yes**	**yes**	
Liu, Yuan et al (2014)[114]	H-FABP	**yes**	**yes**	no	
Ruan, He et al (2014)[115]	H-FABP	**yes**	**yes**	no	
Bajaj, Rathor et al (2015)[116]	H-FABP	**yes**	**yes**	no	
Becattini, Lignani et al (2012)[118]	D-dimer	no	no	**yes**	
ten Wolde, Sôhne et al (2004)[119]	TTE-RVD	no	no	no	**yes**
Vedovati, Germini et al (2013)[120]	CT location/obstruction	**yes**	**yes**	no	
Becattini, Agnelli et al (2014)[121]	CT-RVD	**yes**	**yes**	**yes**	
Meinel, Nance et al (2015)[122]	CT-RVD, location, load	**yes**	**yes**	no	
Becattini C, Cohen AT et al (2015)[123]	Venous US	**yes**	**yes**	no	
Assessing separately stable PE					
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI	yes	yes	yes	
Cavallazzi, Nair et Al (2008)[111]	BNP, NT-proBNP	yes	yes	yes	
Jiménez, Uresandi et al (2009)[124]	cTnT, cTnI, cTnT - cTnI	**yes**	**yes**	**yes**	
Lega, Lacasse et al (2009)[117]	NP, cTn-NP	yes	yes	yes	
Bajaj, Saleeb et al (2015)[125]	cTnT, cTnI, hs-cTn, cTnT-cTnI	**yes**	**yes**	no	
Bajaj, Rathor et al (2015)[126]	NP, H-FABP	**yes**	**yes**	no	
Bajaj, Rathor et al (2015)[116]	H-FABP	yes	yes	no	
Becattini, Lignani et al (2012)[118]	D-dimer	no	no	yes	
Sanchez, Trinquart et al (2008)[129]	TTE/CT-RVD, BNP, NT-proBNP, cTn	**yes**	**yes**	**yes**	
Coutance, Cauderlier et al (2011)[130]	TTE/CT-RVD, BNP, NT-proBNP, NP	**yes**	**yes**	**yes**	
Cho, Sridharan et al (2014)[127]	TTE-RVD	**yes**	**yes**	no	
Trujillo-Santos, Den Exter et al (2013)[128]	CT- RVD	**yes**	**yes**	**yes**	
Becattini, Agnelli et al (2014)[121]	CT- RVD	yes	yes	yes	
Publications excluded					
Conference abstracts (n=2)	Related to H-FABP[116] and US[123]	no	**yes**	no	
Duplicates (n= 4)	Related to CT (n= 3)[121 122] and TTE[127]	no	**yes**	no	
Tan, Zhao et al (2011)[131]	BNP, NT-proBNP	no	**yes**	**yes**	
Coleman, Brunault et al (2015)[132]	Week-end admission	**yes**	**yes**	no	
Shopp, Stewart et al (2015)[133]	12-lead electrocardiography	**yes**	**yes**	no	
Total before exclusion		**20**	**27**	**12**	**1**
Total after exclusion		**18**	**18**	**11**	**1**

Yes in bold character to be used to counting once articles that are reported twice on this table. *DARE is "Database of Abstracts of Reviews of Effect" ("Other Reviews") in the Cochrane Library. The total number of publications in the analysis (n=21) equates to the number of publications found with PubMed and Embase (18) + missed publications by both but found by Cochrane (2) or by other searches (1). Publications reporting both "all PE" and "separately stable PE" appear twice.

Table 2.8: Study quality assessment using AMSTAR. (Green= Yes, Red = No, Orange= Cannot answer and Grey= Not applicable)

AMSTAR Checklist	A priori' design provided?	Duplicate study selection and data extraction?	Comprehensive literature search performed?	Status of publication (i.e. grey literature) used as an inclusion criterion?	List of studies (included and excluded) provided?	Characteristics of the included studies provided?	Scientific quality of the included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest included?	Score
ten Wolde, Sôhne et al (2004)[115]												7
Becattini, Vedovati et al (2007)[106]												6
Cavallazzi, Nair et Al (2008)[107]												7
Coutance, Le Page et al (2008)[108]												8
Klok, Mos et al (2008)[109]												6
Sanchez, Trinquart et al (2008)[123]												11
Jiménez, Uresandi et al (2009)[120]												10
Lega, Lacasse et al (2009)[110]												10
Becattini, Lignani et al (2012)[114]												6
Trujillo-Santos, Den Exter et al (2013)[126]												9
Vedovati, Germini et al (2013)[116]												9

Becattini, Agnelli et al (2014)[117]												8
Cho, Sridharan et al (2014)[125]												6
Liu, Yuan et al (2014)[111]												8
Ruan, He et al (2014)[112]												6
Bajaj, Rathor et al (2015)[113]												8
Bajaj, Saleeb et al (2015)[121]												8
Bajaj, Rathor et al (2015)[122]												8
Becattini C, Cohen AT et al (2015)[119]												11
Coutance, Cauderlier et al (2011)[124]												9
Meinel, Nance et al (2015)[118]												9

Table 2.9: Study characteristic of the included systematic reviews and main conclusions by the original authors

Author (Year)	Population (in reviews)	Prognostic factor	Outcome	Time-point	Data sources	Date of search	N Studies included	Conclusions
cTN								
Becattini, Vedovati et al (2007)[110]	All PE Stable PE	cTnT - cTnI	All-cause mortality Adverse outcomes	In-hospital or short-term i.e. up to 90 days	MEDLINE, Embase and lists of articles and reviews	From January 1998 to November 2006	20	Elevated troponin levels identify patients with acute PE at high risk of short-term death and adverse outcome events. Elevated troponin levels were associated with a high mortality in the subgroup of hemodynamically stable patients. Results were consistent for troponin I or T and prospective or retrospective studies.
Jiménez, Uresandi et al (2009)[124]	Stable PE	cTnT - cTnI	All-cause mortality	In-hospital, 40-day and 3-month all combined	MEDLINE, Embase and a review of cited references	From 1980 through April 2008	9	Elevated troponin levels do not adequately discern normotensive patients with acute symptomatic PE who are at high risk for death from those who are at low risk for death. The prognostic value of troponin levels depends greatly on the cut-off points used. Troponin levels are likely to be most useful when used in combination with echocardiographic or CT scan evidence of right ventricular strain and with clinical prognostic scores
Bajaj, Saleeb et al (2015)[125]	Stable PE	cTnT - cTnI - hs-cTnT	All-cause mortality -	Short-term (in-hospital or	Pubmed, Embase and	Up to December	26	Elevated levels of troponin identify a subgroup of

			PE related mortality - Serious adverse events	30-day)	Cochrane, and references from previous trials, reviews, abstracts from annual meetings and web base	2014		patients with increased risk for short term mortality and serious adverse events. The results are not satisfactory enough to make any change in current clinical practice. More data is needed to define the role of hs-cTnT in acute PE.
NP								
Cavallazzi, Nair et al (2008)[111]	All PE Stable PE	BNP NT-proBNP	Diagnosis of RVD Prognostic factor of all-cause mortality	In-hospital or short-term i.e. up to 90 days	MEDLINE, Embase, and citation review of relevant primary and review articles	Not reported No restriction	16	BNP and NTproBNP are associated with the diagnosis of right ventricular dysfunction (RVD) in patients with an acute PE and are significant predictors of all-cause in-hospital or short term mortality in these patients
Coutance, Le Page et al (2008)[112]	All PE	BNP NT-proBNP	All-cause mortality Serious adverse events	Short-term: up to 90 days	PubMed, BioMed Central, and The Cochrane database and manual review of article bibliographies	Up to March 2008	12	Elevated BNP levels can help to identify patients with acute PE at high risk of death and adverse outcome events. The high negative predictive value of normal BNP levels is certainly more useful for clinicians to select patients with a likely uneventful follow-up.
Klok, Mos et al (2008)[113]	All PE	BNP or NT–pro-BNP	All-cause mortality - Composite outcome of adverse clinical events	Short-term: up to 6 months	MEDLINE, Embase and reference lists of all established studies	Between January 1980 and October 2007	13	High concentrations of BNP distinguish patients with PE at higher risk of complicated in-hospital course and death from those with low BNP levels. Increased BNP or NT–pro- BNP concentrations

								alone, however, do not justify more invasive treatment regimens.
H-FABP								
Liu, Yuan et al (2014)[114]	All PE	H-FABP	Adverse clinical outcomes	Short-term (< 30 days) Long-term (> 30 days up to 3 months)	PubMed, The Cochrane Library, Web of Science and Science Direct, and reference lists of retrieved articles	Up to 2013	6	H-FABP is a good predictor for adverse outcomes in patients with acute PE. The results should be cautiously interpreted and requires a combination of clinical features and other tests.
Ruan, He et al (2014)[115]	All PE	H-FABP	PE-related mortality or serious complications	Short-term (< 30 days)	PubMed, Ovid, and Embase	Up to January 2013	6	H-FABP is associated with an increased risk of mortality or complicated clinical events in patients with acute PE across different studies with a high degree of clinical and methodologic diversity.
Bajaj, Rathor et al (2015)[116]	All PE Stable PE	H-FABP	Complicated clinical course RVD	30-day	PubMed, EMBASE, Cochrane and references from previous trials, abstracts from annual meetings, and Web base	Up to June 2014	11	Elevated H-FABP levels are associated with increased risk of 30-day complicated clinical course, mortality, and RVD. Large scale randomised controlled trials are needed to evaluate the role of thrombolytics in patients with acute PE who have elevated H-FABP levels.
cTn, NP, H-FABP								
Lega, Lacasse et al (2009)[117]	All PE Stable PE	Natriuretic peptides alone or in conjunction	All-cause and PE-related mortality, SAE, TTE-RVD	Up to 1 year	MEDLINE and Embase and conference abstracts	Up to February 2008	23	Raised levels of B-type natriuretic peptides identified a subset of patients with acute PE at higher risk of

		with cTn						adverse outcomes. Among patients with raised natriuretic peptide levels, increased troponins were found to be an independent prognostic marker.
Bajaj, Rathor et al (2015)[126]	Stable PE	cTnT, cTnI, hs-cTnT BNP, NT-proBNP H-FABP	All-cause mortality - PE related mortality - Serious adverse events	Short-term (in-hospital or 30-day)	MEDLINE, Embase and Cochrane, and references from previous meta-analyses, reviews, abstracts from annual meetings and web base	Up to December 2014	38	Elevated levels of all three biomarkers are associated with increased risk for short-term mortality and serious adverse events. None of the biomarkers provide reliable evidence of satisfactory prognostic performance. H-FABP and hs-cTnT showed some promising results and should be investigated further.
D-dimer								
Becattini, Lignani et al (2012)[118]	All PE Stable PE	D-dimer	All-cause mortality - Currently accepted prognostic factors (clinical scores, right ventricular dysfunction and degree of pulmonary artery obstruction at CT scan)	Short-term (< 30 days) and 3-month	MEDLINE and Embase	Not reported Unrestricted	5 studies on short term mortality, 4 on 3-month mortality, 14 on the association between D-dimer and markers of PE severity	Elevated D-dimer is associated with increased short-term and 3-month mortality, suggesting the potential of using this test for both diagnosis and risk stratification. Further studies are needed to assess whether D-dimer, alone or combined with other prognostic tools for PE, may be useful to identify low-risk patients with PE who are potential candidates for outpatient treatment or an abbreviated hospital stay
TTE-RVD								

ten Wolde, Sôhne et al (2004)[119]	All PE Stable PE	TTE-RVD	All-cause mortality - Adverse outcomes - PE-related mortality (for stable PE)	"Short-term" (in-hospital or < 14 days) "Long-term" (≥ 3 months)	Ovid MEDLINE, Embase, PubMed, Cochrane, Web of Science and congress abstracts	Not reported	7	It remains unclear whether echocardiographic right ventricular dysfunction is a prevalent and reliable predictor of adverse outcomes in hemodynamically stable patients with acute PE.
Cho, Sridharan et al (2014)[127]	Stable PE	TTE-RVD	All-cause mortality (adverse clinical events excluded)	Short-term: in-hospital and 30-day (other time-points excluded)	PubMed	Between January 1st 1998 and December 31st 2011	12	In hemodynamically stable patients with acute PE, RVD as assessed by echocardiogram increases short-term mortality by 2.29 times. Consideration should be given to obtaining echocardiogram to identify high-risk patients even if they are hemodynamically stable.
CT-RVD								
Trujillo-Santos, Den Exter et al (2013)[128]	Stable PE	CT-RVD	All-cause mortality - PE-related mortality - PE-related complications	Short-term (from in-hospital to 3-month follow-up)	MEDLINE and Embase, and hand searching of cited bibliographies and investigator files	From 1980 to March 2013	10	Although RVD assessed by CT showed an association with an increased risk of mortality in patients with hemodynamically stable PE, it resulted in only small increases in the ability to classify risk. This suggests that basing therapeutic decision-making solely on CT results is not warranted
Vedovati, Germini et al (2013)[120]	All PE	CT-assessed embolic burden (embolic localisation	All-cause mortality	30-day and 3-month	MEDLINE, Embase and reference lists of retrieved articles and	Up to 30 June 2013	19 studies (5 for the embolic localisation, 16 for the	The localisation of emboli assessed at CT angiography is useful for risk stratification in patients with acute PE. However, a correlation

		and embolic obstruction)			review articles		obstruction index)	between obstruction index and prognosis was not observed.
Becattini, Agnelli et al (2014)[121]	All PE Stable PE	CT right ventricle dilation (right-to-left ventricle diameter) or dysfunction (inter-ventricular septal bowing)	All-cause mortality	30-day and 3-month	MEDLINE, Embase and reference lists of retrieved articles and review articles	Up to April 30, 2013	36	Right-to-left ventricle dilation as assessed by CT angiography can be used to evaluate risk of death in all-comers with pulmonary embolism and in haemodynamically stable patients.
Meinel, Nance et al (2015)[122]	All PE	CT severity quantitative & qualitative parameters (see legend)	All-cause mortality - Adverse outcomes - PE-related mortality	Short-term (≤ 6 months)	PubMed and Embase - Expert opinions - Reference lists of original studies and review articles	Up to February 2014	49	Across all end points, the RV/LV diameter ratio on transverse CT sections has the strongest predictive value and most robust evidence base for adverse clinical outcomes in patients with acute pulmonary embolism.
DVT								
Becattini C, Cohen AT et al (2015)[123]	All PE Stable PE	DVT	All-cause mortality (30-day) - PE-related adverse events (90-day) i.e. PE-related death or non-fatal venous thromboembolic recurrences.	30-day 90-day	PubMed, Embase, and cited bibliographies and investigator files	From 1980 through September 30, 2014	9 studies (10 cohorts)	In patients diagnosed with acute symptomatic PE, concomitant DVT was significantly associated with an increased risk of death within 30 days of PE diagnosis. Since clinical scores (eg, PESI, sPESI) may accurately identify patients at low risk of short-term death after the diagnosis of PE, future studies should assess if the combination of bilateral

								lower limb ultrasound testing (complete vs limited) with prognostic tools indicating myocardial injury or RV dysfunction (ie, cTn and TTE respectively) might offer advantages compared with each test alone regarding enhanced risk stratification of intermediate-risk patients with an objectively confirmed episode of acute symptomatic PE.
RVD/ TTE, CT, Biomarkers								
Sanchez, Trinquart et al (2008)[129]	Stable PE	RVD based on TTE, CT and biomarkers (cTnT, cTnI, hs-cTnT - BNP, NT-proBNP)	All-cause mortality	In-hospital, 40-day and 3-month (all combined)	MEDLINE, Embase and references of primary articles	Between January 1985 and October 2007	12	RV dysfunction assessed by CT, echocardiography, or by cardiac biomarkers are all associated with an increased risk of mortality in patients with haemodynamically stable PE. These findings should be interpreted with caution because of the clinical and methodological diversity of studies. Limitations of available studies preclude the use of these markers for selecting the appropriate candidates to thrombolytic therapy among clinically stable patients with PE.
Coutance, Cauderlier et al (2011)[130]	Stable PE	TTE-RVD, CT-RVD, BNP and NT-proBNP	All-cause mortality - PE-related mortality - Adverse	< 3 months	PubMed and The Cochrane databases, and references in	Up to December 2009	15 studies (8 for TTE-RVD, 3 for CT-RVD, 7 for NP-RVD)	The presence of echocardiographic RV dysfunction or elevated natriuretic peptides is associated with short-term

			outcomes		retrieved articles and reviews (and grey literature)			mortality in patients with pulmonary embolism without hemodynamic compromise. In contrast, the prognostic value of RV dilation on CT has yet to be validated in this population. As indicated both by positive and negative likelihood ratios the current prognostic value in clinical practice remains very limited (predictive performance too low).

cTn: cardiac troponin, hs-cTn: high-sensitivity cTn, NP: natriuretic peptides, BNP: B-type NP, NT-proBNP: N-terminal proBNP, H-FABP: heart-type fatty acid binding protein, DVT: deep vein thrombosis, CT: computerized tomography, TTE: transthoracic echocardiography, RVD: right ventricular dysfunction - Serious adverse events (SAEs), adverse outcome events, adverse clinical events, PE-related complications or complicated clinical course (= composite of death and any of the following adverse outcome events: shock, need for thrombolysis, nonfatal PE recurrence, cardiopulmonary resuscitation, mechanical ventilation, catecholamine administration, admission to the intensive care unit, and surgical embolectomy). CT severity quantitative & qualitative parameters: 1) quantitative parameters of right ventricular (RV) dysfunction (abnormally increased RV/left ventricular [LV] diameter ratio on transverse sections and 4-chamber views), 2) qualitative parameters of RV dysfunction (abnormal septal morphology and contrast reflux), thrombus load, and central thrombus location.

Table 2.10: Systematic reviews and meta-analyses that assessed study results on all PE (combined « Both Stable and Unstable" and "Stable" PE). Odds ratio as reported.

Author (year)	Prognostic Factor (Cut-off value)	Outcome (Time-point)	N Patients (N Studies)	Population Event rate (%)	Low-risk Proportion (%)	Low-risk Event rate (%)	High-risk Event rate (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	OR (95% CI)
Biomarkers										
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI (various)	Death (Short-term)	1985 (20)	173 **(8.71)**	1367 **(68.86)**	51/1367 **(3.7)**	122/618 **(19.7)**	NR	NR	OR: 5.24 (3.28 to 8.38)
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI (various)	Death (Short-term)	1527 (16)	105 **(6.88)**	1110 **(72.69)**	28/1110 **(2.52)**	77/417 **(18.47)**	NR	NR	OR: 6.33 (3.38 to 10.34)
Becattini, Vedovati et al (2007)[110]	cTnI (various)	Death (Short-term)	1303 (12)	108 **(8.29)**	895 **(68.69)**	37/895 **(4.13)**	71/408 **(17.4)**	NR	NR	OR: 4.01 (2.23 to 7.23)
Becattini, Vedovati et al (2007)[110]	cTnT (various)	Death (Short-term)	682 (8)	65 **(9.53)**	472 **(69.21)**	14/472 **(2.97)**	51/210 **(24.28)**	NR	NR	OR: 7.95 (3.79 to 16.65)
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI (various)	PE-death (Short-term)	645 (8)	40 **(6.20)**	438 **(67.90)**	6/438 **(1.37)**	34/207 **(16.43)**	NR	NR	OR: 9.44 (4.14 to 21.49)
Becattini, Vedovati et al (2007)[110]	cTnI (various)	PE-death (Short-term)	153 (3)	9 **(5.88)**	91 **(59.48)**	1/91 **(1.09)**	8/62 **(12.9)**	NR	NR	OR: 7.11 (1.17 to 43.37)
Becattini, Vedovati et al (2007)[110]	cTnT (various)	PE-death (Short-term)	492 (5)	31 **(6.30)**	347 **(70.52)**	5/347 **(1.44)**	26/145 **(17.93)**	NR	NR	OR: 10.16 (4.03 to 25.60)
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI (various)	AO (Short-term)	530 (9)	139 **(26.23)**	319 **(60.19)**	47/319 **(14.7)**	92/211 **(43.6)**	NR	NR	OR: 7.03 (2.42 to 20.43)
Becattini, Vedovati et al (2007)[110]	cTnI (various)	AO (Short-term)	191 (4)	44 **(23.03)**	111 **(58.12)**	7/111 **(6.31)**	37/80 **(46.25)**	NR	NR	OR: 13.43 (4.87 to 37.05)
Becattini, Vedovati et al (2007)[110]	cTnT (various)	AO (Short-term)	339 (5)	95 **(28.02)**	208 **(61.36)**	40/208 **(23.08)**	55/131 **(41.98)**	NR	NR	OR: 4.97 (1.17 to 21.03)

Cavallazzi, Nair et al (2008)[111]	BNP (100pg/mL)	Death (In-hospital)	196 (4)	11 **(5.61)**	76 **(38.77)**	0/76 **(0)**	11/120 **(9.17)**	NR	NR	OR: 6 (1.31 to 27.43)
Cavallazzi, Nair et al (2008)[111]	BNP (75 - 100pg/mL)	Death (In-hospital x2 & 3-month)	225 (3)	18 **(8.0)**	140 **(62.22)**	4/140 **(2.86)**	14/ 85 **(16.47)**	NR	NR	OR: 7.63 (2.08 to 28.07)
Cavallazzi, Nair et al (2008)[111]	BNP (90 pg/mL)	Death (In-hospital)	115 (2)	7 **(6.09)**	66 **(57.39)**	2/66 **(3.03)**	5/49 **(10.20)**	NR	NR	OR: 3.61 (0.67 to 19.52)
Cavallazzi, Nair et al (2008)[111]	NT-proBNP (1,000 ng/L)	Death (30-day)	231 (2)	18 **(7.79)**	111 **(48.05)**	2/111 **(1.8)**	16/120 **(13.33)**	NR	NR	OR: 7.34 (1.85 to 29.03)
Cavallazzi, Nair et al (2008)[111]	NT-proBNP (500 ng/L)	Death (In-hospital)	73 (1)	5 **(6.85)**	31 **(42.46)**	0/31 **(0)**	5/42 **(11.90)**	NR	NR	NR
Coutance, Le Page et al (2008)[112]	NP (various)	Death (< 3 months)	868 (12)	73 **(8.41)**	386 **(44.47)**	5/386 **(1.29)**	68/482 **(14.11)**	93 (85 to 98)	48 (44 to 51)	OR: 6.57 (3.11 to 13.91)
Coutance, Le Page et al (2008)[112]	BNP (various)	Death (< 3 months)	NR	NR	NR	NR	NR	NR	NR	OR: 5.06 (2.02 to 12.65)
Coutance, Le Page et al (2008)[112]	NT-proBNP (various)	Death (< 3 months)	NR	NR	NR	NR	NR	NR	NR	OR:11.15 (3.03 to 40.97)
Coutance, Le Page et al (2008)[112]	NP (various)	PE-death (< 3 months)	684 (10)	51 **(7.45)**	331 **(48.39)**	4/331 **(1.2)**	47/353 **(13.31)**	92 (81 to 98)	52 (48 to 56)	OR: 6.10 (2.58 to 14.25)
Coutance, Le Page et al (2008)[112]	NP (various)	AO (< 3 months)	688 (9)	155 **(22.53)**	273 **(39.68)**	17/273 **(6.2)**	138 /415 **(33.2)**	89 (83 to 93)	48 (44 to 52)	OR 7.47 (4.20 to 13.15)
Klok, Mos et al (2008)[113]	BNP (various)	Death (In-hospital: 3 - 3-month: 1)	261 (4)	20 **(7.66)**	138 **(52.87)**	3/138 **(2.17)**	17/123 **(13.8)**	NR	NR	OR: 6.52 (2.04 to 20.86)
Klok, Mos et al (2008)[113]	BNP (various)	Death (In-hospital)	151 (3)	9 **(5.96)**	64 **(42.38)**	1/64 **(1.56)**	8/87 **(9.2)**	NR	NR	OR: 3.3 (0.6 to 18)

Klok, Mos et al (2008)[113]	BNP (various)	AO (In-hospital: 3, 6-month: 1)	336 (4)	75 **(22.32)**	208 **(61.90)**	28/208 **(13)**	47/128 **(37)**	NR	NR	OR: 6.3 (3.6 to 11)
Klok, Mos et al (2008)[113]	BNP (various)	AO (In-hospital)	185 (3)	44 **(23.78)**	80 **(43.24)**	5/80 **(6.25)**	39/105 **(37.14)**	NR	NR	OR: 9.5 (3.5 to 25)
Klok, Mos et al (2008)[113]	NT-proBNP (1000, 600, 500 pg/ml)	Death (Short-term) Unstable PE	410 (4)	48 **(11.71)**	160 **(39.02)**	2/160 **(1.3)**	46/250 **(18)**	NR	NR	OR: 8.7 (2.8 to 27)
Klok, Mos et al (2008)[113]	NT-proBNP (1000, 600, 500 pg/ml)	AO (In-hospital)	543 (6)	114 **(20.99)**	225 **(41.44)**	12/225 **(5.3)**	102/318 **(32)**	NR	NR	OR: 7.5 (3.8 to 15)
Klok, Mos et al (2008)[113]	NP	Death	671 (8)	68 **(10.13)**	298 **(44.41)**	5/298 **(1.67)**	63/373 **(16.89)**	NR	NR	OR : 7.56 (3.35 to 17.09)
Klok, Mos et al (2008)[113]	NP	AO	909 (10)	209 **(22.99)**	433 **(47.63)**	40/433 **(9.24)**	169/476 **(35.5)**	NR	NR	OR : 6.77 (4.36 to 10.49)
Lega, Lacasse et al (2009)[117]	BNP (various)	Death (< 6 weeks)	570 (11)	39 **(6.84)**	290 **(50.88)**	5/290 **(1.72)**	34/280 **(12.14)**	96 (93 to 99)	91 (86 to 96)	OR: 5.42 (2.41 to 12.21)
Lega, Lacasse et al (2009)[117]	BNP (various)	PE-death (< 6 weeks)	519 (11)	34 **(6.55)**	250 **(48.17)**	3/250 **(1.2)**	31/269 **(11.52)**	NR	NR	OR: 5.11 (2.10 to 12.45)
Lega, Lacasse et al (2009)[117]	BNP (various)	AO (< 6 weeks)	329 (5)	57 **(17.33)**	146 **(44.38)**	5/146 **(3.42)**	52/183 **(28.41)**	NR	NR	OR: 10.85 (4.49 to 26.20)
Lega, Lacasse et al (2009)[117]	NT-proBNP (various)	Death (< 6 weeks)	354 (5)	28 **(7.91)**	143 **(40.39)**	0/143 **(0)**	28/211 **(13.27)**	82 (76 to 88)	59 (52 to 66)	OR: 9.91 (12.6 to 45.39)
Lega, Lacasse et al (2009)[117]	NT-proBNP (various)	PE-death (< 6 weeks)	157 (3)	9 **(5.73)**	48 **(30.57)**	0/48 **(0)**	9/109 **(8.26)**	NR	NR	OR: 4.59 (0.48 to 43.50)
Lega, Lacasse et al (2009)[117]	NT-proBNP (various)	AO (< 6 weeks)	406 (4)	75 **(18.47)**	173 **(42.61)**	12/173 **(6.93)**	63/233 **(27.04)**	NR	NR	OR: 4.92 (2.44 to 9.91)
Lega, Lacasse et al (2009)[117]	NP (various)	Death (< 6 weeks)	924 (16)	67 **(7.25)**	433 **(46.86)**	5/433 **(1.1)**	62/491 **(12.6)**	NR	NR	OR: 6.2 (3.0 to 12.7)

Lega, Lacasse et al (2009)[117]	NP (various)	PE-death (< 6 weeks)	676 (14)	43 **(6.36)**	298 **(44.08)**	3/298 **(1.0)**	40/378 **(10.6)**	NR	NR	OR: 5.0 (2.2 to 11.5)
Lega, Lacasse et al (2009)[117]	NP (various)	AO (< 6 weeks)	735 (9)	132 **(17.96)**	319 **(43.40)**	17/319 **(5.3)**	115/416 **(27.6)**	NR	NR	OR: 6.7 3.9 to 11.6)
Lega, Lacasse et al (2009)[117]	cTn - NP (various)	Death (< 6 weeks)	216 (6)	44 **(20.37)**	119 **(55.09)**	7/119 **(5.9)**	37/97 **(38.1)**	NR	NR	OR: 8.0 (3.0 to 21.4)
Lega, Lacasse et al (2009)[117]	cTn - NP (various)	PE-death (< 6 weeks)	153 (4)	15 **(9.80)**	79 **(51.63)**	2/79 **(2.5)**	13/74 **(17.6)**	NR	NR	OR: 8.6 (2.2 to 34.1)
Lega, Lacasse et al (2009)[117]	cTn - NP (various)	AO (< 6 weeks)	128 (4)	35 **(27.34)**	49 **(38.28)**	8/49 **(16.3)**	27/79 **(34.2)**	NR	NR	OR: 13.3 (2.4 to 74.2)
Liu, Yuan et al (2014)[114]	H-FABP (various)	Death (30-day)	255 (3)	43 **(16.86)**	193 **(75.69)**	7/193 **(3.63)**	36/62 **(58.06)**	NR	NR	OR: 33.11 (6.57 to 166.9)
Liu, Yuan et al (2014)[114]	H-FABP (various)	AO (Short-term)	594 (4)	58 **(9.76)**	475 **(79.96)**	24/475 **(5.05)**	34/119 **(28.57)**	0.60 (0.44 to 0.74)	0.87 (0.79 to 0.92)	OR: 10.81 (3.92 to 29.83)
Liu, Yuan et al (2014)[114]	H-FABP (various)	AO (30-day)	448 (3)	40 **(8.93)**	353 **(78.79)**	13/353 **(3.68)**	27/95 **(28.42)**	NR	NR	OR: 16.25 (4.98 to 53.07)
Ruan, He et al (2014)[115]	H-FABP (various)	Death (30-day)	472 (5)	44 **(9.32)**	332 **(70.34)**	1/332 **(0.30)**	43/140 **(30.71)**	NR	NR	OR: 40.78 (11.87 to 140.09)
Ruan, He et al (2014)[115]	H-FABP (various)	AO (30-day)	472 (5)	83 **(17.58)**	332 **(70.34)**	12/332 **(3.61)**	71/140 **(50.71)**	NR	NR	OR: 32.71 (11.98 to 89.26)
Ruan, He et al (2014)[115]	H-FABP (various)	PE-Death (30-day)	NR	NR	NR	NR	NR	98 (94 to 100)	77 (73 to 82)	OR: 146.73 (19.95 to 1079.34)
Ruan, He et al	H-FABP (various)	AO (30-day)	NR	NR	NR	NR	NR	86 (79 to 94)	82 (79 to 86)	OR: 27.44 (14.12 to 53.34)

(2014)[115]										
Bajaj, Rathor et al (2015)[116]	H-FABP (various)	PE-death (30-day)	676 (6)	73 **(10.8)**	430 **(63.61)**	7/430 **(1.63)**	66/246 **(26.83)**	90 (81 to 96)	72 (68 to 75)	OR : 32.94 (8.80 to 123.2)
Bajaj, Rathor et al (2015)[116]	H-FABP (various)	AO (30-day)	1628 (9)	185 **(11.37)**	1128 **(69.29)**	54/1128 **(4.79)**	131/500 **(26.2)**	71 (64 to 77)	74 (72 to 77)	OR : 17.67 (6.02 to 51.89)
Coagulation										
Becattini, Lignani et al (2012)[118]	D-dimer (various)	Death (15-day)	2917 (5)	113 **(3.87)**	2027 **(69.49)**	57/2027 **(2.81)**	56/890 **(6.29)**	NR	NR	OR: 2.76 (1.83 to 4.14)
Becattini, Lignani et al (2012)[118]	D-dimer (various)	Death (15-day)	Sensitivity analysis					NR	NR	OR: 2.50 (1.69 to 3.68)
Becattini, Lignani et al (2012)[118]	D-dimer (various)	Death (15-day)	Sensitivity analysis					NR	NR	OR: 4.66 (2.18 to 9.98)
Becattini, Lignani et al (2012)[118]	D-dimer (various)	Death (3-month)	1254 (4)	103 **(8.21)**	293 **(23.36)**	7/293 **(2.39)**	96/961 **(9.99)**	NR	NR	OR: 4.29 (1.70 to 10.79)
TTE-RVD										
ten Wolde, Sôhne et al (2004)[119]	TTE-RVD (various criteria)	Death (Short-term)	1773 (6)	NR	NR	NR	NR	NR	NR	NR
CTPA										
Vedovati, Germini et al (2013)[120]	CT-RVD (embolus localisation)	Death (30-day)	2215 (5)	NR	NR	NR	NR	NR	NR	OR: 2.51 (0.88 to 7.15)

Vedovati, Germini et al (2013)[120]	CT-RVD (embolus localisation)	Death (30-day)	1309 (3) (sensitivity analysis)	NR	NR	NR	NR	NR	NR	OR: 2.24 (1.29 to 3.89)
Vedovati, Germini et al (2013)[120]	CT-RVD (embolic obstruction)	Death (30-day)	NR (13)	NR	NR	NR	NR	NR	NR	OR: 1.78 (1.08, to 2.93)
Vedovati, Germini et al (2013)[120]	CT-RVD (embolic obstruction)	Death (30-day)	(9) (sensitivity analysis)	NR	NR	NR	NR	NR	NR	OR: 1.22 (0.99 to 1.51)
Vedovati, Germini et al (2013)[120]	CT-RVD (embolic obstruction)	Death (3-month)	3884 (16)	NR	NR	NR	NR	NR	NR	OR: 1.86 (1.27 to 2.71)
Vedovati, Germini et al (2013)[120]	CT-RVD (embolic obstruction)	Death (3-month)	(12) (sensitivity analysis)	NR	NR	NR	NR	NR	NR	OR: 0.96 (0.92 to 1.00)
Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse or 4-chamber)	Death (30-day)	4661 (15)	398 **(8.54)**	2049 **(43.96)**	105/2049 **(5.12)**	293/2612 **(11.22)**	NR	NR	OR: 2.08 (1.63 to 2.66)
Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse all cut-offs)	Death (30-day)	3982 (11)	301 **(7.56)**	1805 **(45.33)**	78/1805 **(4.32)**	223/2177 **(10.24)**	NR	NR	OR: 2.25 (1.69 to 3.00)
Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse RV/LV : 0.9)	Death (30-day)	2304 (5)	206 **(8.94)**	746 **(32.38)**	39/746 **(5.23)**	167/1558 **(10.72)**	NR	NR	OR: 1.99 (1.38 to 2.86)
Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse RV/LV : 1 - 1.1)	Death (30-day)	1678 (6)	95 **(5.66)**	1059 **(63.11)**	39/1059 **(3.68)**	56/619 **(9.05)**	NR	NR	OR: 2.81 (1.78 to 4.42)
Becattini, Agnelli et al (2014)[121]	CT-RVD (4-chamber)	Death (30-day)	679 (4)	97 **(14.28)**	244 **(35.93)**	27/244 **(11.06)**	70/435 **(16.09)**	NR	NR	OR: 1.67 (1.04 to 2.70)
Becattini, Agnelli et al (2014)[121]	CT-RVD (4-chamber RV/LV: 0.9)	Death (30-day)	1303 (4)	182 **(13.97)**	456 **(34.99)**	45/456 **(9.87)**	137/847 **(16.17)**	NR	NR	OR: 1.79 (1.25 to 2.57)
Becattini, Agnelli et al (2014)[121]	CT-RVD (4-chamber RV/LV: 1)	Death (30-day)	510 (3)	55 **(10.78)**	217 **(42.55)**	12/217 **(5.53)**	43/293 **(14.68)**	NR	NR	OR: 3.41 (1.71 to 6.78)
Becattini, Agnelli et al (2014)[121]	CT-RVD (4-chamber all cut-offs)	Death (30-day)	1813 (7)	237 **(13.07)**	673 **(37.12)**	57/673 **(8.47)**	180/1140 **(15.79)**	NR	NR	OR: 2.08 (1.51 to 2.85)

Becattini, Agnelli et al (2014)[121]	CT-RVD (various views and cut-offs)	PE-death (30-day)	2925 (8)	NR	NR	NR	NR	NR	NR	OR: 7.35 (3.59 to 15.09)
Becattini, Agnelli et al (2014)[121]	CT-RVD (various views and cut-offs)	Death (< 3 months)	782 (7)	NR	NR	NR	NR	NR	NR	OR: 4.65 (1.79 to 12.07)
Becattini, Agnelli et al (2014)[121]	CT-RVD (various views and cut-offs)	Death (< 3-month)	647 (5)	NR	NR	NR	NR	NR	NR	OR: 5.14 (1.45 to 18.19)
Becattini, Agnelli et al (2014)[121]	CT-RVD (various views and cut-offs)	Death (3-month)	4767 (27)	NR	NR	NR	NR	NR	NR	OR: 2.11 (1.61 to 2.76)
Becattini, Agnelli et al (2014)[121]	CT-RVD (various views and cut-offs)	Death (3-month)	(21 retrospectiv.studies)	NR	NR	NR	NR	NR	NR	OR: 2.13 (1.56 to 2.91)
Becattini, Agnelli et al (2014)[121]	CT-RVD (various views and cut-offs)	Death (3-month)	(6 prospective studies)	NR	NR	NR	NR	NR	NR	OR: 1.99 (1.13 to 3.50)
Meinel, Nance et al (2015)[122]	CT-RVD RV/LV (transverse)	Death (< 6 months)	4395 (14)	NR	NR	NR	NR	NR	NR	OR: 2.5 (1.8 to 3.5)
Meinel, Nance et al (2015)[122]	CT-RVD RV/LV (4-chamber)	Death (< 6 months)	3245 (8)	NR	NR	NR	NR	NR	NR	OR: 2.0 (1.3 to 3.0)
Meinel, Nance et al (2015)[122]	CT-RVD Thrombus load	Death (< 6 months)	1092 (10)	NR	NR	NR	NR	NR	NR	OR: 1.6 (0.7 to 3.9)
Meinel, Nance et al (2015)[122]	CT-RVD Central location	Death (< 6 months)	1593 (4)	NR	NR	NR	NR	NR	NR	OR: 1.7 (0.7 to 4.2)
Meinel, Nance et al (2015)[122]	CT-RVD RV/LV (transverse)	AO (< 6 months)	3103 (12)	NR	NR	NR	NR	NR	NR	OR: 2.3 (1.6 to 3.4)
Meinel, Nance et al (2015)[122]	CT-RVD RV/LV (4-chamber)	AO (< 6 months)	1132 (6)	NR	NR	NR	NR	NR	NR	OR: 2.9 (1.9 to 4.5)

Meinel, Nance et al (2015)[122]	CT-RVD Thrombus load	AO (< 6 months)	405 (4)	NR	NR	NR	NR	NR	NR	OR: 2.4 (1.3 to 4.5)
Meinel, Nance et al (2015)[122]	CT-RVD Central location	AO (< 6 months)	1547 (6)	NR	NR	NR	NR	NR	NR	OR: 2.4 (1.4 to 4.3)
Meinel, Nance et al (2015)[122]	CT-RVD RV/LV (transverse)	PE-death (< 6 months)	2698 (9)	NR	NR	NR	NR	NR	NR	OR: 5.0 (2.7 to 9.2)
Meinel, Nance et al (2015)[122]	CT-RVD RV/LV (4-chamber)	PE-death (< 6 months)	1709 (4)	NR	NR	NR	NR	NR	NR	OR: 3.3 (1.4 to 7.6)
Meinel, Nance et al (2015)[122]	CT-RVD Thrombus load	PE-death (< 6 months)	260 (3)	NR	NR	NR	NR	NR	NR	OR: 17.6 (5.0 to 61.7)
Meinel, Nance et al (2015)[122]	CT-RVD Central location	PE-death (< 6 months)	893 (2)	NR	NR	NR	NR	NR	NR	OR: 1.0 (0.3 to 2.7)
Venous ultrasound (US)										
Becattini C, Cohen AT et al (2015)[123]	Venous US (DVT)	Death (30-day)	7868 (7)	405 **(5.15)**	3489/7868 **(44.34)**	133/3489 **(3.81)**	272/4379 **(6.21)**	NR	NR	OR: 1.89 (1.52 - 2.36)
Becattini C, Cohen AT et al (2015)[123]	Venous US (DVT)	Death (30-day)	2793 (5 Prospective studies)	187 **(6.7)**	1483/2793 **(53.1)**	73/1483 **(4.92)**	114/1310 **(8.7)**	NR	NR	OR: 1.89 (1.38 - 2.58)
Becattini C, Cohen AT et al (2015)[123]	Venous US (DVT)	Death (30-day)	5075 (2 Retrospect. studies)	218 **(4.3)**	2006/5075 **(39.53)**	60/2006 **(2.99)**	158/3069 **(5.15)**	NR	NR	OR: 1.73 (0.97 - 3.09)
Becattini C, Cohen AT et al (2015)[123]	Venous US (DVT)	AO (90-day)	5982 (5)	388 **(6.49)**	2409/5982 **(40.27)**	132/2409 **(5.5)**	256/3573 **(7.2)**	NR	NR	OR: 1.63 (0.77 - 3.43)

Various: various assays and cut-off values. NP: Natriuretic peptides (BNP or NT-proBNP). AO: "adverse outcome" events defined as composite of death (1), haemodynamic deterioration (2) (any of the following: shock, need for thrombolysis, endotracheal intubation, catecholamine infusion, cardiopulmonary resuscitation), or recurrent PE (3). AO may include (2) and (3) or (2) only. NR: Not reported. In the study of ten Wolde on TTE-RVD, the meta-analysis was not performed because of the heterogeneity of the included studies (TTE-RVD criteria, patient's characteristics and study quality).

Table 2.11: Systematic reviews and meta-analyses that included separate results on "Stable only" PE. Odds ratio as reported.

Author (year)	Prognostic Factor (Cut-off value)	Outcome (Time-point)	N Patients (N Studies)	Population Event rate (%)	Low-risk Proportion (%)	Low-risk Event rate (%)	High-risk Event rate (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	OR (95% CI)
Biomarkers										
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI (various)	Death (Short-term)	915 (7)	51 **(5.57)**	725 **(79.23)**	17/725 **(2.3)**	34/190 **(17.9)**	NR	NR	OR: 5.90 (2.68 to 12.95)
Becattini, Vedovati et al (2007)[110]	cTnT - cTnI (various)	AO (Short-term)	252 (4)	70 **(27.78)**	149 **(59.13)**	32/149 **(21.5)**	38/103 **(36.9)**	NR	NR	OR: 4.12 (0.71 to 23.86)
Cavallazzi, Nair et Al (2008)[111]	BNP (35 pg/mL)	Death (30-day)	28 (1)	2 **(7.14)**	14 **(50)**	0/14 **(0)**	2/14 **(14.28)**	NR	NR	NR
Cavallazzi, Nair et Al (2008)[111]	BNP (75 pg/mL)	Death (3-month)	110 (1)	11 **(10)**	74 **(67.27)**	2/74 **(2.7)**	9/36 **(25)**	NR	NR	NR
Cavallazzi, Nair et Al (2008)[111]	NT-proBNP (600 ng/L)	Death (30-day)	292 (3)	47 **(16.09)**	81 **(27.74)**	0/81 **(0)**	47/211 **(22.27)**	NR	NR	OR: 16.12 (3.1 to 83.68)
Jiménez, Uresandi et al (2009)[124]	cTnT - cTnI (various)	Death (Short-term)	1366 (9)	94 **(6.88)**	989 **(72.40)**	34/989 **(3.4)**	60/377 **(15.9)**	NR	NR	OR: 4.26 (2.13 to 8.50)
Jiménez, Uresandi et al (2009)[124]	cTnI (various)	Death (Short-term)	NR	NR	NR	NR	NR	NR	NR	OR: 2.65 (1.26 to 5.56)
Jiménez, Uresandi et al (2009)[124]	cTnT (various)	Death (Short-term)	NR	NR	NR	NR	NR	NR	NR	OR: 8.60 (2.72 to 27.22)
Lega, Lacasse et al (2009)[117]	NP (various)	Death (< 6 weeks)	NR	NR	NR	NR	NR	NR	NR	OR: 8.2 (2.5 to 26.4)

Lega, Lacasse et al (2009)[117]	NP (various)	PE-death (< 6 weeks)	NR	NR	NR	NR	NR	NR	NR	OR: 6.6 (1.7 to 25.6)
Lega, Lacasse et al (2009)[117]	NP (various)	AO (< 6 weeks)	NR	NR	NR	NR	NR	NR	NR	OR 15.6 (3.0 to 81.9)
Lega, Lacasse et al (2009)[117]	cTn + NP (various)	Death (< 6 weeks)	NR	NR	NR	NR	NR	NR	NR	OR: 6.9 (2.3 to 20.7)
Lega, Lacasse et al (2009)[117]	cTn + NP (various)	PE-death (< 6 weeks)	NR	NR	NR	NR	NR	NR	NR	OR: 8.4 (2.1 to 33.4)
Lega, Lacasse et al (2009)[117]	cTn + NP (various)	AO (< 6 weeks)	NR	NR	NR	NR	NR	NR	NR	OR: 15.5 (0.8 to 284.7)
Bajaj, Saleeb et al (2015)[125]	cTnT – cTnI (various)	Death (Short-term)	7303 (23)	417 **(5.71)**	4707 **(64.48)**	143/4707 **(3.04)**	274/2596 **(10.6)**	66 (61 to 70)	66 (65 to 67)	OR: 4.80 (3.25 to 7.08)
Bajaj, Saleeb et al (2015)[125]	cTnT (various)	Death (Short-term)	NR (11)	NR	NR	NR	NR	NR	NR	OR:7.58 (4.55 to 12.61)
Bajaj, Saleeb et al (2015)[125]	cTnI (various)	Death (Short-term)	NR (10)	NR	NR	NR	NR	NR	NR	OR: 3.27 (2.01 to 5.34)
Bajaj, Saleeb et al (2015)[125]	hs-cTn (same assay and cut-off)	Death (Short-term)	NR (3)	NR	NR	NR	NR	92 (81 to 98)	43 (39 to 46)	OR: 7.86 (2.94 -to 21.00)
Bajaj, Saleeb et al (2015)[125]	cTnT – cTnI (various)	PE-death (Short-term)	5661 (16)	181 **(3.20)**	3513 **(62.1)**	57/3513 **(1.62)**	124/2148 **(5.77)**	69 (61 to 75)	62 (61 to 64)	OR: 3.80 (2.74 to 5.27)
Bajaj, Saleeb et al (2015)[125]	cTnT – cTnI (various)	AO (Short-term)	3437 (10)	283 **(8.23)**	2047 **(59.56)**	107/2047 **(5.23)**	176/1390 **(12.66)**	64 (58 to 70)	64 (62 to 65)	OR: 3.65 (2.41 to 5.53)
Bajaj, Rathor et al (2015)[126]	NP (various)	Death (Short-term)	1573 (10)	87 (5.53)	765/1573, (48.63)	12/765 (1.57)	75/808 (9.28)	0.86 (0.77–0.93)	0.51 (0.48–0.53)	OR: 7.98 (4.34–14.67)
Bajaj, Rathor	NP	PE-death	885	35	430/885	1/430	34/455	0.97	0.50	OR: 7.57

et al (2015)[126]	(various)	(Short-term)	(10)	(3.95)	(45.59)	(0.2)	(7.47)	(0.85–1)	(0.47–0.54)	(2.89–19.81)
Bajaj, Rathor et al (2015)[126]	NP	AO (Short-term)	3269 (12)	277 (8.47)	1683/3269 (51.48)	62/1683 (3.68)	215/1586 (13.56)	0.78 (0.72–0.82)	0.54 (0.52–0.56)	OR: 4.66 (3.21 -6.77)
Bajaj, Rathor et al (2015)[126]	H-FABP (various)	PE-death (Short-term)	512 (4)	48 **(9.37)**	330/512 **(64.45)**	6/330 **(1.82)**	42/182 **(23.08)**	0.88 (0.75–0.95)	0.70 (0.65–0.70)	OR: 25.97 (6.63–101.66)
Bajaj, Rathor et al (2015)[126]	H-FABP (various)	AO (Short-term)	748 (6)	103 **(13.77)**	521/748 **(69.65)**	29/521 **(5.57)**	74/227 **(32.60)**	0.72 (0.62–0.80)	0.76 (0.73–0.80)	OR:16.81 (5.88-48.09)
Bajaj, Rathor et al (2015)[116]	H-FABP (various)	AO (30-day)	1463 (7)	144 **(9.84)**	1027/1463 **(70.2)**	51/1027 **(4.97)**	93/436 **(21.56)**	65 (56 to 72)	74 (72 to 76)	OR: 12.04 (4.09 to 35.44)
Coagulation										
Becattini, Lignani et al (2012)[118]	D-dimer (various)	Death (30-day)	874 (3)	30 **(3.43)**	600 **(68.65)**	14/600 **(2.33)**	16/274 **(5.84)**	NR	NR	OR: 4.28 (1.88 to 9.71)
RVD										
Sanchez, Trinquart et al (2008)[129]	TTE/CT-RVD (various criteria)	Death (mainly in-hospital)	666 (7)	48 **(7.21)**	362 **(54.35)**	14/362 **(3.87)**	34/304 **(11.18)**	NR	NR	OR: 2.4 3 (1.33 to 4.45)
Sanchez, Trinquart et al (2008)[129]	TTE-RVD (various criteria)	Death (mainly in-hospital)	475 (5)	29 **(6.10)**	264 **(55.58)**	8/264 **(3.03)**	21/211 **(9.95)**	70 (46–86)	57 (47–66)	OR: 2.53 (1.17 to 5.50)
Sanchez, Trinquart et al (2008)[129]	CT-RVD (various criteria)	Death (mainly in-hospital)	191 (2)	19 **(9.95)**	98 **(51.31)**	6/98 **(6.12)**	13/93 **(13.98)**	65 (35–85)	56 (39–71)	OR: 2.28 (0.87 to 5.98)
Sanchez, Trinquart et al (2008)[129]	BNP (various criteria)	Death (mainly in-hospital)	272 (5)	19 **(6.98)**	178 **(65.44)**	2/178 **(1.12)**	17/94 **(10.08)**	88 (65–96)	70 (64–75)	OR: 9.5 (3.2 to 28.6)
Sanchez,	NT-proBNP	Death	170	26	93	6/93	20/77	93	58	OR: 5.7

Trinquart et al (2008)[129]	(various)	(mainly in-hospital)	(2)	**(15.29)**	**(54.71)**	**(6.45)**	**(25.97)**	(14–100)	(14–92)	(2.2 to 15.1)
Sanchez, Trinquart et al (2008)[129]	cTn (various)	Death (mainly in-hospital)	187 (3)	19 **(10.16)**	147 **(78.61)**	6/147 **(4.08)**	13/40 **(32.5)**	81 (23–100)	84 (77–90)	OR: 8.3 (3.6 to 19.3)
Coutance, Cauderlier et al (2011)[130]	CT-RVD RV/LV >1	Death (Short-term)	383 (2)	28 **(7.31)**	226 **(59)**	15/226 **(6.64)**	13/157 **(8.28)**	46 (27-66)	59 (54-64)	OR: 1.54 (0.7 to 3.4)
Coutance, Cauderlier et al (2011)[130]	CT-RVD RV/LV >1	PE-death (Short-term)	277 (2)					87.5 (47-100)	48 (42-54)	OR: 2.17 (0.06 to 79)
Coutance, Cauderlier et al (2011)[130]	NP (various)	Death (Short-term)	582 (7)	49 **(8.42)**	355 **(61)**	2/227 **(0.88)**	47/355 **(13.23)**	96 (86-100)	42 (38-46)	OR: 7.7 (2.9 to 20.2)
Coutance, Cauderlier et al (2011)[130]	NP (various)	PE-death (Short-term)	436 (6)	NR	NR	NR	NR	97 (84-100)	42 (37-47)	OR: 6.4 (2 to 20)
Coutance, Cauderlier et al (2011)[130]	NP (various)	AO (Short-term)	228 (3)	NR	NR	NR	NR	100 (91-100)	36 (30-44)	OR: 15.6 (3 to 82)
Coutance, Cauderlier et al (2011)[130]	NT-proBNP	Death (Short-term)	316 (3)	31 **(9.81)**	99 **(31.33)**	0/99 **(0)**	31/217 **(14.28)**	NR	NR	OR: 9.30 (1.8 to 49)
Coutance, Cauderlier et al (2011)[130]	BNP	Death (Short-term)	266 (4)	18 **(6.77)**	128 **(48.12)**	2/128 **(0.15)**	16/138 **(11.59)**	NR	NR	OR: 6.94 (2.1 to 23)
Coutance, Cauderlier et al (2011)[130]	TTE-RVD (various criteria)	Death (Short-term)	1249 (8)	61 **(4.88)**	656 **(52.52)**	16/656 **(2.44)**	45/593 **(7.59)**	74 (61-84)	54 (51-56)	OR: 2.36 (1.3 to 4.3)
Coutance, Cauderlier et al (2011)[130]	TTE-RVD (various criteria)	PE-death (Short-term)	781 (7)	NR	NR	NR	NR	92 (78-98)	51 (48-55)	OR: 4.44 (1.75 to 11.3)
Coutance, Cauderlier et al (2011)[130]	TTE-RVD (various criteria)	AO (Short-term)	1035 (7)	NR	NR	NR	NR	77 (71-83)	58 (54-61)	OR: 4.03 (2.76 to 5.9)
TTE-RVD										

ten Wolde, Sôhne et al (2004)[119]	TTE-RVD (various criteria)	Death (Short-term)	1773 (6)	NR	NR	NR	NR	NR	NR	NR
Cho, Sridharan et al (2014)[127]	TTE-RVD (various criteria)	Death (In-hospital or 30-day)	3283 (12)	301 **(9.17)**	2060 **(62.75)**	134/2060 **(6.5)**	167/1223 **(13.65)**	NR	NR	OR: 2.29 (1.61 to 3.26)
Cho, Sridharan et al (2014)[127]	TTE-RVD (various criteria)	Death (In-hospital)	1443 (9)	132 **(9.15)**	831 **(57.59)**	48/831 **(5.78)**	84/612 **(13.72)**	NR	NR	OR: 2.60 (1.43 to 4.72)
Cho, Sridharan et al (2014)[127]	TTE-RVD (various criteria)	Death (30-day)	1840 (3)	169 **(9.18)**	1229 **(66.79)**	86/1229 **(6.99)**	83/611 **(13.58)**	NR	NR	OR: 1.98 (1.43 to 2.73)
Cho, Sridharan et al (2014)[127]	TTE-RVD (various criteria)	Death (In-hospital or 30-day)	984 (7 prospective studies)	88 **(8.94)**	503/984 **(51.12)**	33/503 **(6.56)**	55/481 **(11.43)**	NR	NR	OR: 1.61 (1.01 to 2.57)
Cho, Sridharan et al (2014)[127]	TTE-RVD (various criteria)	Death (In-hospital or 30-day)	2299 (5 retrospectiv. studies)	213 **(9.26)**	1557/2299 **(67.72)**	101/1557 **(6.49)**	112/742 **(15.09)**	NR	NR	OR: 2.92 (1.58 to 5.42)
CT-RVD										
Trujillo-Santos, Den Exter et al (2013)[128]	CT- RVD RV/LV (various)	Death (Short-term)	2288 (10)	151 **(6.60)**	1020 **(44.58)**	52/1020 **(5.1)**	99 /1268 **(7.8)**	NR	NR	OR: 1.8 (1.3 to 2.6)
Trujillo-Santos, Den Exter et al (2013)[128]	CT- RVD RV/LV (various)	Death (Short-term)	747 (5 retrospectiv. studies)	64 **(8.57)**	427 **(57.16)**	26/427 **(6.09)**	38/320 **(11.87)**	NR	NR	OR: 2.22 (1.29 to 3.83)
Trujillo-Santos, Den Exter et al (2013)[128]	CT- RVD RV/LV (various)	Death (Short-term)	1541 (5 prospective studies)	87 **(5.65)**	593 **(38.48)**	26/593 **(4.38)**	61/948 **(6.43)**	NR	NR	OR: 1.54 (0.95 to 2.50)
Trujillo-Santos, Den Exter et al (2013)[128]	CT- RVD RV/LV (various)	PE-death (Short-term)	1416 (3)	20 **(1.41)**	543 **(38.35)**	1/543 **(0.18)**	19/873 **(2.17)**	NR	NR	OR: 7.4 (1.4 to 39.5)
Trujillo-Santos, Den Exter et al (2013)[128]	CT- RVD RV/LV (various)	AO (Short-term)	1702 (5)	135 **(7.93)**	701 **(41.18)**	39/701 **(5.56)**	96/1001 **(9.60)**	NR	NR	OR: 2.4 (1.2 to 4.7)

Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse RV/LV: 0.9)	Death (30-day)	1259 (2)	55 **(4.37)**	464 **(36.85)**	16/464 **(3.45)**	39/795 **(4.91)**	NR	NR	OR: 1.45 (0.80 to 2.62)
Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse RV/LV: 1 - 1.1)	Death (30-day)	995 (4)	47 **(4.72)**	520 **(52.26)**	17/520 **(3.27)**	30/475 **(6.32)**	NR	NR	OR: 1.88 (1.01 to 3.52)
Becattini, Agnelli et al (2014)[121]	CT-RVD (transverse all cut-offs)	Death (30-day)	2254 (6)	102 **(4.53)**	984 **(43.66)**	33/984 **(3.35)**	69/1270 **(5.43)**	NR	NR	OR: 1.64 (1.06 to 2.52)
Venous ultrasound (US)										
Becattini C, Cohen AT et al (2015)[123]	Venous US (DVT)	Death (30-day)	1409 (2)	96 (6.81)	806 (57.2)	43/806 (5.33)	53/603 (8.79)	NR	NR	OR: 1.8 (1.2 to 2.8)

Various: various assays and cut-off values. NP: Natriuretic peptides (BNP or NT-proBNP). PE-death: PE-related death. AO: "adverse outcome" events defined as composite of death (1), haemodynamic deterioration (2) (any of the following: shock, need for thrombolysis, endotracheal intubation, catecholamine infusion, cardiopulmonary resuscitation), or recurrent pulmonary embolism (3). AO may include components 2 and 3 or component 2 only. NR: Not reported.

Discussion

Among existing individual prognostic markers, H-FABP shows promising results for the identification of low-risk groups of patients with PE, when results of studies of both stable and unstable PE are included. This is also found for natriuretic peptides for stable PE in studies with moderate sample sizes. On the other hand, most biomarkers provide interesting but inconsistent results for the identification of high-risk groups; while imaging tests seem less powerful. Overall, based on the conclusions of the authors of the identified systematic reviews, no marker can identify adequately low-risk groups for outpatient management or high-risk groups for aggressive therapy. This suggests that biomarkers or other prognostic markers are not sufficient on their own but may be helpful when used along with prognostic models or other strategies.

The 2014 ESC guidelines[1] recommend a 3-step approach to stratifying patients with confirmed PE into high, intermediate-high, intermediate-low, and low risk, with different actions for each risk category. These steps are: assessment of haemodynamic stability, classification according to PESI or sPESI, then laboratory and imaging testing (in stable PE patients). Table 2.12 shows risk classification according to the 2014 ESC guidelines[1]. I will show how findings of this systematic review of systematic reviews compare with PESI and sPESI models or the combination of either PESI model with other biomarkers (when both are negative) for identifying patients at low-risk in the chapters dedicated to my systematic review of prognostic models (Chapter 4) and to the assessment of Net Benefit in direct comparison studies (Chapter 5). Combination of biomarkers seems competitive as this was reported for the association of NT-proBNP with either cTnT[134]or hs-cTnT[135] with a high NPV (100%)[4]. For the identification of higher risk groups (Intermediate-low-risk and Intermediate-high-risk) in stable PE patients, the equivalence in performance assigned in the ESC guidelines[1 136] to the different biomarkers, and to biomarker-based and imaging-based RVD assessments seems inconsistent with the findings of this systematic review of systematic reviews

[4] These combinations were not reported in the systematic reviews

of prognostic markers. Again the combination of biomarkers when they are all positive seems highly competitive for better identifying higher risk patients who might benefit from close monitoring or aggressive therapy. This is the case of the association of NT-proBNP and cTnT[134], and the association of NT-proBNP, hs-cTnT and Copeptin[135]. With this latter association, more patients in the intermediate-high-risk group had an adverse outcome as compared to the algorithm proposed by the 2014 ESC guidelines[1] and the Bova score[137] (a model useful for the identification of a high-risk group among stable PE patients)[5].

The review presented in this chapter shows many limitations in the systematic reviews that were identified. Different prognostic markers measured the same outcome with different prediction performances that may be related to the time the review was performed and the number of studies included. Not all the reviews assessed the factors as independent prognostic markers and their pooled analyses did not take account of confounding variables such as age, sex, renal function, type of assay and cut-off. Furthermore, summary results in the reviews were obtained by combining aggregate results despite important study-level heterogeneity and this might explain inconsistency between the results of the systematic reviews. Heterogeneity concerned types of study, population, outcome and time-point considered, and how outcome and prognostic markers were assessed. Results from different assays (natriuretic peptides, troponins, or troponins and natriuretic peptides), different cut-offs, and different timings of sampling or measurements were combined even though significant differences in outcome may occur that depend on these features, in particular the time of measurement[138-141]. Some reviews did not assess quality of the original studies, and sensitivity analyses might have shown methodological flaws in them influenced the overall results. Some of these limitations may have been resolved if the reviews had used individual patient data to conduct their meta-analysis, but none of the reviews did this.

[5] These combinations were not reported in the systematic reviews.

My systematic review of reviews also has some limitations of its own. Inability to translate the article meant that I excluded a systematic review published in 2011 in Chinese[131] which had assessed the prognostic value of BNP (9 studies) and NT-proBNP (7 studies) for short-term all-cause mortality. However, the 2% event rate found in the low-risk group in this review for either of the biomarkers is consistent with other reviews on NP. My search in two databases was limited to titles and abstracts but was extended by additional searching using each marker-related term in combination with pulmonary embolism. My quality assessment of the systematic reviews used AMSTAR, which is validated for reviews of the effects of healthcare interventions but seems to provide good psychometric properties (comparable to findings in systematic reviews of RCTs) when used for reviews of observational non-randomised studies[142]. As an alternative, I could have used the revised version (R-AMSTAR) but the evidence for its use is limited and its measurement properties have not been studied sufficiently[143]. And, I did not use ROBIS, the recently published tool for risk of bias assessment in systematic review[144] because this was not available at the time. This tool is completed in three phases[144]: (1) assessment of relevance (optional), (2) identification of concerns with the review process covering four domains through which bias may be introduced into a systematic review (study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings), and (3) judgment of overall risk of bias in the review. This is different to the scoring system used by AMSTAR.

Conclusions: Across all the reviews that I identified in this systematic review of systematic reviews, study heterogeneity and inconsistency of results means that none of the prognostic markers can be shown to have particular value on its own for helping clinicians make decisions for early discharge or complete outpatient management in stable PE patients. It seems difficult to choose a type of management for a patient, whether she/he is at low-risk or at high-risk, without considering numerous other prognostic variables that may change his risk profile. For example, biomarker-based (H-FABP, NP, hs-cTn) or imaging-based (CT) RVD/ischemia may be useful supplements to other strategies for decision making in both clinical practice and clinical research.

Table 2.12: Risk stratification in confirmed PE according to the 2014 ESC guidelines[1]

Risk	Haemodynamic status	PESI or sPESI	Biomarker-based and Imaging-based RVD
High	Shock - Hypotension	Not applicable	Not applicable
Intermediate-high	Stable	PESI≥III or sPESI≥1	Both (+)
Intermdiate-low	Stable	PESI≥III or sPESI≥1	Either one or none (+)
Low	Stable	PESI I-II or sPESI=0	If assessed, both (-)

Other individual prognostic markers - Data from systematic reviews and individual studies

Based on my review, I identified additional prognostic markers that have been assessed in PE. I summarise these here. The following may be associated with an increased risk of fatal PE:

- immobilization for neurological disease, age >75 years, and cancer[27]
- markers related to clinical context and comorbidities, and vital signs (table 2.6) almost included in prognostic management strategies
- 12-lead electrocardiography[133].

Other markers that need further validation include atrial fibrillation[145], hyponatremia[146 147] (<130 mmol/L), markers of renal dysfunction[148-150], serum lactate (>2 mmol/L)[151 152], white blood cell count (>12.6 x 10^9/L)[153], mean platelet volume[154], reduced circulating haptoglobin[155-157], growth differentiation factor-15 (GDF-15)[158] and Copeptin[135].

There is controversy about the impact of the delay in diagnosis[159] and syncope[160], and the presence of right-heart thrombi[161 162]. Most recent studies show no association of these variables with outcomes. Weekend admission[132 163] and smaller hospital volume[164] are predictors for in-hospital mortality, and shortened length of hospital stay[165] is a predictor for post-discharge mortality. The high readmission rates for venous thromboembolism and bleeding found in one study suggests that readmission may be linked to socio-economic and medical factors for suboptimal quality of care in the management of PE[166].

Prognosis-based assessment and management strategies

Low-risk and outpatient management

Prognostic strategies for outpatient management may be based on physician's clinical judgment, hospital or home checklists and prognostic models i.e. clinical prediction rules (CPR) used either solely or in combination with prognostic markers.

Although physician's judgment is used in everyday clinical practice, it has not been evaluated in a prospective study nor has it been compared to another strategy. In a retrospective analysis[167], nearly two-thirds of patients presenting to the emergency department with low-risk PE according to PESI model were potentially eligible for outpatient therapy. Relative contraindications to outpatient management were associated with an increased frequency of adverse events at 30 days in these patients. The study was underpowered to show an association with adverse events at 5 days. In a prospective study, Kabrhel et al[168] found that factors independently associated with 5-day clinical deterioration and need for hospital-based interventions were hypotension, hypoxia, coronary disease, residual deep vein thrombosis and right heart strain on echocardiogram. These factors differed from those associated with 30-day all-cause mortality that were active malignancy and congestive heart failure (present in prognostic models: PESI, sPESI and Geneva Prognostic Score). The sensitivity of prognostic models was moderate (39–80%) for 5-day clinical deterioration but higher (67–100%) for 30-day mortality. Thus, a predefined risk limit for sending a patient home (based on prognostic models) is an arbitrary choice that may depend on factors not covered by the models, such as other medical factors, psychological and social barriers related to the lack of adequate management and patient compliance, and physician's and patient's preferences. It may also depend on how much the outcome can be affected by intervention in the hospital e.g. a cancer patient with a poor prognosis due to the cancer will be treated at home because there might be a small or no difference in the effect of hospital versus home management on the outcome (see discussion in Chapter 4).

Systematic reviews and meta-analyses[169-171] support the feasibility and safety of outpatient management in carefully selected low-risk symptomatic PE patients[172-182]. In a systematic review[171], no direct comparison between strategies for selecting patients for out-of-hospital management was available, and the event rates and the number of patients included in studies were too small to draw any valid conclusion from the comparison (11 studies, total of 1258 patients). In a Cochrane Review[183] of outpatient versus inpatient treatment for acute PE, one published RCT[175] in patients identified as low risk by the PESI model was included and was ranked as very low quality evidence (lack of blinding of outcome assessors, small number of events with imprecision and indirectness, and small sample size). According to the authors of the review, the study did not provide sufficient evidence to assess the efficacy and safety of outpatient versus inpatient treatment. Hospital checklists identify a higher proportion of patients who may be treated at home (50%) as compared with the original PESI (40%) and its simplified version sPESI (30%) in retrospective analyses[184 185]. A direct comparison between strategies is necessary to determine the effects on reducing complications and costs and increasing patient satisfaction, because many patients could be discharged early or treated entirely at home with DOACs (which simplify treatment and monitoring).

Others have suggested that outpatient treatment is possible if “dedicated thrombosis clinic including a 24-h service are available to follow patients and to rapidly re-admit them in case of complications”, and that “patients with well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration” could benefit[57 84]. The updated ACCP guidelines[5] suggest that acute PE patients who satisfy all the following criteria are suitable for treatment out of the hospital: (1) clinically stable with good cardiopulmonary reserve; (2) no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (ie <70,000/mm3); (3) expected to be compliant with treatment; and (4) feeling well enough to be treated at home. The guidelines consider CPRs (such as PESI models) as aids to decision making and do not require patients to

have a pre-defined score to be considered suitable for treatment at home. However, although they do not suggest the need for routine assessment, they agree that the presence of RVD or increased cardiac biomarker levels should discourage treatment out of the hospital.

High-risk and intermediate-risk

The ESC guidelines[1 186] suggest that initial risk stratification in acute PE should be based on the presence of shock or hypotension that qualifies patients at high-risk, and on the presence of signs of RVD/ischemia (and high-risk PESI/ sPESI) in non-high-risk patients for distinguishing intermediate-risk patients from those at low-risk. Management strategies based on this model were not successful in intermediate-high-risk patients in a RCT when a thrombolytic was compared with heparin[85]. This may be because of a lack of appropriate selection of patients, problems of response to treatment or risk related to the high doses that were used.

Competing strategies

In the light of these controversies about the competing strategies and because several models and checklists have been proposed for use, a systematic assessment is needed to clarify the validity and utility of these strategies. The important differences between prediction models suggests the need for a systematic review to assess study quality and explain the reasons for such differences. Features that might explain these differences are the lack of adequate development for a model (in construction, validation, update and impact studies) and methodological flaws related to study design, population and patient characteristics (selection, definition, identification and ascertainment of cases), prognostic information (definition of prognostic and outcome variables, and time-points; and how they were assessed), sample size and statistical analysis. Other limitations might be related to the use of complicated models which integrate a large number of items and assign different weights to them, making them non memorable and impractical for routine clinical practice. This highlights the need for a simple prognostic model that could be used easily in clinical practice.

OVERALL CONCLUSIONS

The high-risk of death in untreated PE and the potential for treatment-related bleeding means that a rapid, objective and validated diagnostic strategy is needed to guide adequate treatment and to avoid unnecessary treatment. Patients with PE with unstable haemodynamic status need an “aggressive” or intensive treatment, but, although patients with PE with stable haemodynamic status are still at risk of death and adverse outcomes from the PE, they need to be managed adequately in accordance with their risk profile. Several individual prognostic markers for acute PE have been suggested that may influence these treatment decisions, but my systematic review of reviews shows that their role as independent individual factors is unknown or controversial. Little is known about their validity and their impact on clinical decision making when integrated within prognostic strategies. Other risk stratification tools might help to distinguish between different categories of risk and help clinicians to select appropriate therapy and management for individual patients based on their prognosis, the potential adverse effects of treatment and cost. This underpins the need for my subsequent systematic reviews of prognostic models (Chapters 4 and 5). However, before presenting these, a description of the methodology for assessing study quality and prediction performance of prognostic models is needed and this follows in the next chapter.

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Chapter 3 - Methodology Background

INTRODUCTION

Chapters 1 and 2 introduced my research topic and reviewed recent developments in the epidemiology, diagnosis, prognosis and management of acute PE. This chapter discusses the methodology of prognosis research in general and for PE in particular. It provides the foundation for the critical appraisal of studies of prognostic models in my systematic reviews (chapters 4 and 5) with regard to: 1) design, conduct, analysis and interpretation, and reporting of study results, 2) assessment of study quality and 3) use of performance measures and comparisons of prediction performance between models. This is also relevant to the development and the assessment of my case-ascertainment strategy (Chapter 7) and the development of the protocol for a future study (Chapter 8). (The methodology for my survey is described within that chapter (Chapter 6).)

PROGNOSTIC RESEARCH

In 2013, the PROGnosis RESearch Strategy (PROGRESS) group introduced the framework of four prognosis research themes for better understanding and improving health-related conditions: 1) fundamental prognosis research about future outcomes or course of a disease or health condition[1] "in relation to current diagnostic and treatment practices", 2) prognostic factor research[2] "to identify factors associated with subsequent clinical outcome", 3) prognostic model research[3] as a "combination of multiple predictors from which risks of a specific endpoint can be calculated for individual patients" and 4) stratified medicine research[4] "to identify patients who will have the most clinical benefit or least harm from a specific treatment". As adequate

prediction of clinical outcome often requires the combination of multiple prognostic variables (factors, markers), as discussed in Chapter 2, I focus here on research methodology that applies to prognostic models and prognostic models in the field of acute PE relative to my research topic.

PROGNOSTIC MODELS - DEVELOPMENT STUDIES

A prognostic model is defined as "a combination of at least two separate variables (in the final model) to predict patient outcome"[5]. More precisely, the model will help to "convert observed values in individual to absolute probability"[6] of developing a particular outcome within a specific period of time. When I began my research for this DPhil, I used reference books[7-10] and articles on prognostic research[11-18] and prognostic factor research [19-22] to develop detailed background material on prognostic models, assessment of the quality of studies of models, and interpretation of the findings of these studies. Since then, several publications on research methods, reporting and critical appraisal tools for prediction models and systematic reviews of prediction models (CHARMS[23] and TRIPOD[24-26] checklists[6]) have been published. However, as of October 2016, although there is QUIPS-2 (Quality In Prognosis Studies) tool[22] for studies of prognostic factors, there is no formally published risk of bias assessment tool for prediction models. The PROBAST (Prediction model risk of bias assessment tool) [6 27] is intended to be published soon, and its checklist components have been used in a study of the prediction of recurrence of VTE following treatment[28 29].

The development of a prediction (diagnostic or prognostic) model requires different phases[12-14 17 18] (construction, external validation and updating, and impact studies) before it can be definitely

[6] CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) - TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis).

implemented, and various types of model development studies are displayed in Figures 3.1 and 3.2 and discussed below.

Model construction studies

The classic approach is for a model to be constructed (or developed)[12 17] based on a random subset (two thirds) of a population sample (derivation or training set) by selecting among candidate variables the most significant predictors and "assigning mutually adjusted weights per predictor"[23] in a logistic or Cox regression multivariable analysis. The final model is then applied to the subset of the population sample that was not used in the derivation process (internal validation set) to assess its prediction performance, in terms of calibration[7], discrimination[8] and classification[9] (see footnotes for definitions[13]). This use of a random split-sample for derivation and validation tends to give more optimistic results than a non-random split that would allow for comparison of different locations or times[13 26] (see external validation), and it may lack power if it does not include a large sample size when there is a small number of events. It is now recommended to derive and validate a model using the same data[26] in combination with other internal validation techniques[9]. To quantify optimism in the estimate of performance due to the use of the same data, overfitting (small event rate relative to the number of candidate variables) and variables selection strategies (more predictor-selection techniques based on p-values), resampling (re-use[13]) techniques (such as bootstrapping and cross validation) have been suggested[26]. Various statistical methods[9 30] (shrinkage, lasso[10] penalization procedures, recalibration) are proposed to overcome overfitting, optimism and miscalibration. Model construction and internal validation are both important steps and these might be combined for external validation within the same publication about the model.

[7] Calibration : comparison of observed and predicted event rates for groups of patients
[8] Discrimination : quantification of the model's ability to distinguish between patients who do or do not experience the event of interest
[9] Classification : classifies risk groups (stratified according to the model) in true positive, false positive, false negative and true negative relative to the event of interest
[10] LASSO : least absolute shrinkage and selection operator

From my systematic review of prognostic models (Chapter 4), 19 of the 26 available prognostic models for risk stratification of patients with acute PE have been subject to construction studies. Some (such as the 2008 ESC [31], 2014 ESC[32] and shock index[33 34]) have never been subject to construction studies, while other models used variables that are not specific to PE or its prognosis (the simplified and revised versions of the Geneva prediction rule[35] for the diagnosis of PE, and GRACE[36] for the prognosis assessment for acute coronary events). Furthermore, some have used hospital checklists (Davies[37] and Hestia[38]) based on lists of variables that were chosen by clinicians. Various techniques have been used for the constructed models. For instance, the PESI model was based on a random split-sample including 15,531 patients (67% for derivation and 33% for internal validation). The model's external validation was reported in the original publication using 221 patients, thus combining construction and external validation sets. The 30-day mortality rates in the derivation, internal and external validation samples were 9.2, 9.5, and 2.7%, respectively. Event rates are thus similar in samples from the same cohort, but quite different in the external validation cohort. This is not reflected in risk groups, although the proportion of patients belonging to the extreme risk groups is significantly different. Simplified PESI was derived from the original PESI by removing variables that were not significant in univariable analysis and by simplifying model presentation[39]. It was then compared to PESI in the cohort used to develop sPESI, and externally validated in another cohort within the same publication[39]. A model including two biomarkers (NT-proBNP and D-dimer), pulse rate and the occurrence of active malignancy[40] was developed using the same data for derivation and internal validation. To prevent overfitting, the LASSO method for shrinkage and predictor selection, cross-validation and bootstrapping (2,000 times) were used because of the small numbers of patients (n= 210) and adverse events (n= 12). Thus, bias related to univariable preselection of predictors was avoided. The Geneva prognostic score (GPS)[41] was developed in 296 patients using a random split-sample of 10 equal groups and cross-validation to quantify overfitting (10 times repeated construction on 9 tenths and validation on the remaining tenth). Bootstrap resampling with replacement (300 times a

sample of 268 patients) was used for improving the precision of the area under the curve (AUC) of the receiver operating characteristics (ROC) curve.

Model external validation studies

The second important step for model implementation is external validation [13 18] i.e. the evaluation of model performance (calibration, discrimination and classification) outside the population used to construct it. This might use, for example, patients from other centres. In general, variables as in the final model are applied to the new sample using a similar population, outcome and measurements. The performance of the model in the new dataset is compared to that in the original dataset to check whether it performs as well with the new data. Models might not perform as well because of flaws in model construction (design, modelling, overfitting, variable selection) and important differences between settings (patient characteristics, management or healthcare system) or measurement methods[13]. Although it is recommended that models should be externally validated if they are to be used in clinical practice[13], 12 of the 19 models developed for acute PE have not been externally validated[40 42-53] and only seven have been[39 41 54-58]. Other types of external validation studies may evaluate the model in a different population or setting, or change outcome variables or measurements[17 18 59]. If the model does not perform well in the external validation set, it can be updated or adjusted[18].

Model updating studies

Models are evaluated and adjusted by recalibration, or by adding or deleting variables in order to improve or simplify the model[18]. As models develop, researchers might delete variables, add variables or do both[60], before comparing the "new" and "old" models. For example, to obtain sPESI[39], 5 variables were deleted from the original version and 2 variables were combined into one; resulting in a total of 6 variables instead of 11. Similarly, the PE prediction algorithm[60], a prediction rule to identify low-risk patients with acute PE, was developed in the PESI cohort and includes 8 of 11 PESI variables, with two additional ones. The most common pattern for model

updating is to assess the incremental value of added prognostic variables to existing models (mostly PESI or sPESI), including clinical variables[51 61], biomarkers for right ventricular dysfunction[58 62-64] or myocardial injury[58 62 63 65-70], markers for hypercoagulable states[68], markers of vascular[58 63 71] and cardiac imaging[33 62 64], or multiple markers[58 62-64 68 72 73]. However, inconsistent results in performance have been obtained with the same variables added to the same models. I present further details on studies to update models in chapters 4 and 5.

Model impact studies

Impact studies of prognostic models or strategies are rare and I have found only 10 impact studies for acute PE. Methods for the evaluation of the impact[14 18] of prognostic models or strategies on decision making, clinical and economic outcomes are shown in Figure 3.1. In the existing research, acute stable PE patients at low-risk of adverse events were identified by the GPS[74] model, by low NT-pro-BNP level[75] and stable haemodynamic status, by sPESI and low cTn[76] or by hospital exclusion criteria[37 77 78] to decide to treat them at home (prospective cohort management study); or by the Spanish model[43] or PESI model[54] to compare treatment at home versus treatment in hospital[79 80] in a randomized trial. In another randomized trial, intermediate-high-risk patients were selected according to the ESC-2008 model (combination of TTE-RVD and high cTn level in normotensive) and allocated to thrombolytic versus usual anticoagulant treatments[81]. The impact on physicians' behaviour (frequency of use of models, treatment decisions) and on outcomes was assessed in a retrospective cohort study[82] involving two centres, which found that risk stratification was frequently performed and associated with assignment to higher levels of care and with more advanced treatments, but it did not improve either short-term outcomes or 30-day mortality. I have not found any studies that compared model-based management versus usual care (i.e. using versus not using the prognostic model) in acute PE.

Figure 3.1: Prognostic model development studies - Design for analysis and performance measures (references in text for each type of study)

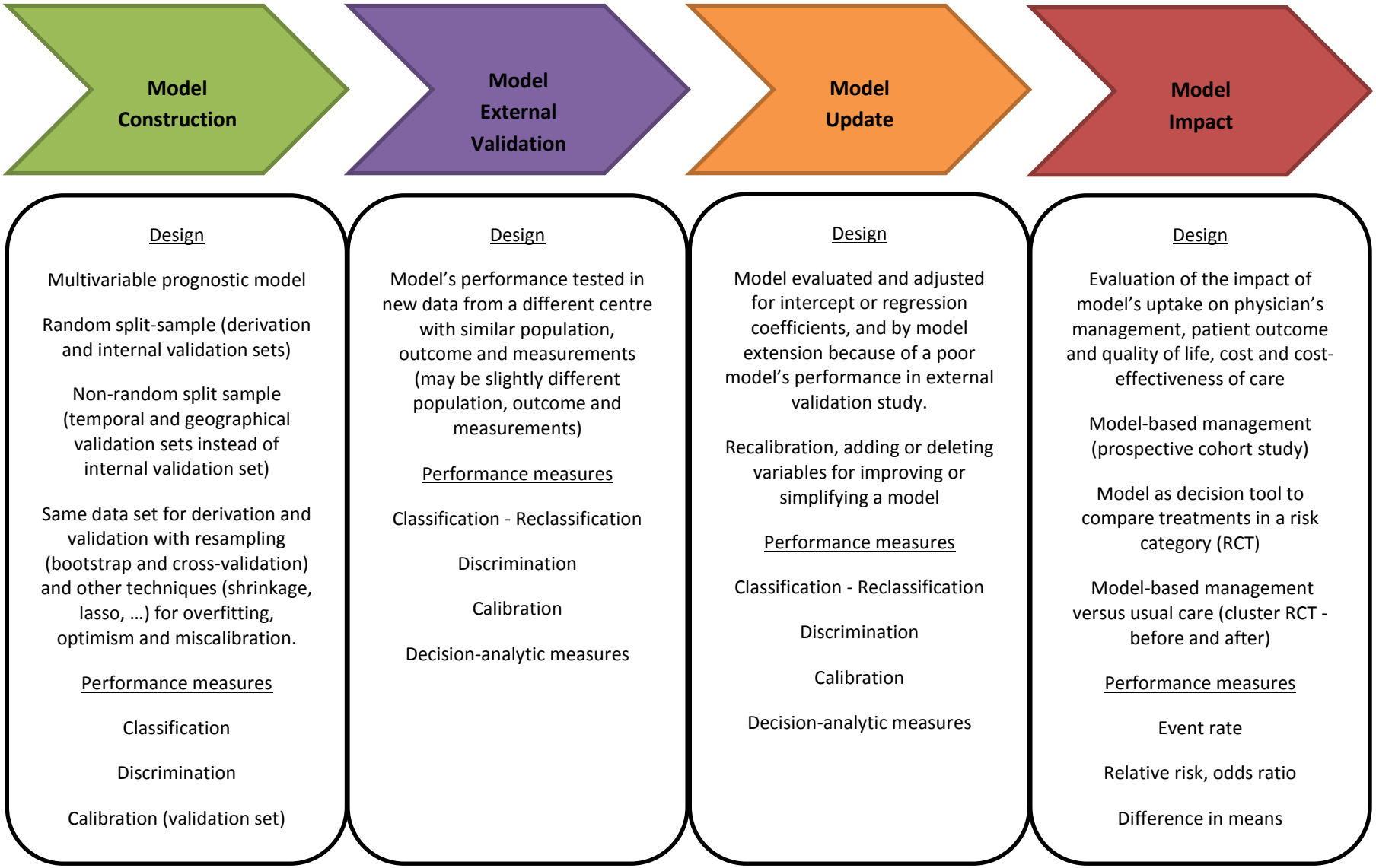
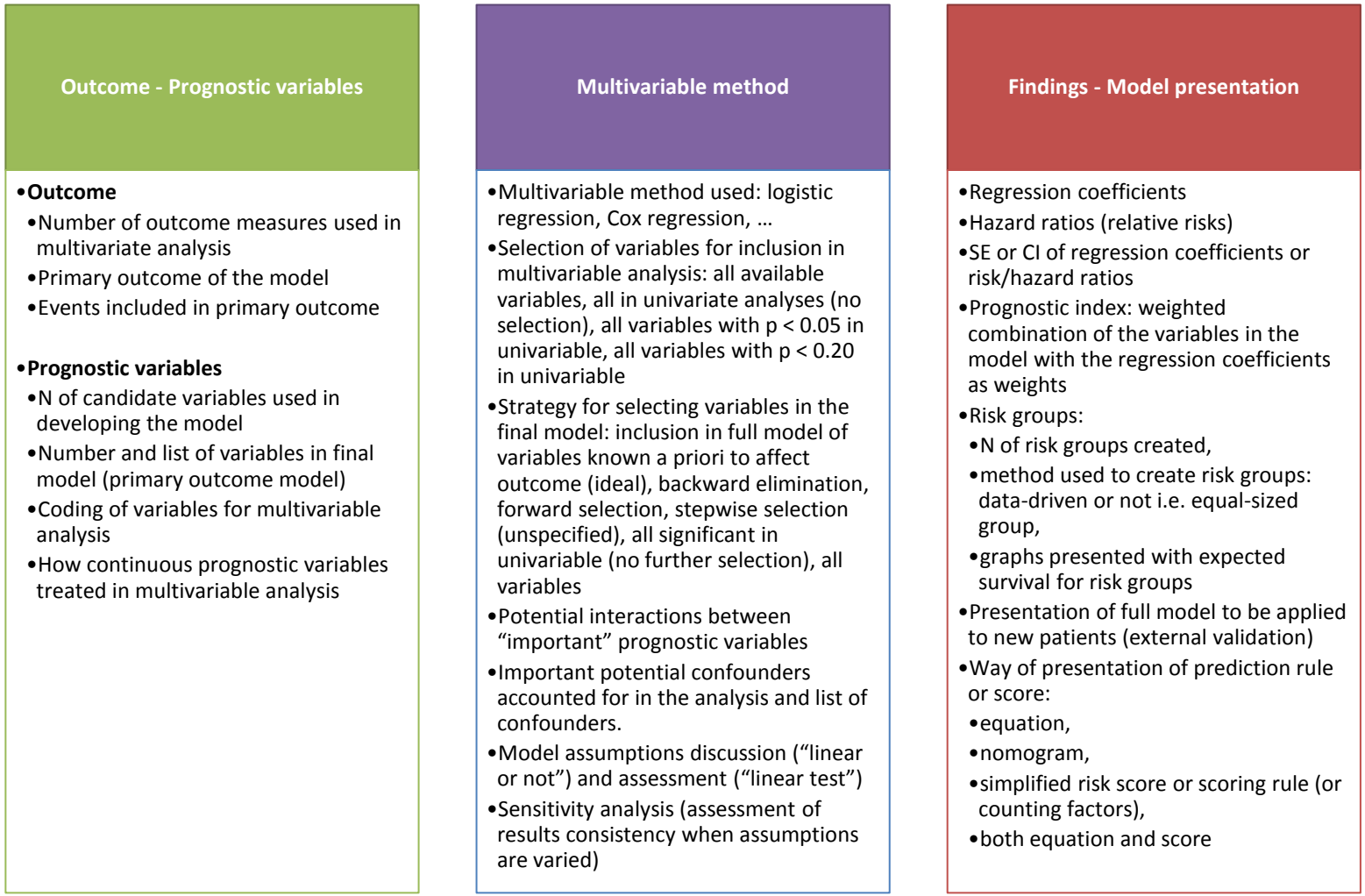


Figure 3.2: Formation of a multivariable model in construction studies[5 7-9 15] used in data collection form for the systematic review (chapter 4)



DESIGN, CONDUCT, ANALYSIS AND REPORTING OF PROGNOSTIC RESEARCH AND PROGNOSTIC MODEL RESEARCH STUDIES

This section is relevant to most chapters in this thesis. The basis of sound methodology for research design, conduct, analysis and reporting of prognostic studies[19 20 23-26] is discussed below and summarized in figures 3.3 to 3.7, with specific applications to acute PE prognosis for participants, predictors, follow-up, outcomes and analysis.

Rationale, research objective and research question

As with research generally; the rationale, objective and question provide the foundations for the next steps in prognostic research (Figure 3.3).

Study design

The design includes the type of study cohort (prospective or retrospective) and its inception, the stage of development of the model and the type of analysis, as well as some other study characteristics (Figure 3.3). In my systematic review of prognostic models (**Chapter 4**), some studies were retrospective using administrative and medical data or retrospective using prospectively collected data for diagnosis.

Participants

The key element is to select a representative sample based on a large disease spectrum with appropriate diagnostic methods. To be representative, a study has to meet all the following criteria as reported in my systematic review of prognostic models (**Chapter 4**): recruitment strategy and inclusion criteria are defined, sample selection is explained, description of diagnostic criteria is adequate, and clinical and demographic characteristics are fully described. Patient

representativeness depends on type of study, patient recruitment (care pathway, geographic area, referral, setting, ascertainment strategy), eligibility criteria, diagnostic strategy for PE, patient typology and risk profile and type of treatment and management. If the prevalence data are to representative, this depends on duration of follow-up, and type and methods of assessment of outcomes. A reliable recruitment strategy (Figure 3.4) for identifying and including all cases is important to avoid selection bias in prognostic studies and to provide appropriate and reliable results about prognosis for the whole population and within risk groups; and I address this challenge in chapter 7. In acute PE research, a systematic and rapid search is needed for patients suspected of having the condition at appropriate sites (diagnostic and medical units), confirmation of PE using diagnostic strategies as recommended by guidelines[31 32] to avoid under-diagnosis or over-diagnosis, early initiation of anticoagulant treatment and enrolment at inception of eligible patients. The flow of patients recruited, those in whom the diagnosis was confirmed (and the strategy used for confirmation), the number and proportion of patients who met inclusion criteria and were enrolled should be reported. There should be a full description of patient characteristics, comorbidities and interventions (treatments). The population in the sample for the prognostic study will depend on setting (i.e. the hospitals and the medical departments where patients are recruited). For example, a sole hospital within a geographic area may see all, or most of the patients with PE. This will be more representative of PE patients as a whole and the population event rate in this non-selective population is likely to be more appropriate. Whereas, patients recruited in emergency department have different characteristics and risk profiles than those recruited in, for example, geriatrics, internal medicine, cardiology, critical care or oncology; and patients selected from a specific department may not be representative of the general PE population. The prediction performance for a model-based risk assessment may vary according to patient selection as it depends not only on the accuracy of the model but also on the population prevalence. In the TROMSO population-based cohort[83] (patients recruited from community and unique hospital in the area), the 3-month all-cause mortality in

confirmed PE patients was as high as 16%, which is close to 3-month all-cause mortality I found with my case-ascertainment strategy (chapter 7) in which patients were ascertained from all departments and services within the only hospital in the geographic area and had complete follow-up. This high prevalence influences the higher event rates found for the PESI/ sPESI low- and high-risk groups in my case-ascertainment study (**Chapter 7**).

Predictors

Predictors vary depending on the type of prognostic research study, and on whether the study is a construction or a validation study for a prediction model. In prognostic research aiming at assessing the course of disease, event rate (as an absolute risk) and associated independent prognostic factors are reported (**Chapter 2**). In prognostic model studies, candidate variables (in construction studies) or the prognostic models (in validation studies) need to be presented and well-defined, including their measurement method (variable, cut-off), accuracy, reliability, and the number and timing of measurements. Ascertainment of prognostic information at inception is important. If many measurements (e.g. systolic blood pressure) are recorded at admission to an emergency department, the type, time and choice of measurement should be specified (e.g. highest, lowest, worst, best, mean, etc). Time of data collection may lack of precision in acute PE because of the delay between clinical onset and presentation, and it might be misreported. Reporting of time of measurement for a biomarker needs to give the time the blood sample was drawn, analysed or recorded. Information needs to be provided on whether variables are measured in the same way and with the same cut-offs for all participants (e.g. trained collectors using standardized methods such as whether pulse oximetry oxygen saturation was at room air or under oxygen), and if they are reported without knowledge of the patient's eventual outcome (Figure 3.5).

Follow-up and Outcome

Ascertainment of outcome on follow-up should use an appropriate length of follow-up and time-point for assessment. The appropriate time-period in acute PE research varies in relation to the research question. For instance, it might be from when the diagnosis was confirmed and treatment was initiated to 3 months or earlier (e.g. first 5 to 10 days more relevant for assessing suitability for outpatient management or first month) in studies assessing the role of prognostic models (as discussed in **Chapter 2**) but might be extended further in prognosis and prognosis factor studies. Outcomes used (Figure 3.5) vary across studies, but death is a main outcome measure that needs be considered systematically. The other common outcomes used for prognostic studies are fatal PE, DVT/PE recurrence and bleeding (Figure 3.6). The assessment criteria for DVT/ PE recurrence[84-86], PE-related mortality[84] and bleeding severity[87 88] are well described in international guidance and are used in RCTs of anticoagulant treatments but there is much less consensus for studies of prognostic models and strategies, where outcome criteria and definition terms are not consistent across studies (as discussed in chapters 4, 5, 7 and 8). For instance, PE-related adverse outcomes, adverse outcome, adverse clinical outcome, complicated clinical course, and complicated clinical events are terms that may have been used for the same outcome, and, conversely, the same term might be used for different outcomes where various component combinations are used, such as for PE-related death, clinical deterioration, DVT/PE recurrence. If PE-related death is reported, this is dependent on both the risk of death from PE and from other causes, and, consequently, the risk of dying from PE is overestimated when the mortality rate from other causes is high. Therefore the (cumulative) incidence of PE-related death needs be estimated by accounting for competing risk of death from other causes. Clinical deterioration is a clinical worsening from a stable to an unstable haemodynamic condition that requires intravenous catecholamine infusion to maintain adequate tissue perfusion and prevent or treat cardiogenic shock, endotracheal intubation, or cardiopulmonary resuscitation[89]. The relevance of an outcome and time-point for a specific clinical question (types of outcomes, single or composite outcome) needs be considered precisely. It is important to report rules for recording

outcomes, whether all participants had the same assessment for the outcome, whether this assessment was blinded to predictors and who was blinded. It is important to show the flow of patients, including the number and proportion of patients who were lost-to-follow-up and whether they were different from those who completed the study.

Sample size - Patients and events

The sample size needed for a reliable prognostic study depends on the number of events. For the construction of a prediction model, a rule of thumb is to have 10 events per candidate variable (EPV). Inconsistency between the number of events and number of candidate variables assessed (EPV less than required) may result in overfitting and requires adjustment of the model. A higher number of EPV (e.g. 20 EPV) is needed when low-prevalence predictors are present in a model "to eliminate bias in regression coefficients and improve predictive accuracy"[90]. Reporting should include a flow chart for participant selection, the number of participants and events in the analysis and justification of the sample size.

Analysis

Analysis should include participant characteristics in individual studies and study characteristics in systematic reviews, and should state whether there are missing data and which confounders are accounted for in the study design and analysis. Participant characteristics include demographics (such as age and gender), clinical characteristics and prognostic variables or models.

Data might be missing for the participants, prognostic or outcome variables and, so, reports should show the completeness of the data for each variable and for the data overall, and describe the method used for dealing with missing data (e.g. complete-case analysis, single or multiple imputation). For instance, in the derivation and internal validation sample for PESI[54], information for arterial oxygen saturation was missing for 64.6% and for 45.2% in the external validation

sample; with the researchers assuming unknown values to be normal and including these in the denominator when calculating the frequency of baseline patient characteristics.

Some of the confounders to account for in the analysis of prognosis research in acute PE are delay to diagnosis, delay to obtaining prognostic information and to initiation of therapy; type and quality of anticoagulant treatment at the initial phase and during follow-up and other types of management (e.g. thrombolytic therapy, insertion of caval filter, compression stockings, duration of confinement to bed, length of hospital stay). Ideally, treatment needs be standardized and follow guidelines[32 91] and this is discussed in Chapter 2.

The analysis of prediction model studies needs to be reported clearly for each stage of model development: construction without or with external validation studies, external validation without or with updating studies, impact studies (Figures 3.1 and 3.2). Results are usually expressed as event rates in the whole population (for all types of prognostic studies) and performance measures. For prognostic models, the proportion of patients in different risk groups and the event rates within risk groups, as well as statistical measures and decision-analytic measures as appropriate (see performance measures section) should be reported.

Reporting

An overview of the construction and validation of risk models[92] identified poor and incomplete reporting as particular problems. Clear reporting improves the transparency of prognosis research, as does data sharing, registration, and protocols[93]. Poor methods and poor reporting of methods, and performance measures were common in prognostic model research until recently[15 94-98]. This encouraged the development of reporting guidelines[24 26], critical appraisal and data extraction[23] and risk of bias assessment[6 27] tools for systematic reviews. In my systematic review (**Chapter 4**), poor quality reporting (Figures 3.3 to 3.7) was a major issue for data collection regarding research objective, study design, case-identification, inclusion criteria, missing information (diagnosis, treatment, prognostic variables and outcome variables), similarity in

patient care, similarity in data collection for obtaining prognostic information about predictors and outcomes, blinding to patient characteristics, treatment and prognostic information in outcome assessment, sample size, and data and statistical analyses.

Figure 3.3: Research question and study design

Research question	Study design

• **Rationale**
  • Why this prognostic study in the context of medical condition and of existing models if any?
• **Objective**
  • Risk-stratification
  • Identification of low-risk category
  • ...
• **Research question including**:
  • population/patient/setting
  • predictors (construction studies) or models (validation studies)
  • outcome and time-point
  • study design
	• **Design**
	  • Cohort prospective or retrospective or RCT (impact studies)
	  • Inception (early phase of development of disease)
	  • Stage of model development
	  • Type of analysis
	• **Other study characteristics:**
	  • country
	  • funder
	  • date trial was conducted (study period)
	  • dates of start and end of recruitment and end of follow-up
	  • number of participating centres
	  • ethical approval

Figure 3.4: Participant - Methods for optimal selection applied to acute PE studies.

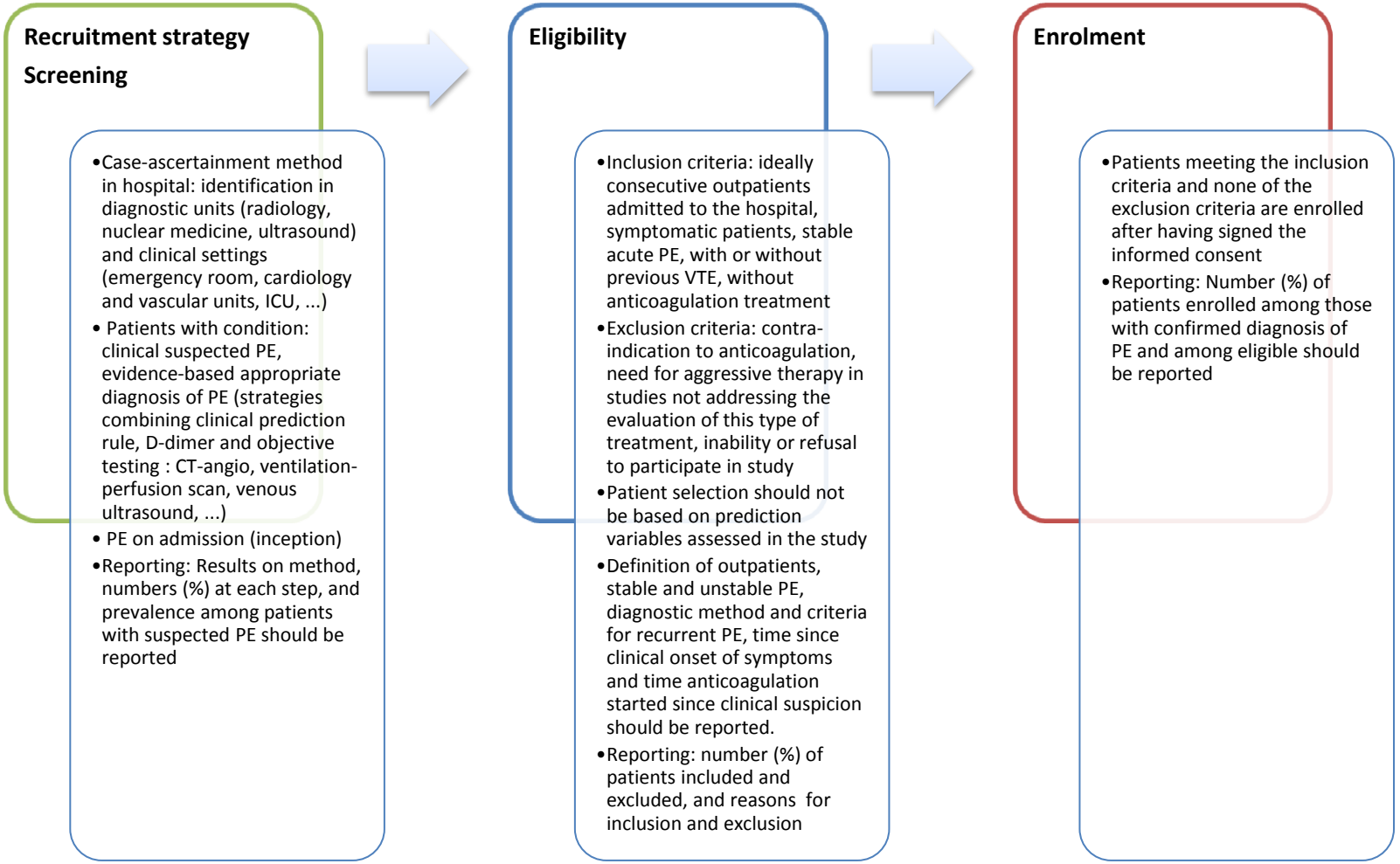
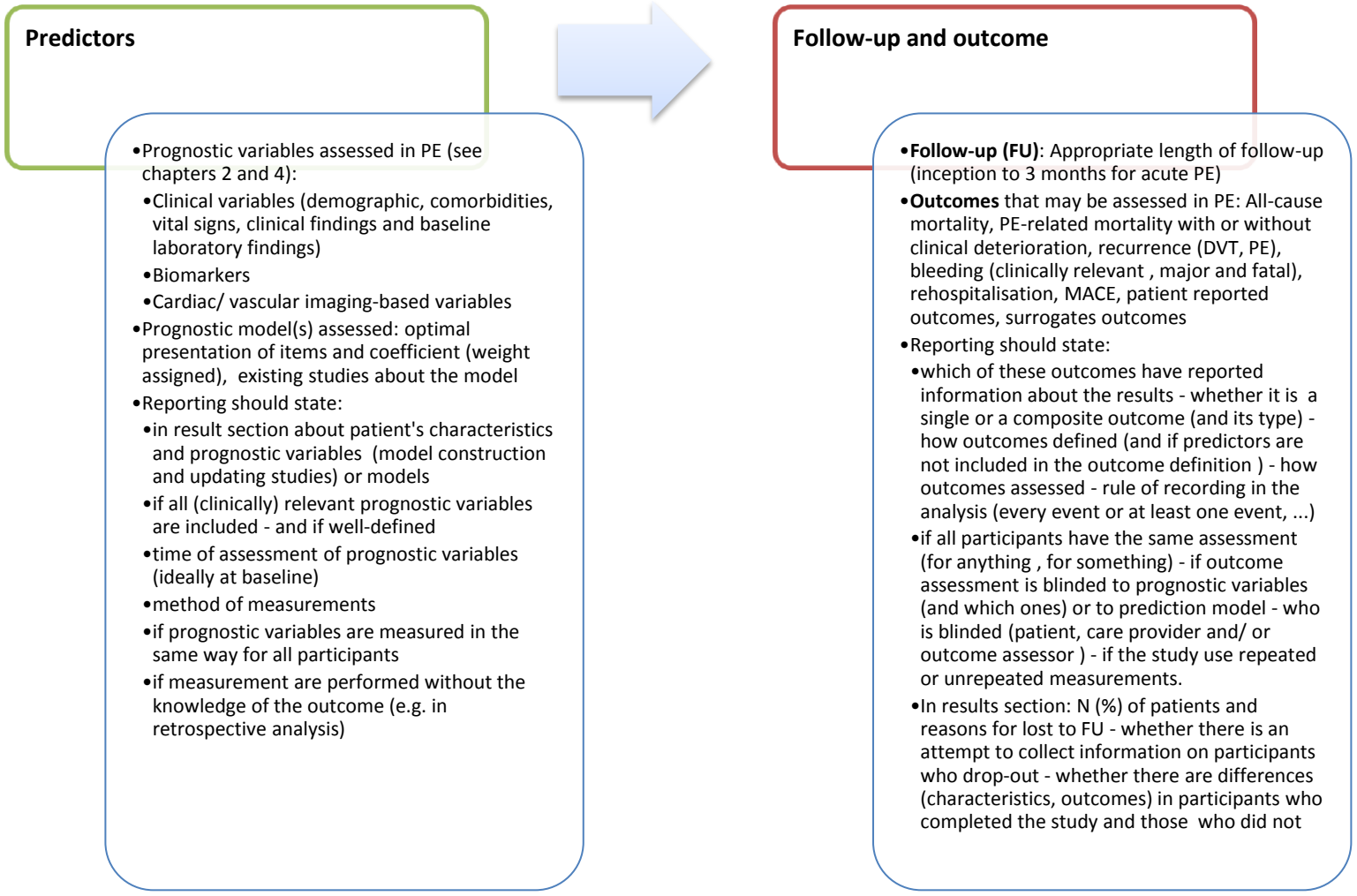


Figure 3.5: Predictors and outcome[19 20]



MACE: major adverse cardiovascular events (myocardial infarction, stroke, systemic embolic events, cardiovascular death)

Figure 3.6: Definition of outcome assessment criteria for DVT/ PE recurrence[84-86], fatal PE[84] and bleeding severity[87 88] according to the guidelines.

Recurrent DVT - PE

- **Recurrent DVT**
  - on venous US: a new non-compressible vein segment, or an increase of the vein diameter by >4 mm compared with the last available measurement
  - on venography: a new intraluminal filling defect
- **Recurrent non fatal PE**
  - on lung scan: a new ventilation–perfusion mismatch
  - on CT-angio: a new intraluminal filling defect

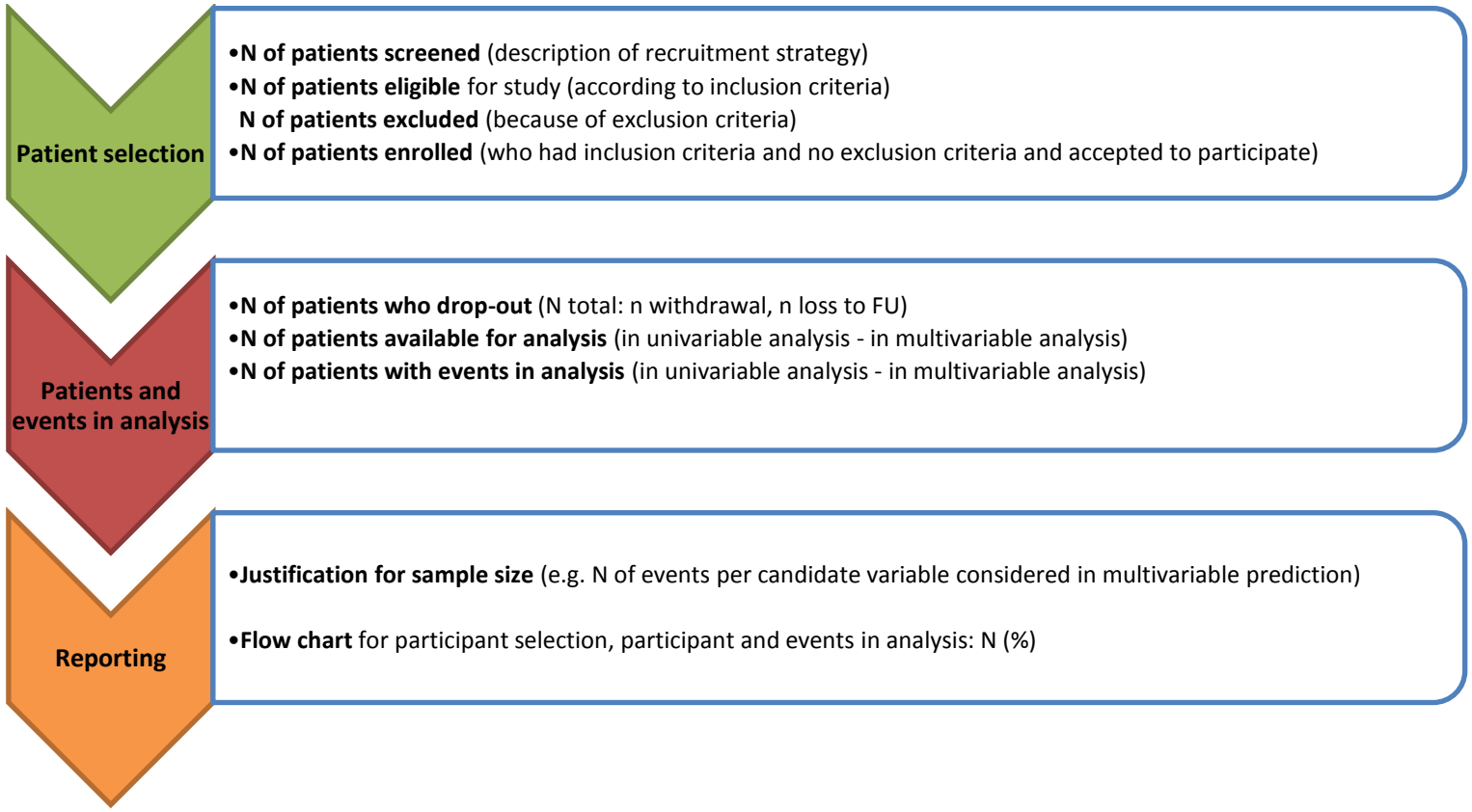
Fatal PE

- **Classified** as “definite or probable” fatal PE or as “any” fatal PE (definite or probable PE and possible PE)
- **Defintions**
  - "definite" fatal PE: confirmed at autopsy
  - "probable" fatal PE: preceded in the immediate period before death by confirmed nonfatal PE or DVT
  - "possible" fatal PE:sudden death occurred that could not be explained by a disease or a condition other than PE

Bleeding

- **Major bleeding**:
  - Fatal bleeding
  - Symptomatic bleeding located in a critical organ (intraocular, intracranial, retroperitoneal, adrenal, spinal, pericardial, intramuscular with compartment syndrome, etc …),
  - Symptomatic bleeding with loss in hemoglobin ≥ 2 g/dl,
  - Symptomatic bleeding requiring red blood cells concentrate or whole blood transfusion ≥ 2 units
- **Clinically relevant non-major bleeding**: overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary/permanent) cessation of study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.
- **Minor bleeding**: non-major or non-clinically relevant

Figure 3.7: Patients and events - Sample size.



ASSESSMENT OF STUDY QUALITY IN MY SYSTEMATIC REVIEW OF PROGNOSTIC MODELS

Assessment of risk of bias in systematic reviews of prognostic research has been reported for prognostic[20] and prognostic factor studies[19 22], but, as mentioned above, the PROBAST guidance has not yet been formally published for prediction models [6 27]. PROBAST is a tool for assessing the risk of bias and applicability of prediction modelling studies. The biases arise from systematic flaws and limitations in the design, conduct or analysis of a study leading to distorted estimates of predictive performance[6 27]. PROBAST has five domains (participant selection, outcome, predictors, sample size and flow, and analysis) and 23 signalling questions grouped within these domains. PROBAST also includes a component to assess the applicability of the model to the review question, where applicability refers to the extent to which the prediction model matches the systematic review question (in terms of the population, predictors or outcomes). PROBAST is completed in 4 steps: (1) specifying the systematic review question, (2) classifying the type of prediction model evaluation, (3) assessing risk of bias and applicability, and (4) providing an overall judgment[6 27].

In my systematic review of prognostic models (chapter 4), I used a prognostic assessment tool (Figure 3.8) derived from articles on prognostic studies[20] and prognostic factors[19 22] that were available when I did my assessment of study quality. I assessed risk of bias for the following domains: participants, follow-up and outcome, prognostic variables or models, treatment, sample size and analysis, including 30 items (standard criteria) relative to these domains (Figure 3.8). This was similar to the approach under development for PROBAST at that time and although PROBAST is a more structured tool which includes a rating for each domain and an assessment of the applicability of a model to the review question, my assessments provide a good guide to the quality of the included studies. I present a “risk of bias summary” for each study and a “risk of bias

graph" for all studies combined, for each phase of model development. Each study is denoted as meeting or not meeting a standard, or as unclear, not reported or not applicable. Risk of bias was not rated for a domain, and I did not assess applicability to the review question as is done in PROBAST. However, my assessment tool helped to assess heterogeneity in study quality, allowing the selection of studies for sensitivity analysis and a better interpretation of summary results from the meta-analysis.

Figure 3.8: Study quality assessment tool used in the systematic review of prognostic models (Chapter 4) derived from publications on prognostic factors[19 20] the only available tools at the time protocol was initiated.

Participants	Follow-up - Outcome	Prognostic variables - Prognostic models	Treatment - Sample size	Analysis
•inclusion criteria defined •sample selection explained •adequate description of diagnostic criteria •clinical and demographic characteristics fully described •representative (of all PE patients/ broad spectrum: setting, type of patients) •assembled at a common point in the course of their disease (inception cohort): time origin specified •complete (case ascertainment, not excluded because of missing data or lost to FU)	•**Follow-up of patients** •adequate length of time •adequate response rate •reasons for lost to FU provided •no important differences in participants who completed the study and those who did not (characteristics, outcome) •**Outcome** •objective •unbiased (assessment blinded to prognostic information) •fully defined •appropriate •known for all or a high proportion of patients •the same for all study participants (method and setting of measurement)	•fully defined including details of method of measurement if relevant •precisely measured •available for all or a high proportion of patients •the same for all study participants (method and setting of measurement)	•**Treatment subsequent to inclusion in cohort** •fully described •treatment standardised or randomised (choice of treatment not related to prognostic information) •**Sample size** •justification of sample size (at least 10 EPV for multivariable prognostic model)	•strategy for model building (i.e., inclusion of variables) is appropriate •continuous prognostic variable analysed appropriately •statistical adjustment of all important prognostic factors (important potential confounders accounted for in the study design and in the analysis) •clear statement on how loss to follow-up treated was in analysis •discussion in text of missing data •number of excluded patients due to missing data reported

ASSESSMENT OF PROGNOSTIC PERFORMANCE

This section discusses the role of existing performance measures and provides the justification for my adoption of specific measures (mainly in ***Chapters 4 and 5***). This work was underpinned by information from books[7-10], articles on prognostic research[11-18] and articles relative to performance measures[98-104] for model presentation, basic statistics, (re)classification and decision-analytic measures.

Model presentation

The initial reporting of models needs to show their variables and their weighting coefficient, the total number of patients and the proportion with the events in the whole population sample (event rate as an absolute risk). Risk categories (2 or more) need be well-defined as to the cut-offs and the proportion of patients in different risk categories or groups (efficiency) and the event rates within these risk categories (in particular, the failure rate for low-risk groups). For instance, in acute PE, if two models have the same failure rate in low-risk groups, the more efficient model may be selected, noting that "the estimated risk or predicted values, and how well these predict actual risk, may be a more important aspect of a prognostic model than sensitivity and specificity, …" [105]. Odds ratio, relative risk and hazard ratio are measures of association that are not useful for prediction because they may be little affected by overall accuracy or discrimination of the model[106]. They do not reflect discrimination power "except for extremely strong associations, and many different pairs of true positive rates (TPRs or "sensitivity") and false positive rates (FPRs or "1-specificity") are consistent with a particular odds ratio value"[107].

Basic statistical measures

Table 3.1 shows the basic statistical measures for this type of research.

Overall performance measures[9] such as the R^2 and the Brier's score that incorporate both calibration and discrimination are helpful to fit the model.

Calibration[9] evaluates the agreement between observed and predicted outcomes (probabilities) that can be displayed on a calibration plot or in a table. The most used method in studies of acute PE models is to present the findings of predicted and observed risks by risk categories or groups. Other types of calibration may be useful to compare means (predicted and observed) between external and development data sets, or as a shrinkage factor to adjust a model in validation sets.

Discrimination[9] evaluates the ability for a model to distinguish patients with different outcomes (e.g. those who develop a VTE event and those who do not). TPRs and FPRs for different cut-offs can be plotted to obtain a ROC curve that can be compared with the 45° line (non-informative line). An optimal cut-off that is a trade-off between benefit (true positives) and costs (false positives) can be defined. The AUC or concordance c-statistic (95% CI) of different models can be compared and difference in AUC (c-index, 95% CI) can be computed. Discrimination is usually represented in prediction model studies (and very often shown in PE studies) and its role as a performance measure has been discussed[105 108] in many publications, mostly when comparing models. The comparison is rank-based and may result in small differences between the AUCs that are not helpful to people trying to choose between models. The overall AUC is not appropriate for prediction, because it combines different parts of the ROC curves that have opposite directions. One part is to help select models with a very high sensitivity at the expense of a low specificity and would lead to the treatment of many patients, while the other one is to select highly specific models that would lead to the avoidance of treatment for patients who will not have the events, at the expense of a low sensitivity. The AUC is not sufficiently helpful for clinical decisions because it assumes that TPR and FPR are of equal value and does not weigh the consequences of one against the other. It has been recommended that the AUC (c-index) should not be relied on solely[108], although it remains a standard measure to quantify a model predictive discrimination.

Classification - Reclassification

Classification compares model-based predicted outcomes (high-risk level versus low-risk level) against observed outcomes (e.g. death versus survival, presence versus absence of adverse outcomes) (Table 3.2). True positive, false positive, false negative and true negative results are displayed in a 2 x 2 table. Results can be expressed as sensitivity, specificity and predictive values, and likelihood ratios (with 95% CI). Classification may help to compare results of sensitivity and specificity between models but it is difficult to make decisions based solely on sensitivity and specificity values even when combined within the "Youden" index. This is because: 1) this is a data driven optimization of cut-off values that provides an overall assessment of performance and one would prefer a model to be more sensitive than specific or vice versa and 2) it does not account for clinical consequences because equal weights are assigned for sensitivity and specificity. Predictive values of the presence or absence of events in high- and low-risk groups are more clinically meaningful and are equivalent to event rates (predicted risk) within risk groups, as noted above. Despite these limitations, most studies of prognostic models in acute PE consider classification-based results as essential. When no direct comparison is available to help selecting between two models (e.g. "old" model without an additional marker or variable and a "new" model with it), the "old" model could help to assess the probability of an outcome for an individual according to the risk categories defined by the model and this could serve as a priori probability. The likelihood ratio of the additive prognostic marker could then be used to estimate post-probability of the outcome and "number needed to test" (NNT). Results of a priori probabilities relative to prognostic models and likelihood ratios relative to prognostic markers can be obtained from individual studies and systematic reviews (**Chapters 2 and 4**).

Reclassification[105] (across the whole population) assesses whether a new model sufficiently classifies patients into different risk categories so that it may alter treatment decisions. More

relevant, net reclassification improvement[109-112] helps to assess the number of patients changing categories in the correct direction for patients with events and for those without events. Results are expressed as overall "net reclassification improvement" or index (NRI) and overall continuous NRI (or "integrated discrimination improvement" IDI) depending on whether the NRI is category-based or not. For events and non-events separately, the proportion of cases reclassified in the correct direction minus the proportion of cases reclassified in the incorrect direction is computed to obtain the event NRI and nonevent NRI. NRI is "the sum of the net percentages of correctly reclassified persons with and without the event of interest"[99] and IDI is "the sum of the net percentages of persons with and without the event of interest correctly assigned a different predicted risk"[99]. According to Leening et al[99], "event and non-events NRI can be interpreted as a percentage with a range of -100% to 100% (negative results corresponding to worsening), and the overall NRI statistic which is implicitly weighted for the event rate cannot be interpreted as a percentage (range: - 2 to 2)". NRI by model 2 versus model 1 can be estimated from the difference in "Youden" index of two models and is equal to the sum of improvement in sensitivity and improvement in specificity (NRI= ΔYouden= ΔSensitivity + ΔSpecificity). Comments about the lack of clinical utility of sensitivity and specificity apply to NRI, a measure that assigns the same weight to TP as to FP findings, explaining why NRI may be replaced by weighted NRI ($wNRI_T$ defined in table 3.3). Despite this limitation, *NRI helps assess whether the "new" model (competing model, old model with additional marker) performs better than the "old" model and how well it reclassifies patients in the correct direction (i.e. the incremental value).* For example, in the PREP study[56], a clinical model (including cardiogenic shock on admission, altered mental status and cancer) was compared with the clinical Model + BNP + RV/LV ratio. A cross-tabulation of the classifications of the predicted risks with the two models into three categories (<5, 5–30, and >30% 30-day risk of adverse events) assessed NRI in patients with adverse events [(12-1)/40] and in patients without adverse events [(69-7)/475] resulting in an overall NRI value of 0.145 to the advantage of the "new" model. AUC was 0.73 (95% CI, 0.65-0.82) for the clinical model and 0.84

(95%CI, 0.78-0.90) for the "new" model. However, NRI is rarely used in prognostic model studies for acute PE.

Decision-analytic performance measures

Decision-analytic measures (Table 3.3) assess whether a prediction model is clinically useful by accounting for benefit and harm (i.e. whether a decision based on a model is likely to do more good than harm) so that the model can be used in clinical practice[113]. For prognostic models, they evaluate the ability to improve therapeutic decision making based on the decision threshold approach[114 115]. Therapeutic threshold follows the concept of indifference between two approaches to managing a patient (same value for both managements at threshold). For instance for acute PE, it is the point at which it is indifferent to treating a patient with PE at home or treating him in the hospital (assuming that keeping patients in the hospital can prevent bad outcomes). This point is very low (around 1%) for acute PE because a much higher value is assigned to FN than to FP misclassification. A 1% threshold probability (odds 1/99) is equivalent to accepting up to 99 false positives (FP) per true positive (TP), and a 2% (odds 2/98) is equivalent to accepting up to 49 false positives (FP) for each true positive (TP).

Net benefit (NB)[116] is the most common measure to assess clinical utility of prediction models in the absence of impact studies but it has never been used in acute PE prognostic research. NB weighs FP against TP. Weight or "exchange rate" [113] is directly related to decision threshold. FP classification is valued in terms of TP. The unit is true positives and NB is expressed in TP/1000.

Decision curve analysis[113 117-119] is a plot of NB over a range of reasonable threshold probabilities that helps to compare competing models between them and to "treat all" and "treat none" strategies. For Vickers et al[113], rank order is more important than the size of the difference in NB between two models and the strategy with the highest NB at a particular threshold probability has the highest clinical value. However from ΔNB one would want to measure a "number needed to test by the new model" to identify one more TP (= *1/ΔNB)*.

Weighted comparison index (or Net Δsensitivity)[108 120] is a weighted comparison of the sensitivity difference and the specificity difference of two models taking into account the relative clinical cost of a false positive compared with a false negative result and event rate. ΔNB is the product of Net Δsensitivity by event rate and is expressed as net increase in TP per 1000.

Relative utility (RU)[121-124] ***and event free life year***[125 126] are less commonly used. RU uses weights for sensitivity and specificity depending on whether the probability threshold is lower or higher than event rate. It is defined as the "net benefit in excess of ''treat all'' or ''treat none'' (whichever is larger) divided by the net benefit of perfect prediction"[104].

Assessment of clinical utility measures need individual patient data because different threshold values induce changes in sensitivity and specificity[127]. Physicians should rely on models in which study population event rates are close to that of their own situation because sensitivity and specificity may vary in relation to event rate[128 129]. Finally, miscalibration may impact on NB[130] results.

Peformance measures used in this thesis

The choice of the performance measures depends on the types of comparison to be made between the models.

In indirect comparisons, inconsistency in results for similar populations, outcomes and time-points can arise because of differences or flaws in recruitment strategies, statistical analyses, publication bias (with studies remaining unpublished if the model performs worse) and other issues related to methodology. Systematic reviews of prognostic models may help by providing more accurate performance measurements by providing summary results that would mostly come from external validation (and updating) studies. Predicted risk (i.e. event rate within risk groups) and the proportion of patients belonging to risk groups are simple and clinically

meaningful measures that have been used in my systematic reviews (**Chapters 2 and 4**), along with sensitivity, specificity, and likelihood ratios when available.

Direct head-to-head comparisons of prognostic models in independent datasets within the same population are a more powerful design, but few studies have directly compared the most relevant, existing models. Some comparative studies have assessed predicted risk in risk groups, NRI and NB. However, because it was not possible to collect individual patient data for this thesis, a formal DCA was not possible across a large range of threshold values. Instead, I performed a sensitivity analysis of NB across a small range of decision threshold values close to 1% (which I found to be an acceptable threshold for early discharge in my survey (**Chapter 6**)) to compare performances between models, assuming no change would occur in TP and FP for such small threshold variations. As the rank order is more important than the size of the difference[113], the NB measure was preferred to delta net benefit.

Choosing a model or strategy for clinical practice

Three questions need be answered when selecting a specific measure for clinical practice: 1) How well does the model predict the outcome in external validation studies, if no impact study is available (addressed in **Chapter 4**: Systematic review of prognostic models)? 2) If many prediction models are available, which one performs best (**Chapter 4**: Systematic review of prognostic models, **Chapter 5:** head-to-head comparison and **Chapter 7**: Case-ascertainment strategy)? 3) What practical advantages does the model have for physicians (e.g. ease of use, cost) and what are the physician's preferences for the various potential advantages (**Chapter 6:** Survey)?

When comparative studies are available, the best model is the one that provides the highest NB for a specific threshold or the one that provides the lowest event rate in the low-risk group. In the absence of comparative studies, one may be confronted with the following situations: 1) A model is dominant if it provides an acceptable event rate in the low-risk or high-risk group, and performs better than other models in similar populations for the same outcome and time-point in external

validation studies, is easily usable in clinical practice or less costly. 2) If a model provides satisfactory performance but is likely to be improved by adding a variable and no updating study is available, one should use the a priori probability of developing the outcome for the model from external validation studies and the likelihood ratio for the marker to be added to the model to assess the post-test probability and compare this to the "old" model or other models; perhaps using the absolute risk difference to calculate the NNT (number needed to test). 3) If the compared models present similar performances that are judged to be acceptable and good; the more practical one should be preferred. This depends not only on prediction performance but requires the model to be simple and memorable, readily available, easy to apply, reproducible (within and between), not costly and safe.

CONCLUSIONS

This chapter highlights the importance of reliable and robust methodology for designing and conducting a prediction model study, assessing its scientific quality and evaluating its performance.

This chapter discusses the issues encountered when seeking to identify a good prognostic model during the period of time that I was working on my DPhil research when reporting, critical appraisal and risk of bias assessment tools were not available. It shows a change in the concept of internal validation with the use of sophisticated statistical measures to overcome optimism and best fit a model, the essential steps of externally validating and updating a model, and the scarcity of impact studies that are needed to support the choice of a model for clinical decision making.

My review of existing performance measures helped to select simple measures for presenting a model, basic statistical measures for evaluating model accuracy (calibration) and discrimination, classification/ reclassification and decision-analytic measures, all with their advantages and

limitations. This provides the foundation for my assessment of performance in the systematic reviews (**Chapters 2 and 4**), and for the selection of the most appropriate measures for assessing performance in direct comparison studies (**Chapter 5**) and in development studies (**Chapters 7 and 8**).

Table 3.1: Basic statistical measures

Statistical measure	Performance measure	Explanation	Objective - Usefulness
Overall performance	R2 (coefficient of determination)	Amount of variation that is explained by the prediction model (the higher the value, the better the prediction: i.e. small errors in prediction out of the total variation)	Comparison of overall performance measures
	Brier's score (Verification measure of prediction for binary and categorical outcomes)	Distance (mean squared difference) between the predicted and the observed outcome (the lower the distance, the better the prediction).	
Calibration	Agreement between observed and predicted outcomes (probabilities)	Calibration plot (predicted on X axis, observed on Y axis)	Plot by deciles of predictions (use for Hosmer-Lemeshow goodness-of-fit test, Chi-squared test) Calibration by risk category or for subgroup
	Calibration-in-the-large (intercept)	Difference in the mean predicted in the training and internal validation sets and the mean observed in the external validation set	Comparison between development data and external data
	Calibration slope	Regression slope	Shrinkage factor to adjust a model (in internal and external validation): recalibration
Discrimination	Discrimination: Area under ROC curve (AUC) Concordance or Harrell's c statistic (c-index) Discrimination slope	Discrimination: Ability for a model to distinguish subjects with different outcomes. The c-index measures how well a risk marker discriminates between individuals at different risk levels Discrimination slope: absolute difference in average predictions for those with and without the outcome	Graphs: false positive rate (FPR) on X axis, true positive rates (TPR) on Y axis for various cut-offs Comparison of ROC curve with the 45° line Comparison of AUC for different models ΔAUC (difference in c statistic)

Table 3.2: Classification – Reclassification (references for "citations" in text)

(Re) classification measure	Performance measure	Explanation	Objective - Usefulness
Classification	2 x 2 table with TP, FP, FN, TN (true positive, false positive, false negative and true negative)	Compare predicted outcomes by the model (high-risk level versus low-risk level) against observed outcomes (e.g. death versus survival)	Results can be expressed as: sensitivity (TPR) and specificity (1-FPR), predictive values (negative or NPV, positive or PPV), likelihood ratio positive (high-risk) and negative (low-risk) diagnostic odds-ratio (LR+/ LR-) Youden index (sensitivity + specificity - 1)
Reclassification	Reclassification tables	Risk stratification and cross-tabulation of categories for 2 models	Change in risk categories and comparison of observed incidence of events with predicted probability in cells
	Net Reclassification Improvement (NRI)	"Sum of the net percentages of correctly reclassified persons with and without the event of interest"	Category-based NRI NRIs for events and non-events useful (%) Overall-NRI (range: - 2 to 2)
	Integrated Dicsrimination Improvement (IDI) or Continuous NRI	"Sum of the net percentages of persons with and without the event of interest correctly assigned a different predicted risk"	Non category-based NRI NRIs for events and non-events useful (%) Overall-NRI (range: - 2 to 2)

Sensitivity (TPR) is the probability of being classified at high-risk among (PE) patients who developed the outcomes. "1-specificity" (FPR) is the probability of being classified at high-risk among (PE) patients who did not develop the outcomes. Specificity (1-FPR) is the probability of being classified at low-risk among (PE) patients who did not develop the outcomes.

Table 3.3: Decision-analytic measures (references for "citations" in text)

Decision-analytic measure	Performance measure	Explanation	Objective - Usefulness
Net Benefit	$\boldsymbol{NB} = \left[TP - \left(\frac{p_T}{1-p_T}\right) * FP\right] * \left[\frac{1}{N}\right]$ $Weight = \frac{Harm}{Benefit} = \frac{p_T}{1-p_T}$ (P_T: Threshold probability, TP: true positive, FP: false positive)	NB accounts for cost of misclassification and weighs FP against TP ("exchange rate"). FP classification is valued in terms of TP. Unit is true positives. NB expressed in TP/1000	NB for a model evaluates the consequence of clinical decision that depends on decision threshold (useful to qualify high-risk or low-risk groups and define the relative weight of TP and FP classification).
Decision Curve Analysis	DCA: plot of NB over a reasonable range of threshold probabilities	Decision curve for competing model(s) compared to "treat all" and "treat none" strategies.	Can compare more than two models. The strategy with the highest NB at a particular P_T has the highest clinical value.
Weighted comparison index or Net Δsensitivity (model2 - model1)	$\boldsymbol{Net\ \Delta Sens} = \Delta Sens + \frac{1-event\ rate}{event\ rate} * \frac{p_T}{1-p_T} * \Delta Spec$ "$\boldsymbol{Equivalent\ Net\ Increase\ in\ TP\ per\ 1000}$" = "$Net\ \Delta\ Sensitivity * event\ rate * 1000 = \boldsymbol{\Delta NB}$	"Weighted comparison of the sensitivity difference and the specificity difference of two models taking into account the relative clinical cost (misclassification costs) of a false positive compared with a false negative results and event rate"	Convertible into ΔNB Compares two models
Weighted NRI	$wNRI_T$ accounts for threshold probability (formulae incorporates either TP and FP or sensitivity and specificity with event rate)	Weights the NRI_T with misclassification cost	Compares two models.
Relative Utility (Relative Utility Curve)	RUC	"Expresses NB_T relative to the net benefit of the baseline strategies and the maximum net benefit"	Uses risk prediction Does not require precise specification of harms and benefits
Disease Free Survival or Event Free Life Year	DFS - EFLY	Accounts for the proportion of patients evaluated who are treated, and the benefit and costs for those treated (in terms of EFLY).	"Accounts for the different costs and benefits accrued over time in populations with different mean risks"

Net benefit can be calculated from sensitivity and specificity, and event rate: $NB = \left[event\ rate * Sens - \left(\frac{p_T}{1-p_T}\right) * (1 - Spec) * (1 - event\ rate)\right] * \left[\frac{1}{N}\right]$.

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Chapter 4: Prognostic Models in Acute Pulmonary Embolism: a Systematic Review and Meta-Analysis.

INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), remains a common and potentially fatal disorder, despite improvements in its management over recent decades. When someone has a PE, his main short-term adverse outcomes are all-cause death, PE-related death, VTE events and bleeding and it is important to identify the most effective way to treat each patient in order to reduce the risk of these outcomes.

In acute PE, there is ongoing debate about how to choose the most appropriate management for a specific patient[1-4]. Usual care in the early phase is to treat patients in hospital and to use anticoagulants in normotensive patients or rescue thrombolysis in patients with hypotension or cardiogenic shock. Other options are also available for normotensive patients and their use might depend on the estimated risk for adverse outcomes for the individual patient. These options include home treatment for patients at low-risk, or closer monitoring and escalating therapy for patients at high-risk.

Prognostic tools seek to classify patients by their risk of adverse outcomes to help select appropriate management for an individual patient. The European Society of Cardiology 2008 guidelines[1] suggest using the haemodynamic status based on systolic blood pressure (SBP) and signs of right ventricular dysfunction (RVD) and ischemia. The subsequent AHA Scientific Statement[2] considers that low-risk stable PE patients with no prognostic markers of RVD/ischemia "may still have significant rates of morbidity and mortality that are functions of older age and comorbidities".

Systematic reviews of individual prognostic variables[5-9] have shown inconsistent results across studies, leading to the development of prognostic models. The large number of studies of these prognostic models and differences between them suggest the need for a systematic review that could assess study quality, synthesize findings across studies, assess the validity of the original models and provide the best estimate from each model. I present such a review in this chapter, because determining which prognostic models work, and which work best, is likely to have an important impact on clinical decisions and on research.

My systematic review assesses the characteristics and quality of studies of prognostic models in acute PE patients. It investigates the performance and utility of the prognostic models, through the phases of their development in construction, validation, update and impact studies. This research will allow me to compare the various prognostic models and strategies with the original and simplified versions of the pulmonary severity index (PESI and sPESI) models, and the strategy recommended by the 2014 ESC[3] guidelines.

METHODS

Selection Criteria

Criteria for considering studies for this review were derived from previous reviews of prognostic models[10-13]. To be eligible, studies had to have developed a prognostic model to predict the outcome of patients with an acute symptomatic PE, with the specific aim of constructing a new prognostic model or validating, updating or studying the impact of an existing one. Any prognostic model which has been used for PE was eligible. The models needed to contain a combination of at least two prognostic variables to predict patient outcome, incorporated from across the following characteristics: demographic/clinical, biological and imaging-related. Patient outcomes were

death, PE related-death or VTE (DVT or PE) recurrence. Only hospital-based studies were considered for inclusion.

The following studies were not eligible: prognostic studies validating individual prognostic indicators, population-based studies, studies performed in selective populations (asymptomatic PE, unstable PE, cancer patients, elder patients, specific risk group except when assessed in impact studies) or considering surrogate outcomes only. Because they include not only prognostic but also practical variables for hospitalisation, checklists that are used to exclude patients from early discharge or home treatment were not considered strictly prognostic. Thus, studies on the safety of early discharge or home treatment based on these criteria were not included unless their objective was clearly to derive and validate the checklist or to compare it to existing prognostic models. Unpublished articles or those published only as conference abstracts, discussion articles on prognostic models or indicators or patient management were not included. If a study was published more than once, the first published article or the article combining cumulative results from different studies was included.

Search Methods and Search Strategy

Studies were sought through electronic databases: OVID versions of MEDLINE and Embase, and the Cochrane Library, from the inception of each source to August 2016. Given that there are many conference presentations in this area, I corresponded with authors and did further searching in Google Scholar and other databases to check for articles that were recently published or were pending. Searching also covered “grey literature” (Table A4.1.1), as well as the reference lists of relevant articles and books, citation indexes and hand-searching of relevant journals. There were no date or language restrictions on the searches.

I used the following MESH terms and text-words: pulmonary embolism.tw., exp Pulmonary Embolism/, exp Venous Thromboembolism/, prognos*.tw., exp Prognosis/, predict*.tw., cohort stud*.tw, exp Cohort Studies/, course.tw., exp Incidence/, score.tw., model*.tw., index.tw.,

rule.tw., criteria.tw., tool*.tw., severity index*.tw., geneva.tw., davies.tw.. These were combined as shown in appendices (Table A4.1.2).

Data Collection

Selection strategy

Potentially eligible studies were identified by examining titles and abstracts or other summaries as available, and their full articles were obtained to assess eligibility criteria, before critical appraisal. Study identification was done by two independent and blinded assessors to minimise selection bias. Disagreements were resolved through discussion.

Data extraction content

The data extraction form had six detailed sections: verification of the study's eligibility, information about the study, assessment of study quality, assessment of methods relevant to the development phase of the model, general findings of the study and results of model performance (Table A4.1.3).

Data extraction management

I created an electronic data collection form in Excel, with an explanation for the data extraction items in corresponding cells, but without coding instructions. Contents were adjusted throughout the data extraction process. I extracted the data and this was checked by a second reviewer to obtain reliable information on study findings and study methodology. Disagreements were resolved by discussion.

Dealing with missing data

Study investigators were contacted by e-mail for details not reported in the published reports. A standard data collection form was used to assist with this, when needed.

Assessment of study quality

All studies were assessed for methodological quality[10 13-18] and risk of bias in regard to study design, analysis and reporting. This used predefined criteria for type of study, sample of patients (proper formation of inception cohort, description of referral pattern), adequacy of prognostic factors, adequacy of outcome measures, blind assessment of outcomes, completeness of follow-up, sample size, treatment, missing data, and adjustment for all potential confounders (Chapter 2 - Figure 2.8). Summary scores were not used to categorise studies as high or low quality[17 19] but "risk of bias" figures were produced to show the findings graphically.

Data Analysis

Descriptive analyses were used for the type and phase of development of the model, study characteristics, population and setting patterns, patient characteristics, prognostic information, prognostic modelling and other data analyses, and study quality.

Quantitative analyses were performed at each relevant model risk cut-off level for various outcomes and time-points. These used data from model validation and model update studies, with and without the results of the model construction study. Outcomes were all-cause mortality, PE-related mortality, VTE recurrence, major or clinically relevant bleeding, and composite outcomes. These outcomes were assessed for the initial phase (i.e the first 5 to 10 days or during hospitalization, called "in-hospital" event rate), at 1 month and at 3 months. Summary estimates (SE) and their 95% confidence intervals (95% CI) were calculated for the population event rate (i.e. the prevalence), the proportion of patients in risk categories and the incidence of events within risk categories. The analyses used the *metaprop* statistical program implemented in Stata by using the ftt option which performs the Freeman-tukey double arcsine transformation, computes the weighted SE and performs a back-transformation to proportions on the SE[20]. SE of sensitivity and specificity and summary ROC curves were obtained using the bivariate random-effects model[21 22]

when data were available from at least four studies. This analysis was performed using *metandi*[23] and *GLLAMM*[24] modules in Stata/SE (version 13.1).

Studies that compared models either within the same article or in different articles or shared the same cohort of patients in various model development phases were included once for the analysis of population event rates and as often as the number of prognostic models that were assessed for the analysis of risk group distribution, the incidence of events within risk groups and the prognostic performance of a model. Because of anticipated between-study variability in the effect size, I used a random-effects model to pool study results and the I^2 statistic to test for heterogeneity. I assessed homogeneity of study designs, differences because of the case mix and statistical heterogeneity (based on Cochran's Q test and Higgins I^2 statistic) to decide whether to combine the results of individual studies. I used funnel plots and Egger's and Begg's statistics if a sufficient number of studies (≥ 10)[25] were available to examine whether there was an association between effect size and study size (expressed by the standard error of the effect size) that might be due to publication bias. I assumed there were no small-study biases when the tests were not statistically significant at the 5% level. I also examined the likely influence of the presence or absence of bias in sensitivity analyses, with subgroup analyses for patient selection ("representative" or "not representative" defined according to study quality criteria as shown below), setting (admission to "emergency department (ED)" or "ED and non-ED"), haemodynamic status ("stable" and "both stable and unstable" PE patient groups), type of study ("prospective" or "retrospective") and the phase development of studies ("derivation/ internal validation" and "external validation/ update"). To be representative (i.e. no selection bias), a study had to meet all the following: recruitment strategy and inclusion criteria defined, sample selection explained, adequate description of diagnostic criteria, and clinical and demographic characteristics fully described.

Data Synthesis

To decide whether a prognostic model would be helpful for clinical practice, the following factors were required in external validation studies: direction and size of effect, and effect consistency across studies in the meta-analysis; and strength of evidence for the effect based on study quality and statistical measure of uncertainty[17]. For a valid model to be acceptable, its utility should ideally have been demonstrated in an impact study, such as in a single group management study using the model or in a randomized trial comparing outcomes for patients in whom the model is used to inform decision making versus those for whom it is not used. However, as discussed below, there are very few such studies.

RESULTS

Search results

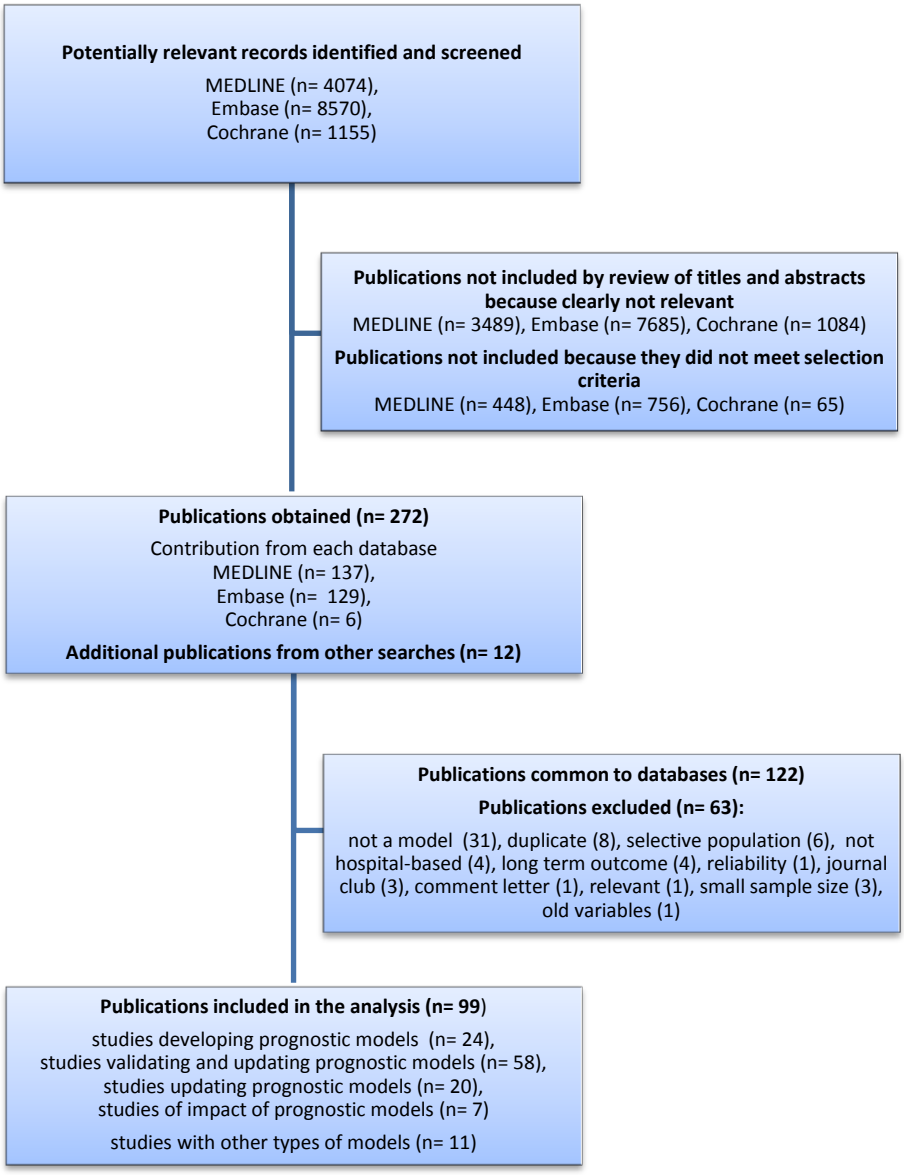
Figure 4.1 shows the flow of studies through my review following PRISMA guidelines[26]. The number of potentially relevant records, identified and screened in each database were 4074 in MEDLINE, 8570 in Embase and 1155 in the Cochrane Library. Most of these were not eligible because they were clearly not relevant (3489, 7685 and 1084, respectively) or because they did not meet selection criteria (448, 756 and 65, respectively). From 272 publications that were retained from these databases (137, 129 and 6 respectively) and from 12 additional publications from other sources, 122 were removed as duplicate records that had been found in more than one database and 63 were excluded[27-89] for various reasons: not a (prognostic) model[27-29 33-36 44-46 49 52-54 56-58 60 62-64 66 70 71 73-76 78 80 81] (n=31), duplicate [31 37 50 51 65 72 88 89] (n= 8), selective population/ patients[32 67 69 79 82 83] (n= 6), not hospital-based[39 40 61 84] (n= 4), long term outcome[38 85-87] (n= 4), reliability study[43] (n= 1), journal club[41 48 68] (n= 3), comment letter[47] (n= 1), not clinically relevant[55] (n= 1), very small sample size (< 80 patients)[30 42 59] (n= 3), very old variables in the model[77] (n= 1).

Finally, 99 studies were included in the review, 87 from the database searches[90-176] and 12 from other sources[177-188] such as lists of references and conference abstacts (some of which were published as journal articles shortly after the search period but one[185] was missed from MEDLINE and Embase). Among studies found in the databases, most were in both MEDLINE and Embase[90-102 104-124 126 128-171 173-176], but one study was not found in MEDLINE[127] and three studies were not in Embase[103 125 172]. The 3 studies identified in the Cochrane Library[97 113 145] were also found in MEDLINE and Embase.

In total, among the 99 studies, 88 includeq variables specific to the domain of PE and its prognosis: 24 were identified as model construction studies[90 92-95 102 110 119 121 124 128 130 131 136 144 157 167 170-174 181 185], 58 as model external validation studies (some of them including model update studies)[96 98 99 101 103-108 110-115 117-119 121-126 129 130 132 135-139 141 143 144 146 148 150 152-155 158 160-162 164-166 168 169 178 182 183 185-187], 20 as model update only studies[93 106 116 120 124 133-135 140 146 150 156 158-160 162 166 177 185 186] and 7 as measuring model impact[91 97 145 147 163 179 184]. For the remaining 11 studies[98 100 109 127 142 149 151 175 176 180 188], variables in the model either were originally not specific to PE [98 127 142 149 151] or to its prognosis[100], or concerned a hospital checklist[109 175 176 180 188] that is a combination of prognostic and practical variables for outpatient management.

Full details about search results are provided in tables A4.1.4 to A4.1.12.

Figure 4.1: Flow chart of search results.



Descriptive analysis

Prognostic models

The review identified three types of models related to risk stratification of patients with PE (table A4.2 and table A4.3). Models of type 1 include variables specific to the domain and to the prognosis of PE: demographic, comorbidities, clinical findings or variables related to RVD or ischemia based on biomarkers and imaging tests (full details in table A4.2). Models of type 2 apply models from other domains such as the Global Registry of Acute Coronary Events GRACE[149], the Charlson's Comorbidity Index[142 151] or other models (sCRB-65[127], APACHE $\geq$ 19[98], GLASGOW COMA SCALE $\leq$ 10[98], EUROSCOREII $\geq$ 5.9[98]), or apply diagnostic prediction rules [100] for the assessment of PE prognosis. Finally, type 3 models incorporate hospital checklist variables as exclusion criteria from early discharge or home treatment[109 175 176].

Among the 24 type 1 prognostic models that were identified in model construction studies, ten[94 95 102 119 121 131 157 167 171 185] underwent external validation or were updated; some of them many times. Three[94 167 171] were assessed in impact studies[97 145 179]. Three other models were tested in impact studies[91 180 184], without being previously reported in a construction study. Table A4.3 shows the variables that were mostly included in final models. These variables were: heart rate, systolic blood pressure, active cancer, age, peripheral oxygen saturation, heart failure or chronic lung disease and altered mental status.

Most studies identified for this review were external validation or update studies.

Study characteristics

Research objective, type of study and study design, setting, country, number of participating centres, patients (age, sex, and haemodynamic status), outcomes, time points and corresponding event rates are displayed in tables A4.4.1 to A4.4.5.

In the 24 model construction studies (table A4.4.1), the objective was usually to risk-stratify patients (18 studies) rather than to identify low-risk patients. Eleven studies were prospective, 8 reported on stable PE subgroup and 8 were prospective and concerned stable PE as well. In 9 studies, patients were recruited in emergency departments (ED) and in 13 studies inception started on admission. Eleven were multicenter studies. The RIETE register[136] included the largest cohort, followed by the PESI[94] and Prognostic algorithm[95] cohort that included large derivation and internal validation sets but the study was retrospective, had missing data and was missing information on PE diagnosis and the type of treatment received. Four studies[102 121 157 170] were sound methodologically and clinically relevant and present the following characteristics: prospective multicenter study, inception on admission, patients from ED, stable PE patients reported, adequate early outcome and time point.

In the 58 model external validation studies (table A4.4.2), the main objective was to identify low-risk patients. Other objectives were to assess added value of prognostic variables, head-to-head comparison or the identification of stable PE patients at high risk. Among the prospective studies (n=10), those that included both stable and unstable PE were as follows: one study[148] validated the ESC model for 30-day mortality, another study[175] compared Hestia checklist criteria with sPESI for 7-day, 30-day and 3-month death, another one[153] compared PESI, sPESI and shock index, one study[135] assessed the additive value of HFABP, BNP and hs-cTnI to PESI, and one study[144] compared a modified sPESI to sPESI. In studies of stable PE patients, GPS[101 125], PESI[125 150], sPESI[110 125 146], 2008-ESC[110], FAST[110] and TELOS[185] models were validated in six studies. One study[110] compared three models FAST, sPESI and ESC, one study[125] compared GPS, PESI and sPESI, another study[185] compared TELOS and sPESI, and one study[146] assessed the value of adding RVD markers to sPESI. Reliability was assessed in two studies[104 152].

Model update studies (n=20) (table A4.4.3) assessed the value of adding a two-test or a three-test strategy to PESI, based on a combination of RVD, cTnI, US-detected DVT, to identify high-risk PE

patients[120]; assessed the additive value of TTE-RVD to shock index[166], the additive value of CT-RVD to Hestia[176], the additive value of TTE-RVD[158], CT-RVD [106 159], BNP[135 158], NT-proBNP[106], cTn[106 140 150 162], high-sensitive cTnI[116 135], HFABP[135] or WBC and SIRS[124]to PESI[116 135 150 158], the additive value of TTE-RVD and BNP to PREP[157], or the additive value of cTn[146 162], high-sensitive cTnT [133 146], NT-proBNP[134] or lactates[185] to sPESI, or the additive value of lactates[186] to Bova in order to identify patients at lower risk or at higher risk; or assessed the effect of cause of death classification on sPESI whether combined or not to cTnI[156], or the effect of combining a new model with sPESI[93]. Nine studies collected data prospectively and were specific to stable PE.

Seven studies measured model impact (table A4.4.4). Five were performed in patients identified as low-risk by the model, assessing the safety of early discharge or outpatient treatment. This was done in a single group management study for GPS[179], NTproBNP[91] and sPESI combined to cTn[147], and in a randomized trial where outpatient management was compared with standard hospitalisation (in-patient treatment) either by using the Spanish model[145] or by using PESI in the OTPE study[97]. The PEITHO randomized double-blind trial [184] assessed the role of fibrinolytic therapy Tenecteplase in normotensive PE patients considered at intermediate-high risk by TTE-RVD or CT-RVD, and myocardial injury as indicated by a positive test for cTnI or cTnT. Another study assessed the use and the impact of model-based risk stratification on treatment decisions and outcome in clinical practice[163]. All studies were prospective, except the latter[163].

The characteristics of the type 2 and type 3 model studies are displayed in appendices (Table A4.4.5). For type 2 models[100 127 142 149 151] (variables originally not specific to PE or to its prognosis), studies were most often single centre and retrospective, conducted outside emergency departments, had inception on admission and an objective of risk stratification, and rarely reported separately on stable PE alone. For type 3 models (using hospital criteria checklists), the focus was on identifying low-risk patients for outpatient management in derivation [109]validation[175]

[176] or impact[109 180 189] studies, and comparison of checklists without and with markers of RVD (CT-RVD[176], NTproBNP[180]).

Population and patient characteristics

Study population – settings: Patients were included at clinical suspicion or diagnosis confirmation. Objective methods used to confirm the diagnosis of PE were not always integrated within a diagnostic strategy. Most studies included out-patients from emergency departments (ED) at university hospitals. They rarely included patients from a medical department other than an ED and rarely included in-patients. Reasons for excluding specific groups varied across studies and were related to the diagnostic protocol, treatment, consent (for randomized trials and other study designs), delay in obtaining prognostic variables, lack of information from databases in retrospective studies, unavailability of participants for follow-up, patient characteristics (unstable PE, short life expectancy and severe comorbid conditions) and delay from clinical symptoms to diagnosis or inclusion. There were failings in the reporting of the recruitment strategy, the proportion of eligible patients and the proportion enrolled in most studies; except those that assessed model impact.

Patients: Demographic characteristics (age, sex), risk factors (including history of VTE, cancer and others), comorbidity (chronic cardiac/ lung/ cerebrovascular/ renal diseases), haemodynamic status and vital signs (systolic blood pressure, heart rate, respiratory rate, altered mental status and arterial oxygen saturation), and therapeutic management (initial treatment, duration of hospitalisation) are displayed for each study, showing the types of patient across the studies (tables A4.5.1a to A4.5.5.b). The main differences in patient characteristics were related to VTE risk factors and comorbidities. Reporting on demographic characteristics and vital signs varied across studies and does not help in exploring differences between them. For example, although considered as stable, patients in the Palmieri[150] study were selected on the basis of CT only, had worse vital signs and more VTE risk factors. In the model impact studies that assessed outpatient

management in patients identified as low-risk, patient characteristics were not comparable across studies: patients in OTPE study[97] were younger, there were more cancer patients in Agterof study[91], and a higher proportion of patients with low arterial oxygen saturation were in Otero study[145]. This might explain the higher mortality rate with this model despite the longer duration of hospitalization even in the early discharge group. The Otero study[145] used Uresandi's model [167] (with other variables) but vital signs were not considered as potential prognostic factors, unlike the OTPE study[97] that used the PESI model[94] and considered demographic variables and comorbidity as well as vital signs.

Prognostic information: Some studies did not report the methods of collecting information on prognostic variables and outcomes (see study quality section, below).

Study quality

Quality of individual studies and a summary of study quality at different model development phases are shown in figures A4.7.1 to A4.7.12.

Among model construction studies (figure A4.7.1, figure A4.7.2), PREP[157], esTiMaTe[121], Bova[102] and TELOS[185] models satisfied most of the study quality criteria. Criteria that were met in at least 70% of the included studies are: inclusion criteria definition, sample selection, length of follow-up, criteria about the outcome (objectiveness, full definition, appropriateness, and full definition of prognostic variables. Criteria that were met in less than 30% of the included studies are: sample completeness (selection bias), reasons for lost to follow-up reporting, availability of prognostic variables, description of treatment, justification of sample size and statement on how lost to follow-up treated in analysis.

In model validation studies (figure A4.7.3a, figure A4.7.3b, figure A4.7.3c and figure A4.7.4), including those that also updated the model, the most recent validation studies[121 135 146 148 158 185] satisfied most of the study quality criteria. The most often met criteria concerned specification of

inclusion criteria, sample selection, follow-up, outcome (objective, fully defined, appropriate), and full definition of prognostic variables. Major concerns in the quality assessment related to sample completeness, reporting on reasons for lost to follow-up and differences with participants who did not complete the study, justification of sample size and statistical analysis.

In model update studies (figure A4.7.5, figure A4.7.6), four studies[134 135 146 158] satisfied most of the quality criteria. Most of the criteria were often met but there are concerns about sample completeness, and reporting on reasons for lost to follow-up and differences with participants who did not end the study, justification of sample size and how lost to follow-up was treated.

Model impact studies (figure A4.7.7, figure A4.7.8) had the best compliance with the study quality criteria, as most of the key factors are provided[91 97 145 184].

For type 2 and type 3 studies, the number of studies is too small to draw general conclusions. In type 2 studies (figure A4.7.9, figure A4.7.10), although inclusion criteria were well defined, there are problems with sample selection and sample completeness in all[98 127 142 149 151] but one study[100], in justification of sample size, and data analysis. In type 3 studies (figure A4.7.11, figure A4.7.12), the main concerns are about a lack of information on reasons for lost to follow-up, justification of sample size, and data analysis (missing data, lost to follow-up, statistical adjustment).

Quantitative analysis - Event rates

Population event rates

There were a total of 59,896 patients in the included studies if patients in each cohort are counted once only, regardless of how many studies analyzed them[11] and if impact studies that involved only low-risk or intermediate-risk patients are excluded. One study[113] that performed a

[11] Patients in study cohorts used for assessment of multiple prognostic models or for merged cohorts were accounted for once only

post-hoc analysis of a randomized trial with a selection bias arising from the randomized open label design was excluded.

Population event rate (prevalence) was reported in different ways. Most studies reported on in-hospital (n=31) and 30-day (n= 32) all-cause death, feweron in-hospital (n= 9) and 30-day (n= 12) "PE-related mortality" or in-hospital (n= 9) "Death and Adverse outcome". Analysis based on the Freeman-Tukey double arcsine transformation method with back-transformation on the pooled estimate with random-effects model (table 4.1.a) showed overall in-hospital, 30-day and 3-month summary estimates [95% CI] of the prevalence to be 6% [95% CI: 4.8 – 7.4] (31 studies), 7% [5.9 – 8.1] (32 studies) and 6.7% [5.5 – 8] (12 studies) for all-cause mortality; 3% [2 – 4.2] (9 studies), 4.1% [3.1 – 5.2] (12 studies) and 1.9% [0.8 – 3.3] (7 studies) for PE-related mortality; and 0.2% [0.0 – 1] (5 studies), 1.3% [0.8 – 1.8] (5 studies) and 1.8% [0.7 – 3.4] (5 studies) for VTE recurrence. Table 4.1.a displays these results, as well as composite event rates ("Death VTE Major bleeding", "Death Adverse outcome", "Adverse outcome"), major and non-major clinically relevant bleeding, and fatal bleeding. Among all events rates, in-hospital "Death Adverse outcome" had the highest summary population event rate after all-cause mortality and PE-related mortality i.e. 7.3% [4.3 – 11.1] (9 studies). The major limitation in this analysis was the presence of high clinical, methodological and statistical heterogeneity. When analysis was restricted to stable PE patients from emergency departments in prospective studies, event rates regarding "All-cause mortality" (4 studies) and "Death Adverse outcome" (4 studies) remained high: 5.7% (0.3 – 16.4) and 9.5% (2.3 – 20.6) respectively (Tables 4.1.b and 4.1.c). They decreased if analysis was further restricted to studies with no apparent selection bias. However, the number of studies was too small to draw firm conclusions. Subgroup analysis for in-hospital, 30-day and 3-month "all-cause death" and for in-hospital "Death Adverse outcome" did not reveal any clear difference in prevalence between subgroups but interpretation is difficult due to statistical heterogeneity and the small number of studies.

Table 4.1.a: Population event rates

Outcome	Haemodynamic status	N of studies	In-hospital			N of studies	30-day			N of studies	3-month		
				0.95 CI				0.95 CI				0.95 CI	
All-cause mortality	Both stable & unstable	15	0.057	0.039	0.079	10	0.071	0.052	0.094	2	0.048	0.031	0.067
	Stable	5	0.046	0.004	0.126	9	0.072	0.052	0.096	1	0.090	0.057	0.137
	Not reported	11	0.072	0.051	0.095	11	0.067	0.048	0.087	6	0.071	0.055	0.09
	Unclear					2	0.053	0.034	0.076	3	0.061	0.034	0.096
	Overall	31	0.06	0.048	0.074	32	0.07	0.059	0.081	12	0.067	0.055	0.08
PE-related mortality	Both stable & unstable	4	0.047	0.037	0.058	5	0.042	0.03	0.057	1	0.031	0.011	0.088
	Stable	3	0.018	0.004	0.04	5	0.041	0.022	0.065				
	Not reported	2	0.023	0.017	0.031	1	0.020	0.1	0.04	5	0.014	0.005	0.027
	Unclear					1	0.08	0.046	0.135	1	0.047	0.028	0.078
	Overall	9	0.03	0.02	0.042	12	0.041	0.031	0.052	7	0.019	0.008	0.033
VTE recurrence	Both stable & unstable	3	0.007	0.000	0.022	4	0.013	0.007	0.021				
	Stable									2	0.011	0.003	0.025
	Not reported	2	0.002	0.001	0.003	1	0.012	0.006	0.024	2	0.036	0.02	0.055
	Unclear									1	0.007	0.002	0.024
	Overall	5	0.002	0.000	0.01	5	0.013	0.008	0.018	5	0.018	0.007	0.034
Death VTE Major bleeding	Both stable & unstable	1	0.045	0.03	0.069								
	Stable	1	0.057	0.033	0.097					1	0.095	0.062	0.144
	Not reported	2	0.037	0.034	0.039	1	0.049	0.035	0.07				
	Unclear									1	0.101	0.072	0.141
	Overall	4	0.048	0.033	0.066	1	0.049	0.035	0.07	2	0.099	0.074	0.127

Outcome	Haemodynamic status	N of studies	In-hospital			N of studies	30-day			N of studies	3-month		
				0.95 CI				0.95 CI				0.95 CI	
Death Adverse outcome	Both stable & unstable	3	0.073	0.031	0.13	2	0.079	0.06	0.10				
	Stable	4	0.095	0.023	0.206	1	0.21	0.142	0.30				
	Not reported	2	0.044	0.033	0.057								
	Unclear												
	Overall	9	0.073	0.043	0.111	3	0.12	0.055	0.204	0			
Adverse outcome	Both stable & unstable	3	0.176	0.097	0.273								
	Stable					1	0.064	0.044	0.093				
	Not reported												
	Unclear												
	Overall	3	0.176	0.097	0.273	1	0.064	0.044	0.093	0			
Major bleeding	Both stable & unstable	3	0.02	0.005	0.045	3	0.023	0.018	0.029				
	Stable	1	0.023	0.011	0.048					1	0.025	0.011	0.057
	Not reported	3	0.021	0.008	0.039	2	0.031	0.02	0.044	2	0.04	0.023	0.061
	Unclear									1	0.01	0.003	0.029
	Overall	7	0.021	0.012	0.032	5	0.024	0.019	0.03	4	0.026	0.012	0.046
Fatal bleeding	Both stable & unstable	1	0.014	0.006	0.033	1	0.005	0.002	0.01				
	Stable									1	0.01	0.003	0.036
	Not reported	1	0.006	0.002	0.015								
	Unclear									1	0.003	0.001	0.019
	Overall	2	0.008	0.003	0.015	1	0.005	0.002	0.01	2	0.006	0.000	0.015

Not accounted for in the analysis of population event rates studies that included only specific risk groups. Cohorts that were used by more than one study were included once.

Table 4.1.b: All-cause mortality in acute PE patients at the emergency department in relation to haemodynamic status, type of study and patient selection

Haemodynamic staus	Number of studies	Number of prospective studies	Number of representative studies	Event rate (95% CI)	Outcome
All studies	14			0.062 (0.033 – 0.099)	In-hospital "All-cause mortality"
Both stable & unstable	6			0.049 (0.020 – 0.089)	
Stable	5			0.046 (0.004 – 0.126)	
Stable	4	4		0.057 (0.003 – 0.164)	
Stable	2	2	2	0.008 (0.002 – 0.019)	
All studies	17			0.071 (0.051 – 0.092)	30-day "All-cause mortality"
Both stable & unstable	8			0.069 (0.044 – 0.098)	
Stable	3			0.066 (0.033 – 0.109)	
Stable	2	2		0.048 (0.030 – 0.068)	
Stable	2	2	2	0.048 (0.030 – 0.068)	
All studies	10			0.067 (0.053 – 0.082)	3-month "All-cause mortality"
Both stable & unstable	2			0.048 (0.031 – 0.067)	
Stable	1			0.090 (0.057 – 0.137)	
Stable	1	1		0.090 (0.057 – 0.137)	
Stable	1	1	1	0.090 (0.057 – 0.137)	

Table 4.1.c: In-hospital "Death and Adverse outcome" in acute PE patients at the emergency department in relation to haemodynamic status, type of study and patient selection

Haemodynamic staus	Number of studies	Number of prospective studies	Number of representative studies	Event rate (95% CI)	Outcome
All studies	5			0.089 (0.030 – 0.174)	In-hospital "Death and Adverse outcome"
Both stable & unstable	1			0.071 (0.041 – 0.121)	
Stable	4			0.095 (0.023 – 0.206)	
Stable	4	4		0.095 (0.023 – 0.206)	
Stable	2	2	2	0.045 (0.028 – 0.065)	

Representativeness means that all the following criteria to avoid selection bias are met: recruitment strategy and inclusion criteria defined, sample selection explained, adequate description of diagnostic criteria, and clinical and demographic characteristics fully described (see study quality assessment).

Risk groups - All-cause mortality

The distribution of risk groups for a model (proportion of patients in low-risk or in high-risk groups) according to specified cut-off levels and the incidence of all-cause mortality within risk groups, expressed in % [95% CI], are shown in detail (table 4.2a, table 4.2.b and table 4.2.c) and summarised next.

For GPS≥ 3 vs GPS≤ 2 cut-off (table 4.2.b), mortality was reported in three external validation studies; the prevalence of the low-risk group is 79.7% [74.1 – 84.7] and the incidence of 30-day mortality in the low-risk group is 6.8% [1.5 – 15.3]. The prevalence of high-risk group is 20.3% [15.3 – 25.9] and their incidence of 30-day mortality is 16.7% [9.7 – 25.1].

For PESI≥ III vs PESI≤ II cut-off, the overall prevalence of low-risk group is 41.1% [38.9 – 43.2] and the overall in-hospital, 30-day and 3-month mortality rates within the low-risk group are 1% [0.6 – 1.3] (6 studies), 1.3% [0.8 – 2] (12 studies) and 0.6% [0.2 – 1.2] (6 validation studies). The overall prevalence of high-risk patients is 58.8% [54.8 – 62.6] and their overall in-hospital, 30-day and 3-month mortality rates are 9.4% [8 – 11], 10.4% [8.8 – 12.1] and 12.9% [8.4 – 18.1]. Summary estimates of the prevalence and the mortality rates in low-risk groups from external validation studies are consistent with those of the derivation and internal validation samples. Results for 30-day all-cause death in high-risk and low-risk PESI gropus are displayed in figures 4.2.

For sPESI, the overall prevalence of low-risk group is 36.8% [34.1 – 39.6]. The overall in-hospital, 30-day and 3-month mortality rates are 0.3% [0 – 2.1] (4 external validation studies), 0.8% [0.4 – 1.5] (15 studies) and 0.4% [0 – 1.3] (3 external validation studies). The overall proportion of high-risk patients is 63.2% [60.4 – 65.9] and the overall in-hospital, 30-day and 3-month mortality rates are 8.4% [2.5 – 17.3], 8.8% [7.1 – 10.8] and 13.6% [8.5 – 19.6]. Results are consistent across derivation, internal validation and external validation samples. Results for 30-day all-cause death in high-risk and low-risk sPESI gropus are displayed in figures 4.2.

With the Algorithm (4 studies), 21.8% [19.1 – 24.6] of patients are classified as low-risk. The in-hospital and 30-day mortality rates are 0.4% [0.1 – 0.7] and 0.8% [0.2 – 1.7]. The results in the validation and the derivation samples are similar.

For the PREP model (mortality reported in 1 external validation study), 67.2% [61.7 – 72.3] of patients are classified at low-risk. The 30-day and 3-month mortality rates are 1% [0.3 – 3.5] and 1.5% [0.5 – 4.3] in the low-risk group, and 7.1% [3.5 – 13.9] and 9.1 [4.9 – 16.4] in the high risk group. In the original study (table 4.3), the incidence of a 30-day composite outcome is 2.5% (1.3-4.8), 37.3% [33.2 – 41.5] of patients are classified at high-risk and the incidence of events is 17.7% [13 – 23.7].

Shock Index classifies 83.5% [81.6 – 85.4] of patients in the low-risk group, but with high 30-day mortality rates of 8.9% [7.3 – 10.6] in this group and 21.4% [16.3 – 26.9] in the high-risk group.

With 2008 ESC, the low-risk group prevalence is 39.5% [25.6 – 54.3] (table 4.2a) and 30.9% [24.4 – 37.8] (table 4.2.b); the in-hospital and 30-day mortality rates are 1.7% [0.8 – 2.8] (3 studies) and 2.2% [0.9 – 4] (4 studies) in the low-risk group, and 10.8% [8.3 – 13.5] and 12.9% [8.9 – 17.4] in the higher risk group. These results apply for “Both stable and unstable” patients. For the stable PE patient subgroup, for “Intermediate-high” risk cut-off (Intermediate-high risk patients have both RVD and myocardial injury and the lower risk that includes Intermediate-low and Low risk groups either one of them or none), the proportion of the lower risk group is 73.7% [53.1 – 89.9] (3 studies) and the in-hospital mortality rate is 7.3% [3.8 – 11.7] in the Intermediate-high risk group and 3.1% [1.1 – 6.1] in the lower risk group.

Similar results are obtained for 2014 ESC at the “Intermediate-high-risk" cut-off with an in-hospital all-cause mortality rate of 7.8% [4.2 – 14.2] in the “Intermediate-high-risk” group and 2.6% [1.7 – 3.9] in the lower risk group (1 study), and a 30-day mortality rate of 7.1% [4.5 – 10.2] in the “Intermediate-high-risk” group and 4.2% [3.2 – 5.4] in the lower risk group (2 studies). With

2014 ESC, at "intermediate-risk" cut-off, the 30-day all-cause death rate in the low-risk group (corresponding to PESI ≤ II or sPESI=0) is 0.4% [0 – 1.2] (2 studies).

Given the high event rate within the 'low-risk' groups from GPS≥ 3, Shock Index and ESC at high cut-off levels, these would not qualify as suitable for the identification of a low-risk patient group. This holds true for the Bova and TELOS models but the number of studies for these two models is too small to draw any firm conclusion.

The performance of models recently constructed is discussed in the model update section (below).

Risk groups - Outcomes other than all-cause mortality

Table 4.3 and table 4.4 show summary estimates with results from studies that report outcomes in terms of PE-related death, adverse outcome (clinical deterioration, haemodynamic collapse), VTE and their combinations in "both stable and unstable" (table 4.3) and separately in "stable" (table 4.4) patient groups. Although many studies were retrospective or were single studies, the results confirm the predictive ability for PESI and sPESI at the optimal cut-offs or less, preferably in combination with biomarkers, and for RIETE PE score for identifying patients at low-risk for these specific outcomes as well, mainly in stable PE. They also confirm the ability of some models to use higher cut-offs to identify patients at very high-risk (30-day event rate over 15 or 20%) such as PREP - Clin ≥ III without or with BNP - TTE-RVD, PESI ≥ IV, PESI V without or with TTE-RVD, ESC high, Shock index, eStiMaTe high, FAST 3, Bova stage III and TELOS. Most of the models combine biomarkers or imaging-based modalities to clinical variables or to preexisting models. In most of the studies, only a small proportion of patients are at very low or at very high risk.

Risk groups - Type 2 and type 3 model studies

Table 4.5 shows the results of type 2 and type 3 model studies. Revised Geneva Score[100] (RGS) and Simplified Geneva Score[100] (SGS) which were originally for the diagnosis of PE may provide a low

3-month mortality rate (0.9% [0.1-12.3]) in patients at low-risk using low cut-offs. Similarly, at the lowest cut-offs, GRACE ACS[149] and GRACE PE[149] risk scores show 1.3% [0.1-17.1] and 1.1% [0.1-15.1] 30-day mortality rate respectively within the low-risk patient groups. Of note, is the large CI for both Geneva and GRACE scores due to the small number of patients in the low-risk groups. Interestingly, there are high event rates (23 to 30%) in the high risk groups of GRACE scores whatever the cut-offs with a high proportion (49 to 81%) of patients in these risk groups, and the high event rate in the high-risk groups of APACHE, GSC and Euroscore. These models need to be validated in prospective studies with larger samples in stable PE. Davies[109] and Hestia[175 176] checklists (table 4.5) show a high proportion of patients at low-risk (42 to 55%) with a small 3-month mortality rate: 1.9% [0.4-5.5] and 1.2% [0.4-3.7] respectively. The low event rate with Hestia is confirmed in an external validation study[188] and an impact study[180], but more research is needed to compare with PESI/sPESI models in impact studies.

Event rates along the risk scale

As expected, the event rates for different outcomes and time-points increase along the risk scale. Table 4.2a, table 4.2.b and table 4.2.c, table 4.3 and table 4.4 show how the predicted outcomes in the derivation samples compare with the observed outcomes in the validation samples (internal, external) at different cut-offs for GPS PESI and other models (2008 ESC, 2014 ESC and Bova). Shifting the cut-off to a lower level or to a higher level provides more appropriate event rates in low-risk groups and in high-risk groups respectively but at the expense of a decrease in the proportion of patients within these risk groups. Thus, improvement in efficacy is associated with a decline in efficiency.

Table 4.2.a: Distribution of risk groups and in-hospital all-cause mortality. Risk cut-offs named after the closest high-risk group; e.g. for Bova III cut-off, the high-risk group is Bova III and the low-risk group includes Bova II and Bova I classes; for Bova II cut-off, the high-risk group includes Bova III and Bova II classes and the low-risk group is Bova I.

Prognostic model Cut-off - Risk groups	Prevalence of risk groups N (%) [95% CI]				Incidence of events within risk groups N (%) [95% CI]			
	Derivation	Internal validation	External validation	Overall	Derivation	Internal validation	External validation	Overall
Algorithm[95 182] - **High** - **Low**	1 (78.4) [77.6 – 79.2] (21.6) [20.8 – 22.4]	1 (78.4) [77.3 – 79.5] (21.6) [20.5 – 22.7]	2 (80.9) [78.6 – 83] (19.1) [17 – 21.4]	4 (78.2) [75.4– 80.9] (21.8) [19.1 – 24.6]	1 (5.2) [4.7 – 5.7) (0.4) [0.2 – 0.8]	1 (6.1) [5.4 – 6.9] (0.9) [0.5 – 1.6]	2 (5.9) [4.5 – 7.5] (0.3) [0 – 1.7]	4 (5.5) [4.4 – 6.7] (0.4) [0.1 – 0.7]
Bova III[138 186] - **High** - **Low**			2 (6.6) [5.3 – 8] (93.4) [92 – 94.7]				2 (11.6) [5.3– 19.6] (3.4) [2.4 – 4.5]	
Bova II[138] - **High** - **Low**			1 (43.5) [37.6 – 49.5] (56.5) [50.5 – 62.4]				1 (11.5) [6.8 – 18.7] (4.8) [2.3 – 9.5]	
2008 ESC High[103 129 168 183] - **High** - **Low**			4 (11.7) [5.8 – 19.2] (88.3) [80.8 – 94.2]				4 (37.2) [25 – 50.2] (4.3) [3 – 5.8]	
2008 ESC High Intermediate[103 168 183] - **High** - **Low**			3 (60.5) [45.7 – 74.4] (39.5) [25.6 – 54.3]				3 (10.8) [8.3 – 13.5] (1.7) [0.8 – 2.8]	
2008 ESC Intermediate High[99 129 168] - **High** - **Low**			3 (26.3) [10.1 – 46.9] (73.7) [53.1 – 89.9]				3 (7.3) [3.8 – 11.7] (3.1) [1.1 – 6.1]	
2008 ESC Intermediate[99 129 168 183] - **High** - **Low**			4 (65.2) [47.9 – 80.7] (34.8) [19.3 – 52.1]				4 (6) [3.8 – 8.5] (0.8) [0 – 2.9]	
2014 ESC Intermediate High[168] - **High** - **Low**			1 (11.6) [9.7 – 13.7] (88.4) [86.3 – 90.3]				1 (7.8) [4.2 – 14.2] (2.6) [1.7 – 3.9]	
GPS-3[101] - **High** - **Low**			1 (18.9) [14.1 – 24.9] (81.1) [75.1 – 85.9]				1 7.9 [2.7 – 20.8] 0.6 [0.1 – 3.4]	

Hestia[175 188] - **High** - **Low**			2 (62.4) [59.5 – 65.4] (37.6) [34.6 – 40.5]				2 (3.4) [2.1 – 5] (0) [0 – 0.5]	
PESI-II[94 143] - **High** - **Low**	1 (80.6) [79.8 – 81.3] (19.4) [18.7 – 20.2]	1 (80.4) [79.3 – 81.5] (19.6) [18.5 – 20.7]	1 (71.4) [64.1 – 77.7] (28.6) [22.3 – 35.9]	3 (80) [78.3 – 81.6] (20) [18.4 – 21.7]	1 (6.9) [6.4 – 7.5] (0.8) [0.5 – 1.3]	1 (7.7) [6.9 – 8.6] (1.1) [0.6 – 1.9]	1 (9.2) [5.2 – 15.7] (2.1) [0.4 – 10.9]	3 (7.2) [6.5 – 7.9] (0.6) [0.3 – 1]
PESI-III[94 112 143 150 168] - **High** - **Low**	1 (59.1) [58.1 – 60] (40.9) [40 – 41.9]	1 (59.3) [57.9 – 60.6] (40.7) [39.4 – 42.1]	4 (59) [46.7 – 70.7] (41) [29.3 – 53.3]	6 (59.2) [56 – 62.4] (40.8) [37.6 – 44]	1 (8.8) [8.1 – 9.5] (1.3) [1 – 1.7]	1 (9.8) [8.8 – 10.9] (1.5) [1.1 – 2.1]	4 (11.1) [6.7 – 16.4] (0.9) [0 – 3]	6 (9.4) [8 – 11] (1) [0.6 – 1.3]
PESI-IV[94 143] - **High** - **Low**	1 (37.4) [36.5 – 38.3] (62.6) [61.7 – 63.5]	1 (37.1) [35.8 – 38.4] (62.9) [61.6 – 64.2]	1 (26.8) [20.7 – 33.9] (73.2) [66.1 – 79.3]	3 (36.5) [34.4 – 38.6] (63.5) [61.4 – 65.6]	1 (11.4) [10.5 – 12.5] (2.3) [2 – 2.7]	1 (12.8) [11.4 – 14.4] (2.6) [2.1 – 3.2]	1 (11.1) [4.8 – 23.5] (5.7) [2.8 – 11.3]	3 (11.7) [10.7 – 12.7] (2.5) [1.9 – 3.2]
PESI-V[94 143 168] - **High** - **Low**	1 (21) [20.2 – 21.8] (79) [78.2 – 79.8]	1 (21.3) [20.2 – 22.4] (78.7) [77.6 – 79.8]	2 (17.6) [14.7 – 20.7] (82.4) [79.3 – 85.3]	4 (20.3) [18.7 – 22] (79.7) [78 – 81.3]	1 (15.8) [14.3 – 17.4] (3.1) [2.7 – 3.5]	1 (17.2) [15 – 19.5] (3.5) [3 – 4.1]	2 (20.1) [13 – 28.3] (5.1) [3.4 – 7.3]	4 (15.9) [14.6 – 17.2] (3.5) [2.8 – 4.2]
sPESI[112 130 144 175] - **High** - **Low**			4 (53.4) [37 – 69.5] (46.6) [30.5 – 63]				4 (8.4) [2.5 – 17.3] (0.3) [0 – 2.1]	
Shock Index[166] - **High** - **Low**			1 (17.4) [12.3 – 24.2] (82.6) [75.8 – 87.7]				1 (22.2) [10.6 – 40.8] (3.9) [1.7 – 8.8]	
TELOS[186] - **High** - **Low**			1 (5.7) [4.5 – 7.4] (94.3) [92.6 – 95.5]				1 (15.8) [8.5 – 27.4] (2.5) [1.6 – 3.7]	

N of studies, (%) and [95% CI] - Event rates in blue for models/ cut-offs useful for low-risk PE, and in red for high-risk PE.

Table 4.2.b: Distribution of risk groups and 30-day all-cause mortality - Risk cut-offs named after the closest high-risk group.

Prognostic model Cut-off - Risk groups	Prevalence of risk groups N (%) [95% CI]				Incidence of events within risk groups N (%) [95% CI]			
	Derivation	Internal validation	External validation	Overall	Derivation	Internal validation	External validation	Overall
Algorithm[95 182] - **High** - **Low**	1 (78.4) [77.6 – 79.2] (21.6) [20.8 – 22.4]	1 (78.4) [77.3 – 79.5] (21.6) [20.5 – 22.7]	2 (80.9) [78.6 – 83] (19.1) [17 – 21.4]	4 (78.2) [75.4 – 80.9] (21.8) [19.1 – 24.6]	1 (11.5) [10.8 – 12.2] (0.6) [0.3 – 1]	1 (11.7) [10.7 – 12.7] (1.5) [1– 2.4]	2 (11.3) [9.4 – 13.4] (1) [0 – 2.9]	4 (11.2) [9.8 – 12.8] (0.8) [0.2 – 1.7]
Bova III[122] - **High** - **Low**			1 (4.4) [3.2 – 6] (95.6) [94 – 96.8]				1 (5.4) [1.5 – 17.7] (4.4) [3.2 – 6.1]	
Bova II[122] - **High** - **Low**			1 (15.9) [13.6 – 18.5] (84.1) [81.5 – 86.4]				1 (8.1) [4.6 – 14] (3.8) [2.6 – 5.5]	
2008 ESC High[132 148 149 178] - **High** - **Low**			4 (10.5) [8.9 – 12.2] (89.5) [87.8 – 91.1]				4 (24.1) [16.9 – 32.1] (7.9) [4.8 – 11.7]	
2008 ESC High Intermediate High[178] - **High** - **Low**			1 (45.5) [42.3 – 48.7] (54.5) [51.3 – 57.7]				1 (10.7) [8.1 – 14] (4.3) [2.8 – 6.4]	
2008 ESC High Intermediate[132 148 149 178] - **High** - **Low**			4 (69.1) [62.2 – 75.6] (30.9) [24.4 – 37.8]				4 (12.9) [8.9 – 17.4] (2.2) [0.9 – 4]	
2008 ESC Intermediate High[178] - **High** - **Low**			1 (38.3) [35 – 41.7] (61.7) [58.3 – 65]				1 (6.8) [4.5 – 10.2] (4.3) [2.8 – 6.4]	
2008 ESC Intermediate[149 178] - **High** - **Low**			2 (71.9) [69 – 74.7] (28.1) [25.3 – 31]				2 (9.1) [7.1 – 11.3] (1.3) [0.1 – 3.2]	
2014 ESC High[178] - **High** - **Low**			1 (11.6) [9.7 – 13.8] (88.4) [86.2 – 90.3]				1 (21.9) [15.1 – 30.7] (5.2) [3.9 – 7]	

2014 ESC High Intermediate High[178] - **High** - **Low**			1 (41.6) [38.4 – 44.8] (58.4) [55.2 – 61.6]				1 (11.7) [8.8 – 15.3] (4) [2.6 – 6]	
2014 ESC High Intermediate[108 178] - **High** - **Low**			2 (74.7) [72.5 – 76.9] (25.3) [23.1 – 27.5]				2 (5.9) [4.6 – 7.4] (0.5) [0 – 1.6]	
2014 ESC Intermediate High[122 178] - **High** - **Low**			2 (17.9) [16.1 – 19.8] (82.1) [80.2 – 83.9]				2 (7.1) [4.5 – 10.2] (4.2) [3.2 – 5.4]	
2014 ESC Intermediate[122 178] - **High** - **Low**			2 (69.3) [67.1 – 71.5] (30.7) [28.5 – 32.9]				2 (6.8) [5.4 – 8.4] (0.4) [0 – 1.2]	
GPS-3[123 125 149] - **High** - **Low**			3 (20.3) [15.3 – 25.9] (79.7) [74.1 – 84.7]				3 (16.7) [9.7 – 25.1] (6.8) [1.5 – 15.3]	
Hestia[175 188] - **High** - **Low**			2 (62.4) [59.5 – 65.4] (37.6) [34.6 – 40.5]				2 (6.7) [4.8 – 8.7] (0.4) [0 – 1.4]	
PESI-II[94 104 119 123 126 139 159] - **High** - **Low**	1 (80.6) [79.8 – 81.3] (19.4) [18.7 – 20.2]	1 (80.4) [79.3 – 81.5] (19.6) [18.5 – 20.7]	6 (83.6) [79.4 – 87.5] (16.4) [12.5 – 20.6]	8 (82.6) [80.4 – 84.6] (17.4) [15.4 – 19.6]	1 (11.1) [10.4 – 11.8] (1.1) [0.7 – 1.7]	1 (11.4) [10.5 – 12.4] (1.6) [1 – 2.6]	6 (7) [4.9 – 9.4] (0.3) [0 – 1.3]	8 (8.4) [6.8 – 10.1] (0.6) [0.3 – 1]
PESI-III[94 104 112 119 123-126 139 154 159] - **High** - **Low**	1 (59.1) [58.1 – 60] (40.9) [40 – 41.9]	1 (59.3) [57.9 – 60.6] (40.7) [39.4 – 42.1]	10 (58.8) [54.8 – 62.6] (41.2) [37.4 – 45.2]	12 (58.9) [56.8 – 61.1] (41.1) [38.9 – 43.2]	1 (14) [13.1 – 14.9] (2.1) [1.8 – 2.6]	1 (14.2) [13.1 – 15.5] (2.6) [2 – 3.3]	10 (9.3) [7.6 – 11.1] (0.9) [0.2 – 1.8]	12 (10.4) [8.8 – 12.1] (1.3) [0.8 – 2]
PESI-IV[94 104 119 123 126 139 159] - **High** - **Low**	1 (37.4) [36.5 – 38.3] (62.6) [61.7 – 63.5]	1 (37.1) [35.8 – 38.4] (62.9) [61.6 – 64.2]	6 (35.7) [30.1 – 41.5] (64.3) [58.5 – 69.9]	8 (35.9) [33.3 – 38.6] (64.1) [61.4 – 66.7]	1 (18.3) [17.1 – 19.6] (3.7) [3.2 – 4.1]	1 (18.5) [16.9 – 20.3] (4.1) [3.5 – 4.9]	6 (12.8) [9.4 – 16.5] (1.7) [0.4 – 3.7]	8 (15) [12.7 – 17.5] (2.6) [1.7 – 3.6]
PESI-V[94 104 119 123 126 139 159] - **High** - **Low**	1 (21) [20.2 – 21.8] (79) [78.2 – 79.8]	1 (21.3) [20.2 – 22.4] (78.7) [77.6 – 79.8]	6 (18) [13.5 – 22.9] (82) [77.1 – 86.5]	8 (18.6) [16 – 21.4] (81.4) [78.6 – 84]	1 (24.5) [22.8 – 26.4] (5) [4.6 – 5.5]	1 (23.9) [21.4 – 26.5] (5.6) [4.9 – 6.3]	6 (17.5) [12.4 – 23.2] (3) [1.2 – 5.6]	8 (20.6) [17.4 – 24] (3.9) [2.8 – 5.1]
sPESI[108 112 115 119 125 133 139 146 148 149 152 154 169 175] - **High** - **Low**	1 (69.3) [66.4 – 72.1] (30.7) [27.9 – 33.6]		14 (62.7) [59.8 – 65.5] (37.3) [34.5 – 40.2]	15 (63.2) [60.4 – 65.9] (36.8) [34.1 – 39.6]	1 (10.9) [8.8 – 13.4] (1) [0.3 – 2.9]		14 (8.7) [6.8 – 10.8] (0.8) [0.3 – 1.5]	15 (8.8) [7.1 – 10.8] (0.8) [0.4 – 1.5]

PREP Clin II[105] - **High** - **Low**			1 (32.8) [27.7 – 38.3] (67.2) [61.7 – 72.3]				1 (7.1) [3.5 – 13.9] (1) [0.3 – 3.5]	
Shock Index[149 155] - **High** - **Low**			2 (16.5) [14.6 – 18.4] (83.5) [81.6 – 85.4]				2 (21.4) [16.3 – 26.9] (8.9) [7.3 – 10.6]	

N of studies, (%) and [95% CI] - Event rates in blue for models/ cut-offs useful for low-risk PE, and in red for high-risk PE.

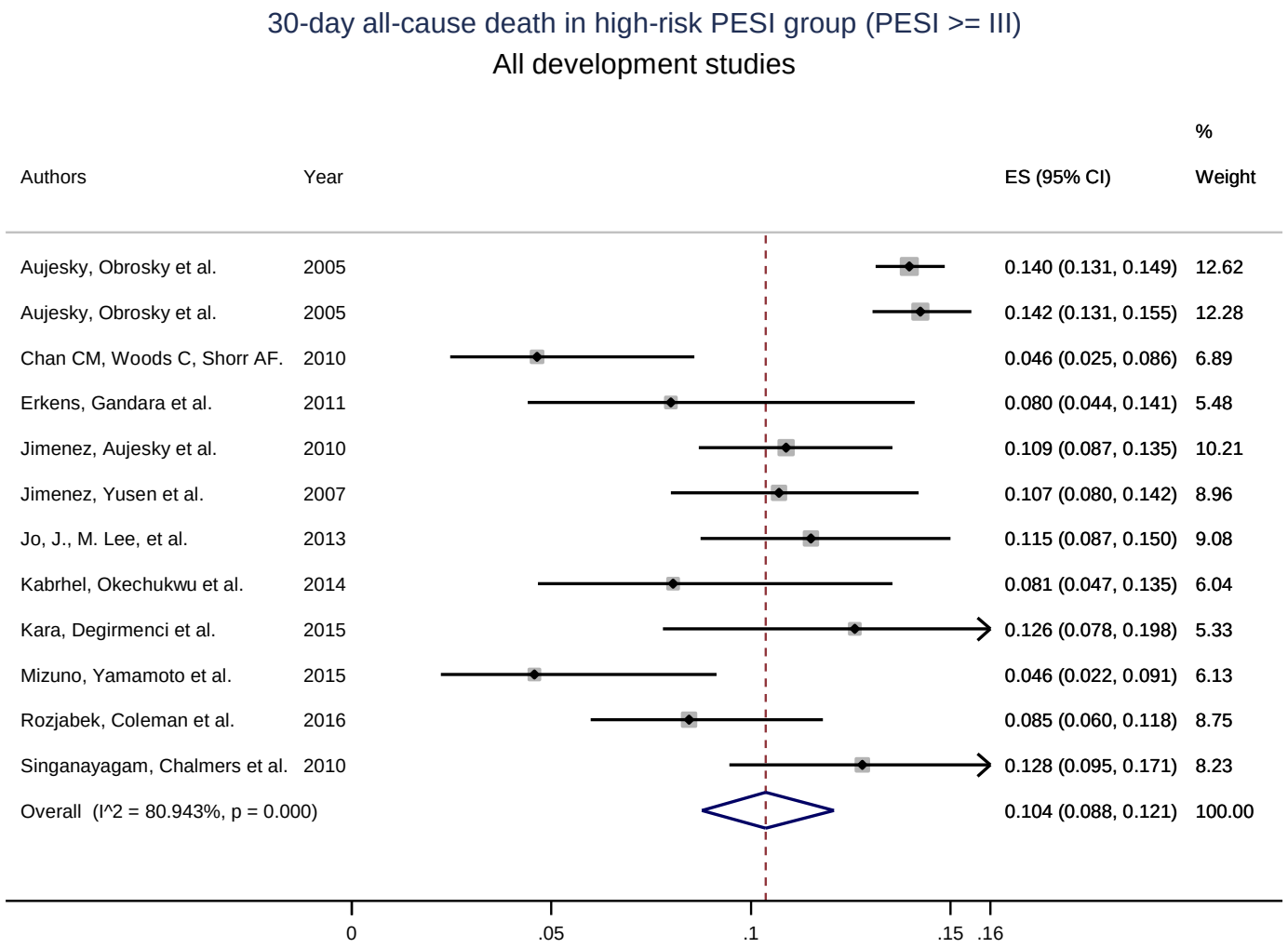
Table 4.2.c: Distribution of risk groups and 3-month all-cause mortality - Risk cut-offs named after the closest high-risk group

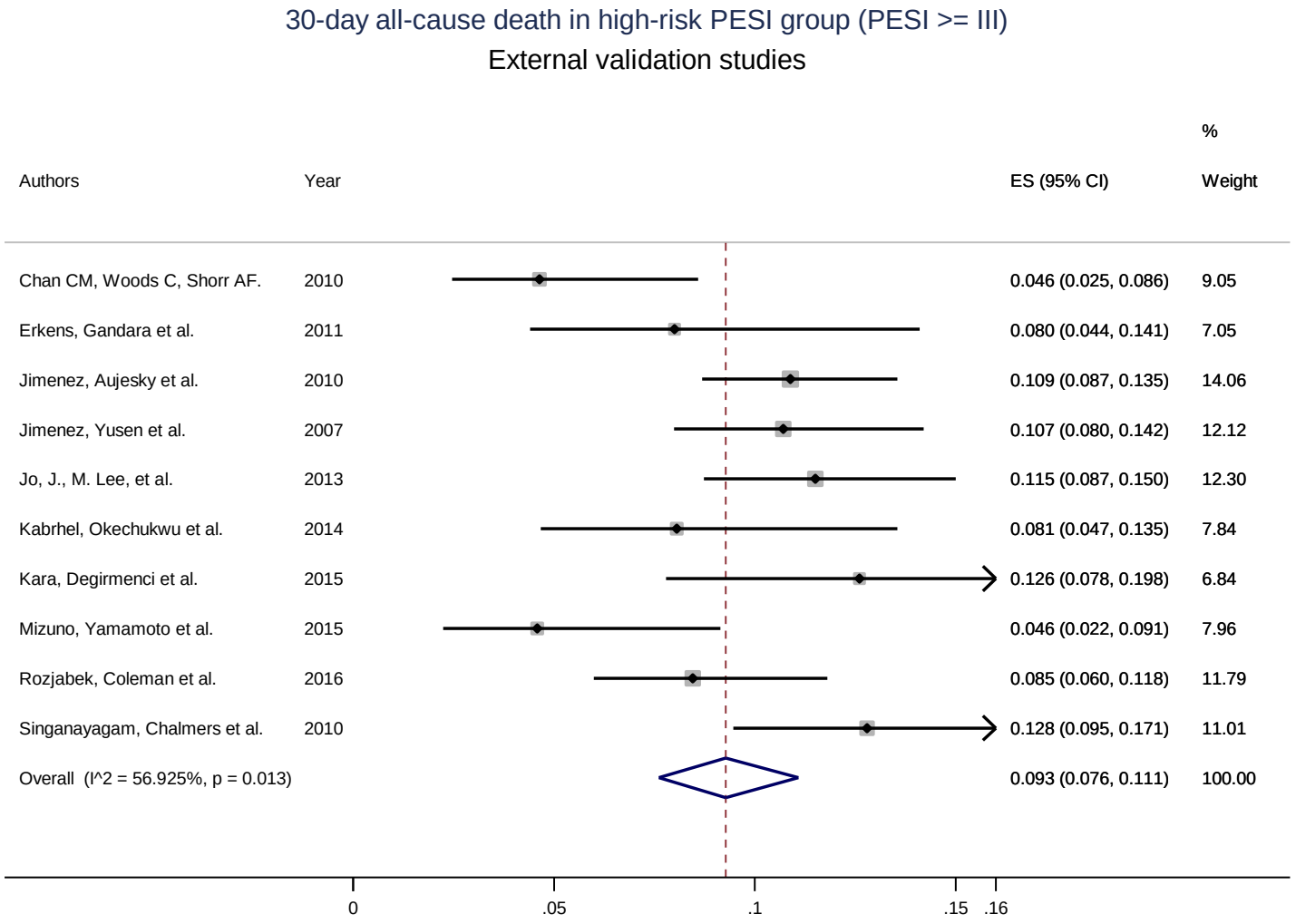
Prognostic model Cut-off - Risk groups	Prevalence of risk groups N (%) [95% CI]				Incidence of events within risk groups N (%) [95% CI]			
	Derivation	Internal validation	External validation	Overall	Derivation	Internal validation	External validation	Overall
GPS-1[164] - **High** - **Low**			1 (62.9) [53.3 – 71.5] (37.1) [28.5 – 46.7]				1 (10.6) [5.2 – 20.3] (0) [0 – 9]	
GPS-2[164] - **High** - **Low**			1 (39) [30.3 – 48.6] (61) [51.4 – 69.7]				1 (14.6) [6.9 – 28.4] (1.6) [0.3 – 8.3]	
GPS-3[101 164] - **High** - **Low**			2 (17.9) [13.8 – 22.5] (82.1) [77.5 – 86.2]				2 23.5 [12.8 – 36] 4.7 [2.3 – 7.8]	
GPS-4[164] - **High** - **Low**			1 (4.8) [2.1 – 10.7] (95.2) [89.3 – 97.9]				1 (20) [3.6 – 62.4] (6) [2.8 – 12.5]	
GPS-5[164] - **High** - **Low**			1 (1.9) [0.5 – 6.7] (98.1) [93.3 – 99.5]				1 (50) [9.5 – 90.5] (5.8) [2.7 – 12.1]	
GPS-6[164] - **High** - **Low**			1 (0) [0 – 3.5] (1) [96.5 – 100]				1 No value (6.7) [3.3 – 13.1]	
Hestia[175] - **High** - **Low**			1 (46.9) [42.4 – 51.4] (53.1) [48.6 – 57.6]				1 (9.6) [6.4 – 14..3] (1.2) [0.4 – 3.5]	
PESI-II[96 104 111 161] - **High** - **Low**			4 (73.7) [64 – 82.3] (26.3) [17.7 – 36]				4 (7.2) [5.2 – 9.4] (0.1) [0 – 1]	
PESI-III[96 100 104 111 112 161] - **High** - **Low**			6 (49.6) [43.1 – 56] (50.4) [44 - 56.9]				6 (12.9) [8.4 – 18.1] (0.6) [0.2 – 1.2]	

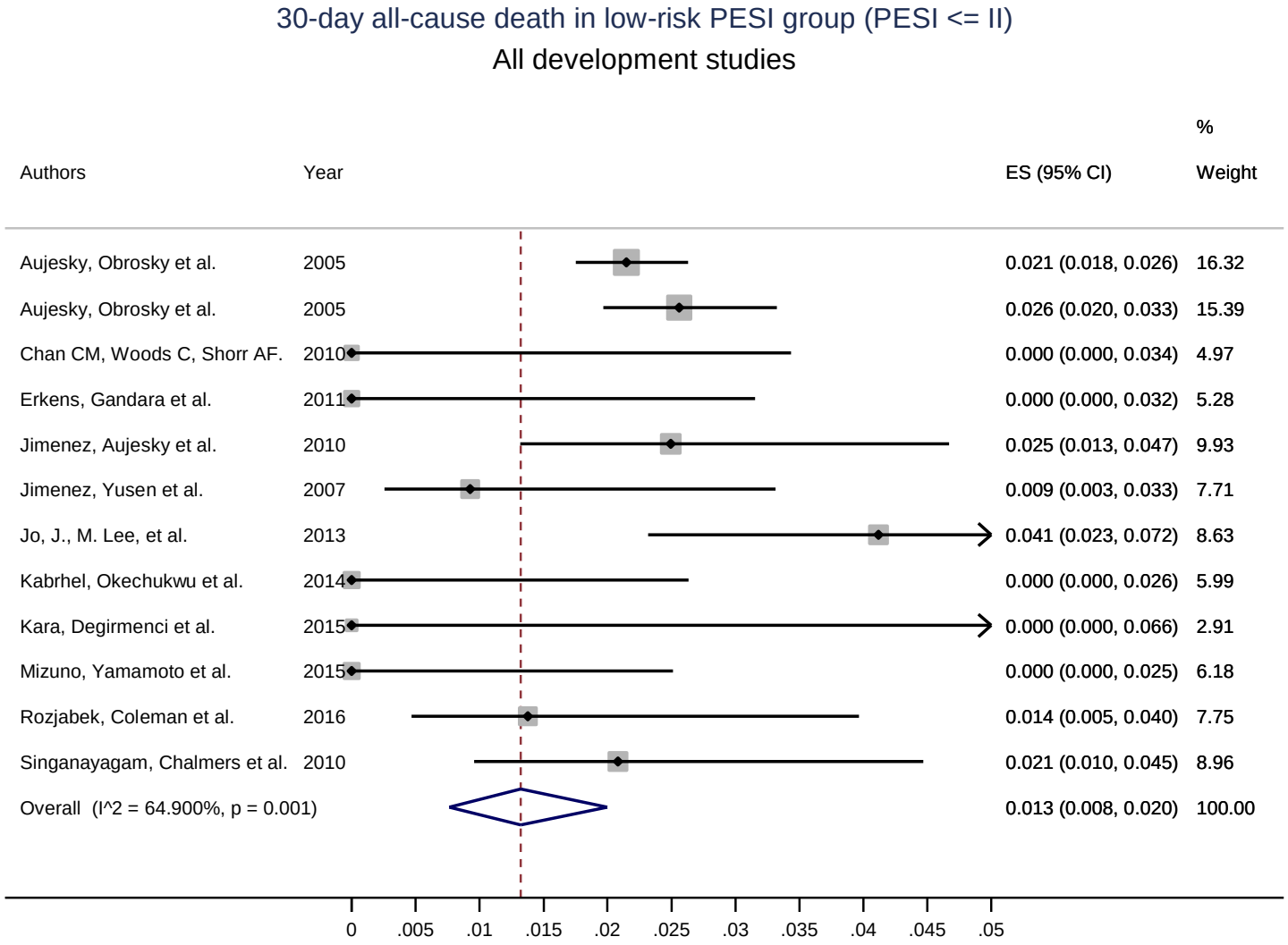
PESI-IV[96 104 111 161] - **High** - **Low**			4 (27.2) [18 – 37.5] (72.8) [62.5 – 82]				4 (15) [9.1 – 22] (1.5) [0.3 – 3.5]	
PESI-V[96 104 111 161] - **High** - **Low**			4 (12) [6 – 19.7] (88) [80.3 – 94]				4 (16.3) [8.3 – 25.8] (3.8) [2.5 – 5.3]	
sPESI[112 152 175] - **High** - **Low**			3 (53 7) [39.3 – 67.9] (46.3) [32.1 – 60.7]				3 (13.6) [8.5 – 19.6] (0.4) [0 – 1.3]	
PREP Clin II[105] - **High** - **Low**			1 (32.8) [27.7 – 38.3] (67.2) [61.7 – 72.3]				1 (9.1) [4.9 – 16.4] (1.5) [0.5 – 4.3]	

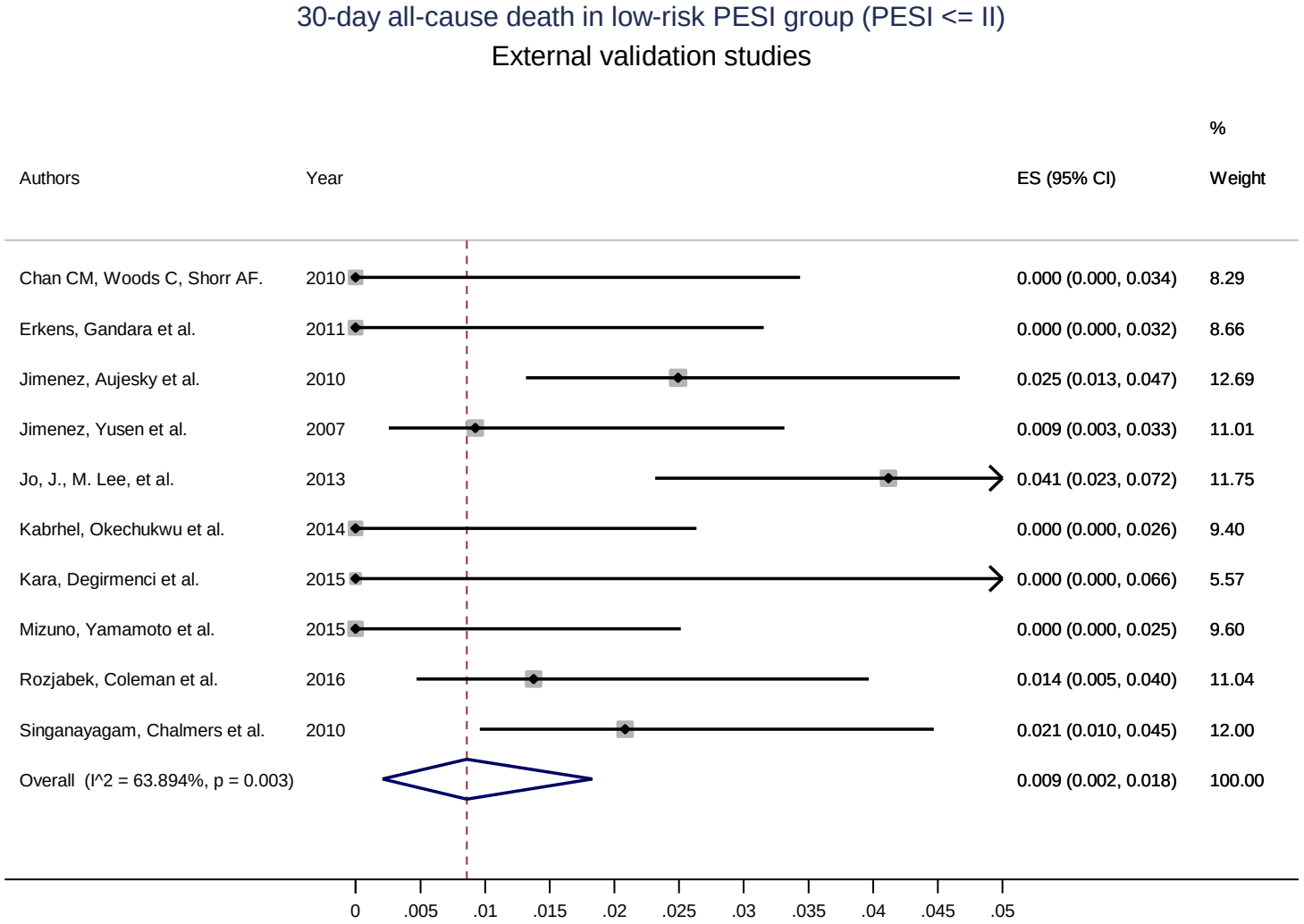
N of studies, (%) and [95% CI] - Event rates in blue for models/ cut-offs useful for low-risk PE, and in red for high-risk PE.

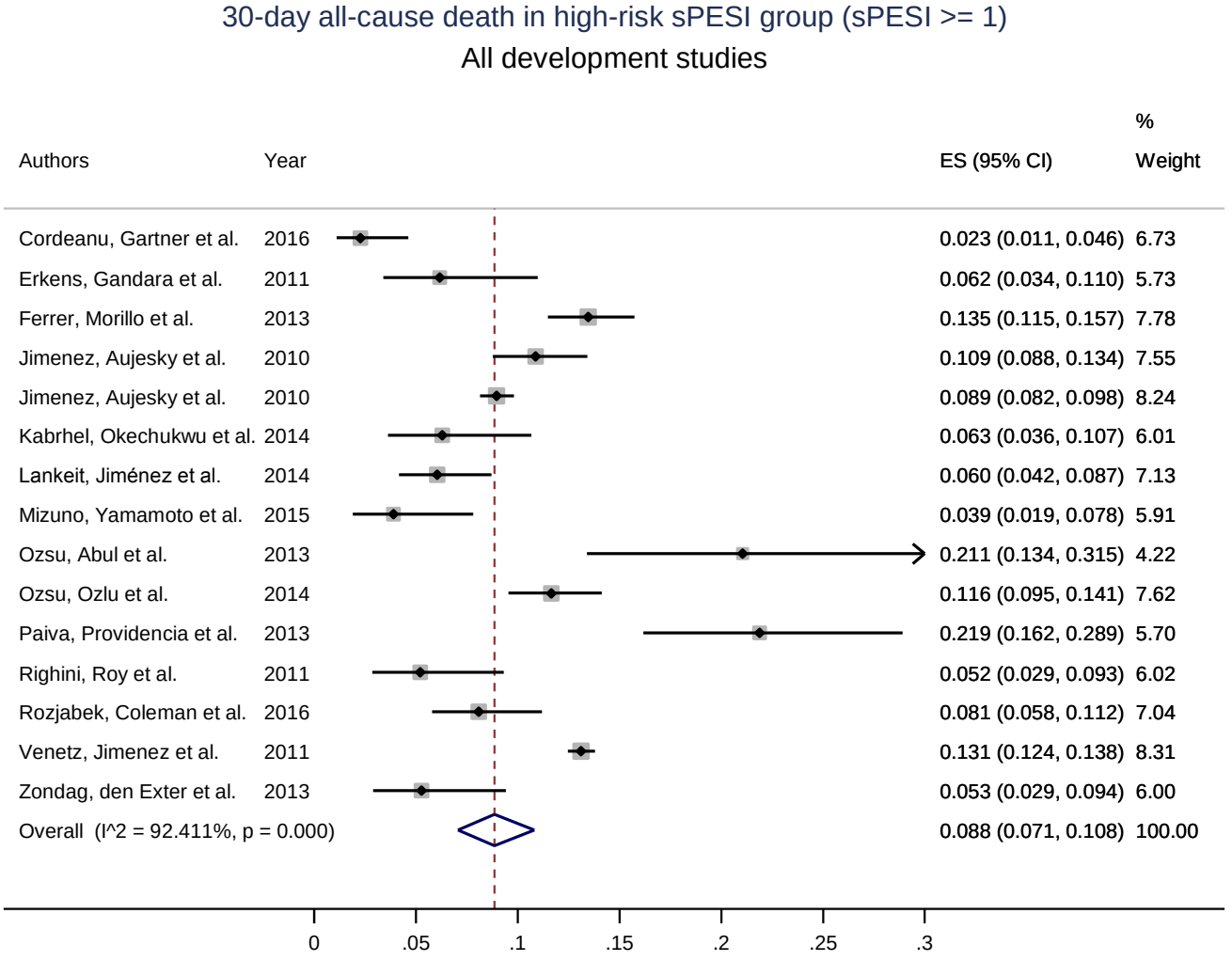
Figures 4.2: Forest plots.

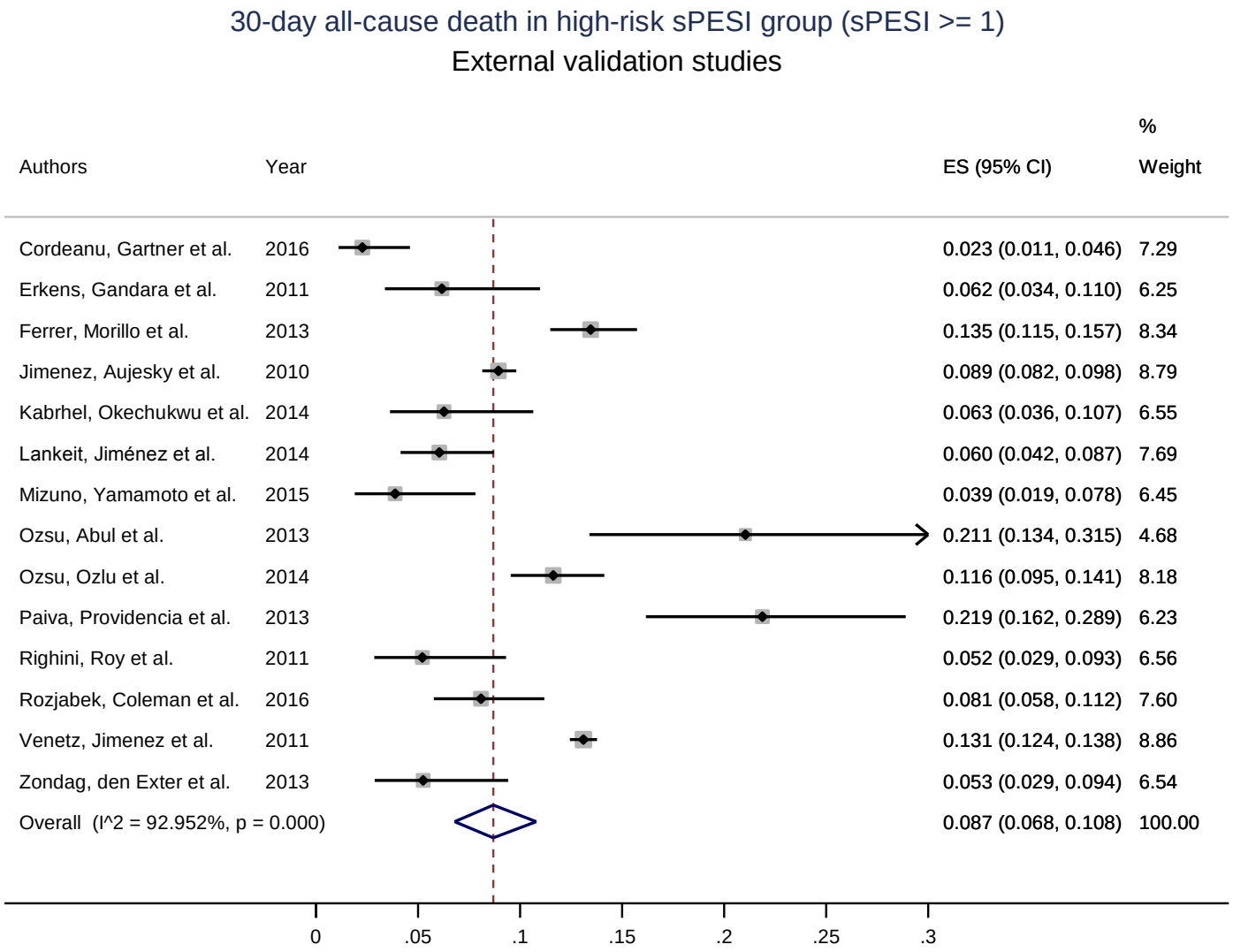


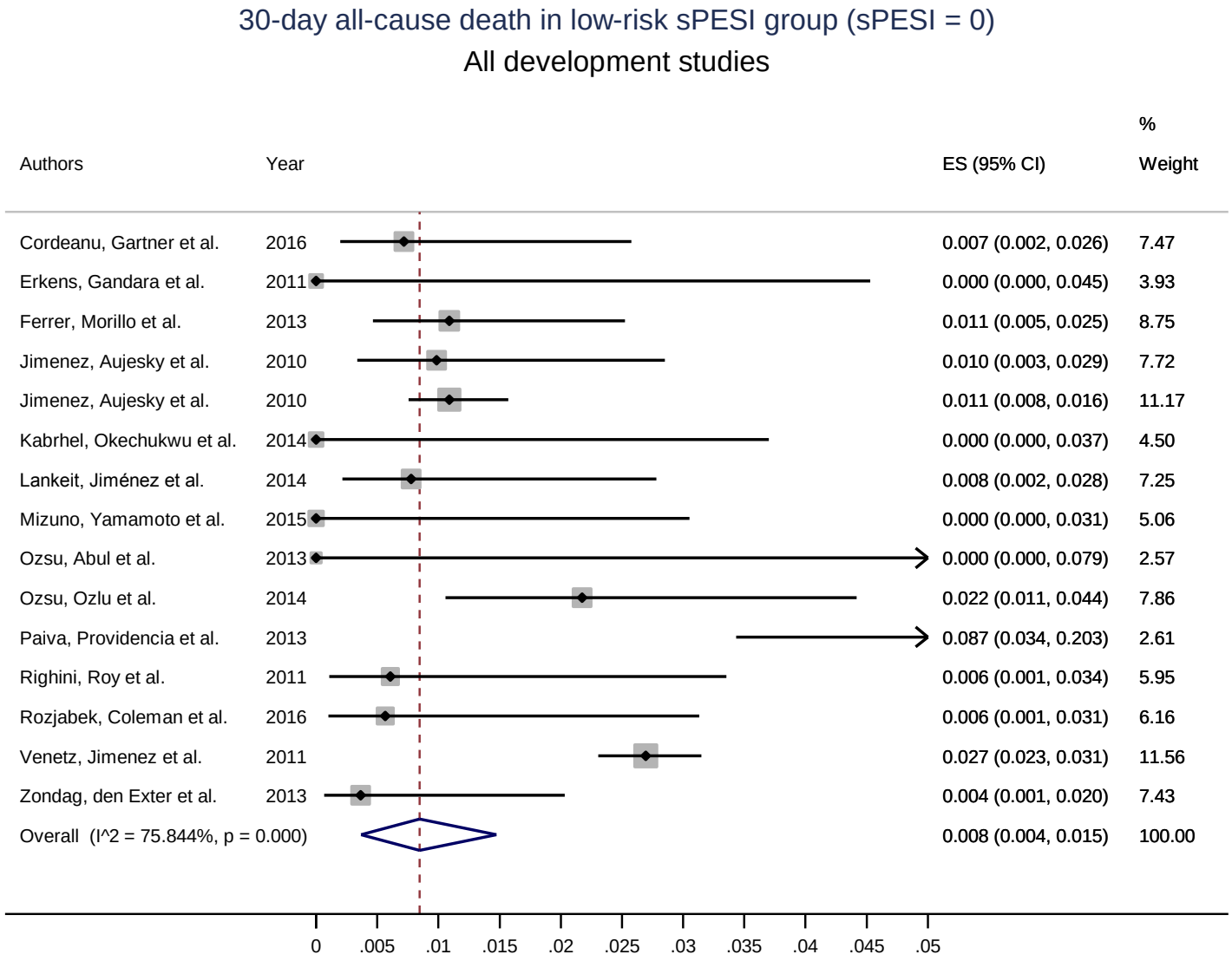

30-day all-cause death in high-risk PESI group (PESI >= III)
External validation studies
Authors
Year
ES (95% CI)
%
Weight
Chan CM, Woods C, Shorr AF. 2010 0.046 (0.025, 0.086) 9.05
Erkens, Gandara et al. 2011 0.080 (0.044, 0.141) 7.05
Jimenez, Aujesky et al. 2010 0.109 (0.087, 0.135) 14.06
Jimenez, Yusen et al. 2007 0.107 (0.080, 0.142) 12.12
Jo, J., M. Lee, et al. 2013 0.115 (0.087, 0.150) 12.30
Kabrhel, Okechukwu et al. 2014 0.081 (0.047, 0.135) 7.84
Kara, Degirmenci et al. 2015 0.126 (0.078, 0.198) 6.84
Mizuno, Yamamoto et al. 2015 0.046 (0.022, 0.091) 7.96
Rozjabek, Coleman et al. 2016 0.085 (0.060, 0.118) 11.79
Singanayagam, Chalmers et al. 2010 0.128 (0.095, 0.171) 11.01
Overall (I^2 = 56.925%, p = 0.013) 0.093 (0.076, 0.111) 100.00
0
.05
.1
.15
.16


30-day all-cause death in low-risk PESI group (PESI <= II)
All development studies
Authors
Year
ES (95% CI)
%
Weight
Aujesky, Obrosky et al. 2005 0.021 (0.018, 0.026) 16.32
Aujesky, Obrosky et al. 2005 0.026 (0.020, 0.033) 15.39
Chan CM, Woods C, Shorr AF. 2010 0.000 (0.000, 0.034) 4.97
Erkens, Gandara et al. 2011 0.000 (0.000, 0.032) 5.28
Jimenez, Aujesky et al. 2010 0.025 (0.013, 0.047) 9.93
Jimenez, Yusen et al. 2007 0.009 (0.003, 0.033) 7.71
Jo, J., M. Lee, et al. 2013 0.041 (0.023, 0.072) 8.63
Kabrhel, Okechukwu et al. 2014 0.000 (0.000, 0.026) 5.99
Kara, Degirmenci et al. 2015 0.000 (0.000, 0.066) 2.91
Mizuno, Yamamoto et al. 2015 0.000 (0.000, 0.025) 6.18
Rozjabek, Coleman et al. 2016 0.014 (0.005, 0.040) 7.75
Singanayagam, Chalmers et al. 2010 0.021 (0.010, 0.045) 8.96
Overall (I^2 = 64.900%, p = 0.001) 0.013 (0.008, 0.020) 100.00
0
.005
.01
.015
.02
.025
.03
.035
.04
.045
.05


30-day all-cause death in low-risk PESI group (PESI <= II)
External validation studies
Authors
Year
ES (95% CI)
%
Weight
Chan CM, Woods C, Shorr AF. 2010 0.000 (0.000, 0.034) 8.29
Erkens, Gandara et al. 2011 0.000 (0.000, 0.032) 8.66
Jimenez, Aujesky et al. 2010 0.025 (0.013, 0.047) 12.69
Jimenez, Yusen et al. 2007 0.009 (0.003, 0.033) 11.01
Jo, J., M. Lee, et al. 2013 0.041 (0.023, 0.072) 11.75
Kabrhel, Okechukwu et al. 2014 0.000 (0.000, 0.026) 9.40
Kara, Degirmenci et al. 2015 0.000 (0.000, 0.066) 5.57
Mizuno, Yamamoto et al. 2015 0.000 (0.000, 0.025) 9.60
Rozjabek, Coleman et al. 2016 0.014 (0.005, 0.040) 11.04
Singanayagam, Chalmers et al. 2010 0.021 (0.010, 0.045) 12.00
Overall (I^2 = 63.894%, p = 0.003) 0.009 (0.002, 0.018) 100.00
0
.005
.01
.015
.02
.025
.03
.035
.04
.045
.05


30-day all-cause death in high-risk sPESI group (sPESI >= 1)
All development studies
Authors
Year
ES (95% CI)
% Weight
Cordeanu, Gartner et al. 2016 0.023 (0.011, 0.046) 6.73
Erkens, Gandara et al. 2011 0.062 (0.034, 0.110) 5.73
Ferrer, Morillo et al. 2013 0.135 (0.115, 0.157) 7.78
Jimenez, Aujesky et al. 2010 0.109 (0.088, 0.134) 7.55
Jimenez, Aujesky et al. 2010 0.089 (0.082, 0.098) 8.24
Kabrhel, Okechukwu et al. 2014 0.063 (0.036, 0.107) 6.01
Lankeit, Jiménez et al. 2014 0.060 (0.042, 0.087) 7.13
Mizuno, Yamamoto et al. 2015 0.039 (0.019, 0.078) 5.91
Ozsu, Abul et al. 2013 0.211 (0.134, 0.315) 4.22
Ozsu, Ozlu et al. 2014 0.116 (0.095, 0.141) 7.62
Paiva, Providencia et al. 2013 0.219 (0.162, 0.289) 5.70
Righini, Roy et al. 2011 0.052 (0.029, 0.093) 6.02
Rozjabek, Coleman et al. 2016 0.081 (0.058, 0.112) 7.04
Venetz, Jimenez et al. 2011 0.131 (0.124, 0.138) 8.31
Zondag, den Exter et al. 2013 0.053 (0.029, 0.094) 6.00
Overall (I^2 = 92.411%, p = 0.000) 0.088 (0.071, 0.108) 100.00
0
.05
.1
.15
.2
.25
.3


30-day all-cause death in high-risk sPESI group (sPESI >= 1)
External validation studies
Authors
Year
ES (95% CI)
%
Weight
Cordeanu, Gartner et al. 2016 0.023 (0.011, 0.046) 7.29
Erkens, Gandara et al. 2011 0.062 (0.034, 0.110) 6.25
Ferrer, Morillo et al. 2013 0.135 (0.115, 0.157) 8.34
Jimenez, Aujesky et al. 2010 0.089 (0.082, 0.098) 8.79
Kabrhel, Okechukwu et al. 2014 0.063 (0.036, 0.107) 6.55
Lankeit, Jiménez et al. 2014 0.060 (0.042, 0.087) 7.69
Mizuno, Yamamoto et al. 2015 0.039 (0.019, 0.078) 6.45
Ozsu, Abul et al. 2013 0.211 (0.134, 0.315) 4.68
Ozsu, Ozlu et al. 2014 0.116 (0.095, 0.141) 8.18
Paiva, Providencia et al. 2013 0.219 (0.162, 0.289) 6.23
Righini, Roy et al. 2011 0.052 (0.029, 0.093) 6.56
Rozjabek, Coleman et al. 2016 0.081 (0.058, 0.112) 7.60
Venetz, Jimenez et al. 2011 0.131 (0.124, 0.138) 8.86
Zondag, den Exter et al. 2013 0.053 (0.029, 0.094) 6.54
Overall (I^2 = 92.952%, p = 0.000) 0.087 (0.068, 0.108) 100.00
0
.05
.1
.15
.2
.25
.3


30-day all-cause death in low-risk sPESI group (sPESI = 0)
All development studies
Authors
Year
ES (95% CI)
% Weight
Cordeanu, Gartner et al. 2016 0.007 (0.002, 0.026) 7.47
Erkens, Gandara et al. 2011 0.000 (0.000, 0.045) 3.93
Ferrer, Morillo et al. 2013 0.011 (0.005, 0.025) 8.75
Jimenez, Aujesky et al. 2010 0.010 (0.003, 0.029) 7.72
Jimenez, Aujesky et al. 2010 0.011 (0.008, 0.016) 11.17
Kabrhel, Okechukwu et al. 2014 0.000 (0.000, 0.037) 4.50
Lankeit, Jiménez et al. 2014 0.008 (0.002, 0.028) 7.25
Mizuno, Yamamoto et al. 2015 0.000 (0.000, 0.031) 5.06
Ozsu, Abul et al. 2013 0.000 (0.000, 0.079) 2.57
Ozsu, Ozlu et al. 2014 0.022 (0.011, 0.044) 7.86
Paiva, Providencia et al. 2013 0.087 (0.034, 0.203) 2.61
Righini, Roy et al. 2011 0.006 (0.001, 0.034) 5.95
Rozjabek, Coleman et al. 2016 0.006 (0.001, 0.031) 6.16
Venetz, Jimenez et al. 2011 0.027 (0.023, 0.031) 11.56
Zondag, den Exter et al. 2013 0.004 (0.001, 0.020) 7.43
Overall (I^2 = 75.844%, p = 0.000) 0.008 (0.004, 0.015) 100.00
0
.005
.01
.015
.02
.025
.03
.035
.04
.045
.05

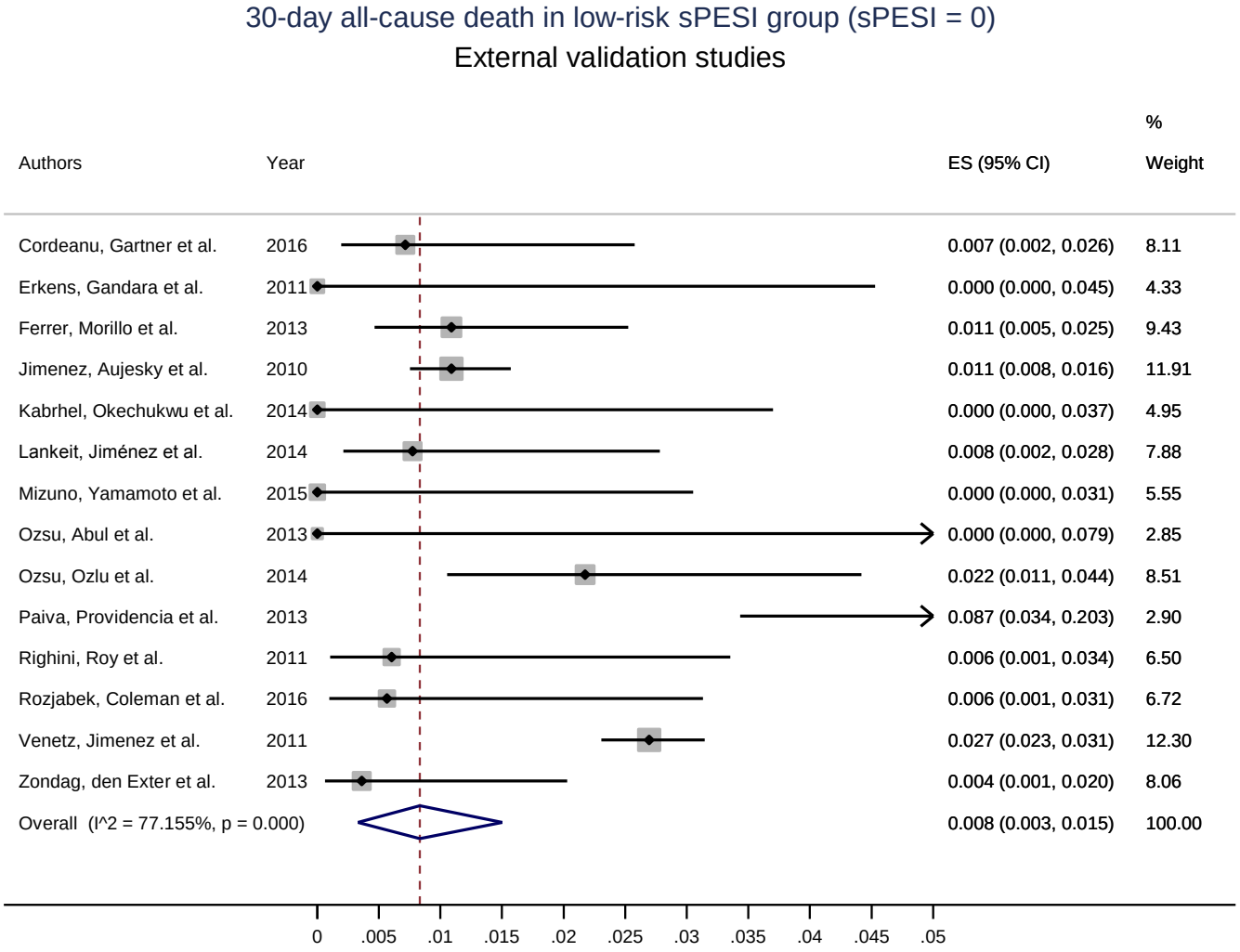

30-day all-cause death in low-risk sPESI group (sPESI = 0)
External validation studies
Authors
Year
ES (95% CI)
%
Weight
Cordeanu, Gartner et al. 2016 0.007 (0.002, 0.026) 8.11
Erkens, Gandara et al. 2011 0.000 (0.000, 0.045) 4.33
Ferrer, Morillo et al. 2013 0.011 (0.005, 0.025) 9.43
Jimenez, Aujesky et al. 2010 0.011 (0.008, 0.016) 11.91
Kabrhel, Okechukwu et al. 2014 0.000 (0.000, 0.037) 4.95
Lankeit, Jiménez et al. 2014 0.008 (0.002, 0.028) 7.88
Mizuno, Yamamoto et al. 2015 0.000 (0.000, 0.031) 5.55
Ozsu, Abul et al. 2013 0.000 (0.000, 0.079) 2.85
Ozsu, Ozlu et al. 2014 0.022 (0.011, 0.044) 8.51
Paiva, Providencia et al. 2013 0.087 (0.034, 0.203) 2.90
Righini, Roy et al. 2011 0.006 (0.001, 0.034) 6.50
Rozjabek, Coleman et al. 2016 0.006 (0.001, 0.031) 6.72
Venetz, Jimenez et al. 2011 0.027 (0.023, 0.031) 12.30
Zondag, den Exter et al. 2013 0.004 (0.001, 0.020) 8.06
Overall (I^2 = 77.155%, p = 0.000) 0.008 (0.003, 0.015) 100.00
0
.005
.01
.015
.02
.025
.03
.035
.04
.045
.05

Table 4.3: PE-related death, adverse outcome (death, clinical deterioration or haemodynamic collapse), VTE, major bleeding and their combinations in "both stable and unstable" PE patient risk groups.

Risk cut-off (Author, year)	Development phase	N studies	Type of study	Haemodynamic status	Outcome	Timepoint	Proportion(95% CI) High Risk Group Low Risk Group	Event rate(95% CI) High Risk Group Low Risk Group
Algorithm ≥ 1 (Jakobsson, Jimenez et al. 2010)[182]	External Validation	1	Retrospective	Not reported	PE-related death	30-day	83.7 (81.3-85.9) 16.3 (14.1-18.7)	6.6 (5.1-8.5) **0.6 (0.1-3.5)**
Agterof (Herat rate - Ddimer) (Agterof, van Bladel et al. 2009)[92]	Derivation	1	Retrospective	Both stable and unstable	Death VTE Major bleeding	In-hospital	67.1 (61.7-72.1) 32.9 (27.9-38.3)	5.3 (3.0-9.2) **0 (0-3.6)**
Bova ≥ II (Masotti, Verdiani et al. 2016)[138]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	43.5 (37.6-49.5) 56.5 (50.5-62.4)	6.2 (3-12.2) 2.7 (1.1-6.8)
Bova ≥ III (Masotti, Verdiani et al. 2016)[138]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	9.6 (6.6-13.8) 90.4 (86.2-93.4)	8(2.2-25) 3.5 (2.3-4.9)
2008 ESC High								
(Vanni, Nazerian et al. 2011)[168]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	5.6 (3.9-8) 94.4 (92-96.1)	29.6 (15.9-48.5) 4.1 (2.7-6.4)
(Labyk, Ciurzynski, et al. 2012)[183]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	6.5 (4.4-9.6) 93.5 (90.4-95.6)	43.5 (25.2-63.2) 2.7 (1.4-5.1)
	Overall	2					6 (4.4-7.7) 94 (92.3-95.6)	**35.9 (22.8-49.9)** 3.5 (2.3-4.9)
2008 ESC High - Intermediate High (Becattini, Agnelli et al. 2016)[178]	External validation	1	Retrospective	Both stable and unstable	PE-related death	30-day	45.5 (42.3-48.7) 54.5 (51.3-57.7)	7 (4.9-9.9) 1.6 (0.8-3.2)
2008 ESC High - Intermediate								
(Vanni, Nazerian et al. 2011)[168]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	60 (55.6-64.3) 40 (35.7-44.4)	8.6 (5.9-12.4) 1 (0.3-3.7)
(Labyk, Ciurzynski, et al. 2012)[183]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	47.9 (42.7-53.1) 52.1 (46.9-57.3)	9.5 (5.9-14.8) 1.6 (0.6-4.7)
	Overall	2					54.9 (51.5-58.3) 45.1 (41.7-48.5)	8.9 (6.4-11.7) 1.3 (0.3-2.8)
(Becattini, Agnelli et al. 2016)[178]	External validation	1	Retrospective	Both stable and unstable	PE-related death	30-day	75.4 (72.5-78.1) 24.6 (21.9-27.5)	5.4 (4-7.4) 0 (0-1.7)

2014 ESC High (or 2008 ESC high) (Becattini, Agnelli et al. 2016)[178]	External validation	1	Retrospective	Both stable and unstable	PE-related death	30-day	11.6 (9.7-13.8) 88.4 (86.2-90.3)	15.2 (9.6-23.3) 2.6 (1.7-4)
2014 ESC High - Intermediate High (Becattini, Agnelli et al. 2016)[178]	External validation	1		Both stable and unstable	PE-related death	30-day	41.6 (38.4-44.8) 58.4 (55.2-61.6)	7.7 (5.4-10.8) 1.5 (0.8-3)
2014 ESC High - Intermediate (Becattini, Agnelli et al. 2016)[178]	External validation	1		Both stable and unstable	PE-related death	30-day	78.4 (75.6-80.9) 21.6 (19.1-24.4)	5.1 (3.7-6.9) **0.5 (0.1-2.8)**
(Cordeanu, Gartner et al. 2016)	External validation	1	Retrospective	Both stable and unstable	Death VTE Major bleeding	30-day	68.7 (64.8-72.3) 31.3 (27.7-35.2)	5.7 (3.8-8.4) 3.3 (1.5-6.9)
GPS ≥ 1 (Wicki, Perrier et al. 2000)[171]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	3-month	80.6 (75.4-84.9) 19.4 (15.1-24.6)	12.5 (8.7-17.6) 0 (0-6.9)
(Nendaz, Bandelier et al. 2004)[141]	External validation	1	Retrospective	Unclear	Death VTE Major bleeding	3-month	71.4 (64.7-77.2) 28.6 (22.8-35.3)	12.0 (7.6-18.3) 3.5 (1-11.9)
	Overall	2			Death VTE Major bleeding	3-month	76.8 (72.9-80.5) 23.2 (19.7-25.1)	12.3 (9-15.9) 1.2 (0-4.6)
GPS ≥ 2 (Wicki, Perrier et al. 2000)[171]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	3-month	51.1 (45.2-57) 48.9 (43-54.8)	18.2 (12.7-25.6) 1.5 (0.4-5.4)
(Nendaz, Bandelier et al. 2004)[141]	External validation	1	Retrospective	Unclear	Death VTE Major bleeding	3-month	44.2 (37.5-51.2) 55.8 (48.8-62.5)	18.2 (11.5-27.5) 2.7 (0.9-7.6)
	Overall	2			Death VTE Major bleeding	3-month	48.2 (43.6-52.7) 51.8 (47.3-56.4)	**18.2 (13.4-23.6)** 2 (0.5-4.3)
GPS ≥ 3 (Wicki, Perrier et al. 2000)[171]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	3-month	32.8 (27.5-38.7) 67.2 (61.3-72.5)	26.1 (18.1-36.2) 2.2 (0.9-5.6)
(Nendaz, Bandelier et al. 2004)[141]	External validation	1	Retrospective	Unclear	Death VTE Major bleeding	3-month	20.1 (15.1-26.2) 79.9 (73.8-84.9)	27.5 (16.1-42.8) 5.0 (2.6-9.6)
	Overall	2			Death VTE Major bleeding	3-month	27.2 (23.2-31.3) 72.8 (68.7-76.8)	**26.5 (19.1-34.6)** 3.4 (1.7-5.7)
GPS ≥ 4 (Wicki, Perrier et al. 2000)[171]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	3-month	11.9 (8.6-16.4)	40.6 (25.5-57.7)

							88.1 (83.6-91.4) 8.0 (5.0-12.7) 92.0 (87.3-95.0)	5.9 (3.6-9.7) 31.3 (14.2-55.6) 7.7 (4.6-12.4)
(Nendaz, Bandelier et al. 2004)[141]	External validation	1	Retrospective	Unclear	Death VTE Major bleeding	3-month		
	Overall	2			Death VTE Major bleeding	3-month	10.2 (7.6-13.1) 89.8 (86.9-92.4)	**37.4 (23.9.1-51.9)** 6.7 (4.4-9.3)
GPS ≥ 5								
(Wicki, Perrier et al. 2000)[171]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	3-month	3.7 (2.0-6.7) 96.3 (93.3-98.0)	70.0 (39.7-89.2) 7.8 (5.1-11.7)
(Nendaz, Bandelier et al. 2004)[141]	External validation	1	Retrospective	Unclear	Death VTE Major bleeding	3-month	2.5 (1.1-5.7) 97.5 (94.3-98.9)	80.0 (37.6-96.4) 7.7 (4.7-12.4)
	Overall	2			Death VTE Major bleeding	3-month	3.2 (1.7-5) 96.8 (95-98.3)	**73.7 (46.5-94.7)** 7.7 (5.4-10.4)
GPS = 6								
(Wicki, Perrier et al. 2000)[171]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	3-month	1.1 (0.4-3.2) 98.9 (96.8-99.6)	100 (43.9-100) 9.1 (6.2-13.1)
(Nendaz, Bandelier et al. 2004)[141]	External validation	1	Retrospective	Unclear	Death VTE Major bleeding	3-month	0.5 (0.1-2.8) 99.5 (97.2-99.9)	NA 9.6 (6.2-14.5)
	Overall	2			Death VTE Major bleeding	3-month	0.8 (0.1-1.9) 99.2 (98.1-99.9)	**85.4 (22.2-100)** 9.3 (6.8-12.1)
Hestia and CT-RVD **(Zondag, Vingerhoets et al. 2013)[176]**	External validation	1	Prospective	Both stable and unstable	Death Adverse outcome	30-day		
Hestia							44.6 (40.2-49) 55.4 (51-59.8)	**19.9 (15.2-25.7)** **0.7 (0.2-2.6)**
Hestia – CT-RVD							63.7 (59.4-67.8) 36.3 (32.2-40.6)	14.2 (10.8-18.5) **0.6 (0.1-3.1)**
PESI ≥ II (Maestre, Trujillo-Santos et al. 2015)[136]	External validation	1	Retrospective	Not reported	Death VTE Major bleeding	In-hospital	82.7 (82.1-83.2) 17.3 (16.8-17.9)	4.2 (3.9-4.5) **0.9 (0.6-1.3)**
(Aujesky, Perrier et al. 2007)[96]	External validation	1	Retrospective	Both stable and unstable	PE-related death	3-month	79.5 (76.8-82) 20.5 (18-23.2)	2.9 (1.9-4.4) **0 (0-2)**
PESI ≥ III (Vanni, Nazerian et al. 2011)[168]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	68.7 (64.3-72.7) 31.3 (27.3-35.7)	7.5 (5.1-11) **0.7 (0.1-3.8)**

(Maestre, Trujillo-Santos et al. 2015)[136]	External validation	1	Retrospective	Not reported	Death VTE Major bleeding	In-hospital	56.4 (55.7-57.1) 43.6 (42.9-44.3)	5.3 (4.9-5.8) 1.4 (1.2-1.7)
(Aujesky, Perrier et al. 2007)[96]	External validation	1	Retrospective	Both stable and unstable	PE-related death	3-month	52.6 (49.3-55.9) 47.4 (44.1-50.7)	3.8 (2.4-5.9) **0.7 (0.2-2)**
PESI ≥ III and H-FABP (Lauque, Maupas-Schwalm et al. 2014)[135]	External validation	1	Prospective	Both stable and unstable	Adverse outcome	30-day		
H-FABP > 6							15.2 (10-22.3) 84.8 (77.7-90)	**45 (25.3-66.4)** 4.5 (1.9-10.3)
PESI ≥ III							36.4 (28.6-44.9) 63.6 (55.1-71.4)	**27.1 (16.4-41.2)** 1.2 (0.2-8)
PESI ≥ III - H-FABP > 6							11.4 (7-18) 88.6 (82-93)	**53.3 (29.3-75.9)** 5.1 (2.3-10.9)
PESI ≥ III or H-FABP > 6							40.2 (32.1-48.7) 59.8 (51.3-67.9)	**26.4 (16.3-39.8)** **0.6 (0-9.2)**
PESI ≥ IV (Choi, Cha et al 2014)[106]	External validation	1	Retrospective	Both stable and unstable	Adverse outcome	In-hospital	18 (15.3-21.2) 82 (78.8-84.7)	**24.8 (17.8-33.3)** 7.3 (5.4-9.9)
(Aujesky, Perrier et al. 2007)[96]	External validation	1	Retrospective	Both stable and unstable	PE-related death	3-month	25 (22.3-28) 75 (72-77.7)	6.7 (4.1-10.7) 0.9 (0.4-1.9)
PESI ≥ IV and other prognostic factors* (Choi, Cha et al 2014)[106]	External validation	1	Retrospective	Both stable and unstable	Adverse outcome	In-hospital		
NT-proBNP ≥ 1,136 pg/ml							34.2 (29.7-39.0) 65.8 (61.0-70.3)	**22.4 (16.1-30.2)** 4.7 (2.7-8.0)
cTnI ≥ 0.05 ng/ml							39.1 (34.8-43.6) 60.9 (56.4-65.2)	**21.6 (16.3-28.1)** 5.2 (3.2-8.5)
CT RV/LV diameter ratio ≥ 1							36.1 (32.5-39.9) 63.9 (60.1-67.5)	**20.1 (15.4-25.7)** 5.1 (3.3-7.7)
PESI ≥ IV - NT-proBNP ≥ 1,136 pg/ml							6.2 (4.2-9.1) 93.8 (90.9-95.8)	**50.0 (31.0-69.0)** 8.0 (5.6-11.3)
							10.3 (7.8-13.4)	**41.7 (28.7-55.9)**

PESI ≥ IV - cTnI ≥ 0.05 ng/ml PESI ≥ IV – CT RV/LV ratio ≥ 1 PESI ≥ IV - NT-proBNP – cTnI PESI ≥ IV - NT-proBNP – RV/LV PESI ≥ IV – cTnI – RV/LV PESI ≥ IV - NT-proBNP - cTnI – RV/LV							89.7 (86.6-92.2) 7.9 (6.0-10.2) 92.1 (89.8-94.0) 4.6 (2.9-7.3) 95.4 (92.7-97.1) 4.2 (2.6-6.7) 95.8 (93.3-97.4) 6.0 (4.2-8.6) 94.0 (91.4-95.8) 3.8 (2.3-6.3) 96.2 (93.7-97.7)	8.1 (5.9-11.1) **43.1 (30.4-56.9)** 7.7 (5.8-10.2) **64.7 (40.4-83.2)** 8.2 (5.8-11.6) **62.5 (37.7-82.1)** 8.4 (6.0-11.7) **60.7 (42.0-76.7**) 8.5 (6.2-11.5) **71.4 (43.9-88.9)** 8.5 (6.0-11.9)
PESI ≥ V (Vanni, Nazerian et al. 2011)[168]	External validation	1	Retrospective	Both stable and unstable	PE-related death	In-hospital	19.9 (16.5-23.7) 80.1 (76.3-83.5)	**15.2 (9.3-23.9)** 3 (1.7-5.2)
(Aujesky, Perrier et al. 2007)[96]	External validation	1	Retrospective	Both stable and unstable	PE-related death	3-month	10.3 (8.5-12.5) 89.7 (87.5-91.5)	7.5 (3.7-14.7) 1.7 (1-2.9)
PREP (Sanchez, Trinquart et al. 2010)[157] PREP - Clin ≥ II PREP - Clin ≥ III PREP - Clin ≥ II - BNP - RVD PREP - Clin ≥ III - BNP - RVD	Derivation	1	Prospective	Both stable and unstable	Death VTE	30-day	 37.3 (33.2-41.5) 62.7 (58.5-66.8) 7.2 (5.3-9.7) 92.8 (90.3-94.7) 34.8 (30.8-39) 65.2 (61-69.2) 5.6 (3.9-8) 94.4 (92-96.1)	 **17.7 (13-23.7)** 2.5 (1.3-4.8) **43.2 (28.7-59.1)** 5.4 (3.7-7.9) **18.4 (13.4-24.8)** 2.1 (1-4.3) **44.8 (28.1-62.8)** 5.6 (3.8-8)
RIETE (Maestre, Trujillo-Santos et al. 2015)[136]	Derivation	1	Retrospective	Not reported	Death VTE Major bleeding	In-hospital	75.6 (75-76.2) 24.4 (23.8-25)	4.6 (4.3-5) **0.6 (0.4-0.9)**
Shock (Sanchez, Trinquart et al. 2010)[157]	External validation	1	Prospective	Both stable and unstable	Death Adverse outcome VTE	30-day	7.2 (5.3-9.6) 92.8 (90.4-94.7)	**41.5 (27.8-56.6)** 4.7 (3.2-6.9)

Shock Index (Toosi, Merlino et al. 2008)[166]	External validation	1	Retrospective	Not reported	Adverse outcome	In-hospital	17.6 (12.4-24.5) 82.4 (75.5-87.6)	**25.9 (13.2-44.7)** 10.3 (6.1-16.9)
sPESI ≥ 1 (Tong, Zhang et al. 2014)[165]	External validation	1	Retrospective	Both stable and unstable	Death Adverse outcome	In-hospital	41.4 (34.1-49.1) 58.6 (50.9-65.9)	**26.9 (17.7-38.5)** 2.1 (0.6-7.4)
(Maestre, Trujillo-Santos et al. 2015)[136]	External validation	1	Retrospective	Not reported	Death VTE Major bleeding	In-hospital	65.3 (64.6-66) 34.7 (34-35.4)	5 (4.6-5.4) **1 (0.8-1.3)**
(Cordeanu, Gartner et al. 2016)[108]	External validation	1	Retrospective	Both stable and unstable	Death VTE Major bleeding	30-day	52.5 (48.4 – 56.5) 47.5 (43.5-51.6)	6.5 (4.2-9.8) 3.2 (1.7-6)
(Righini, Roy et al. 2011)[152]	External validation	1	Retrospective	Unclear	PE-related death	30-day	53.8 (48.6-58.9) 46.2 (41.1-51.4)	3.1 (1.4-6.6) **0.6 (0.1-3.4)**
(Spirk, Aujesky et al. 2011)[162]	External validation	1	Retrospective	Both stable and unstable	Death VTE	30-day	70.8 (65.7-75.4) 29.2 (24.6-34.3)	8.1 (5.2-12.3) **1 (0.2-5.6)**
(Righini, Roy et al. 2011)[152]	External validation	1	Retrospective	Unclear	PE-related death	3-month	53.8 (48.6-58.9) 46.2 (41.1-51.4)	4.2 (2.1-8) **0.6 (0.1-3.4)**
sPESI ≥ 1 - cTn (Spirk, Aujesky et al. 2011)[162] cTn sPESI ≥ 1 – cTn	Update	1	Retrospective	Both stable and unstable	Death VTE	30-day	 28.3 (65.7-75.4) 71.7 (66.6-76.3) 24.4 (20.1-29.3) 75.6 (70.7-79.9)	 12.8 (7.4-21.1) 3.4 (1.7-6.6) 13.6 (7.7-22.9) 3.6 (1.9-6.7)

In the first column, the cut-off is indicated by the corresponding higher risk group for the cut-off. *Information from authors. Event rates for models with cut-offs suitable for low-risk PE in blue and for high-risk PE in red.

Table 4.4: PE-related death, adverse outcome (death, clinical deterioration or haemodynamic collapse), VTE, major bleeding and their combinations in "stable" PE patient risk groups.

Risk cut-off (Author, year)	Development phase	N studies	Type of study	Haemodynamic status	Outcome	Timepoint	Proportion (95% CI) High Risk Group Low Risk Group	Event rate (95% CI) High Risk Group Low Risk Group
Bova								
(Bova, Sanchez et al. 2014)[102]	Derivation and Internal validation	6 (IPD)	Both	Stable				
Stage III					PE-related death, collapse, VTE	In-hospital	5.8	28
Stage II							18.6	9.7
Stage I							75.5	3.6
Stage III					PE-related death, collapse, VTE	30-day	5.8	**29.2**
Stage II							18.6	10.8
Stage I							75.5	4.2
Stage III					PE-related death	30-day	5.8	**15.5**
Stage II							18.6	5.0
Stage I							75.5	1.7
Bova ≥ II								
(Bova, Sanchez et al. 2014)[102]	Derivation and Internal validation	6 (IPD)	Both	Stable	PE-related death Adverse outcome	30-day	24.5 (22.9-26.1) 75.5 (73.9-77.1)	15.2 (12.8-18.1) 4.2 (3.4-5.1)
(Fernandez, Bova et al. 2015)[114]	External validation	1	Retrospective	Stable	PE-related death Adverse outcome	30-day	20.1 (17.8-22.6) 79.9 (77.4-82.2)	24.3 (19.1-30.4) 4.4 (3.2-6)
	Overall	2					23.2 (21.9-24.6) 76.8 (75.4-78.1)	**17.2 (14.8-19.7)** 4.2 (3.6-5)
(Jimenez, Lobo et al. 2016)[122]	External validation	1	Retrospective	Stable	Death Adverse outcome	30-day	15.9 (13.6-18.5) 84.1 (81.5-86.4)	**16.3 (11-23.4)** 5.8 (4.3-7.7)
Bova ≥ III								
(Bova, Sanchez et al. 2014)[102]	Derivation and Internal validation	6 (IPD)	Both	Stable	PE-related death Adverse outcome	30-day	5.8 (5-6.8) 94.2 (93.2-95)	29.2 (22.8-36.4) 5.5 (4.7-6.4)
(Fernandez, Bova et al. 2015)[114]	External validation	1	Retrospective	Stable	PE-related death Adverse outcome	30-day	5.3 (4.1-6.8) 94.7 (93.2-95.9)	42.1 (30.2-55) 6.5 (5.2-8.2)
	Overall	2					5.7 (5-6.4) 94.3 (93.6-95)	**32.3 (26.3-38.6)** 5.8 (5-6.5)

(Jimenez, Lobo et al. 2016)[122]	External validation	1	Retrospective	Stable	Death Adverse outcome	30-day	4.4 (3.2-6) 95.6 (94-96.8)	**21.6 (11.4-37.2)** 6.8 (5.2-8.7)
Bova and Lactate (Vanni, Nazerian et al. 2016)[186]	External Validation	1	Retrospective	Stable	PE-related complications	In-hospital		
Bova ≥ III							5.9 (4.6-7.6) 94.1 (92.4-95.4)	**18.6 (10.7-30.4)** 5.6 (4.3-7.2)
Bova ≥ III - Lactate							11.3 (9.4-13.4) 88.7 (86.6-90.6)	**25.9 (18.6-34.8)** 3.9 (2.8-5.3)
2008 ESC Intermediate High								
(Vanni, Nazerian et al. 2011)[168]	External Validation	1	Retrospective	Stable	PE-related death	In-hospital	14.8 (11.9 – 18.4) 85.2 (81.6 – 88.1)	11.8 (6.0 – 21.5) 2.8 (1.6 – 5.0)
(Becattini, Casazza et al 2013)[99]	External Validation	1	Prospective	Stable	PE-related death	In-hospital	41.8 (38.5 – 45.1) 58.2 (54.9 – 61.5)	1.9 (0.9 – 3.9) **1.0 (0.4 – 2.3)**
	Overall	2		Stable	PE-related death	In-hospital	31.6 (29.1-34.1) 68.4 (65.9-70.9)	2.7 (1.3-4.6) 1.7 (0.9-2.6)
(Becattini, Casazza et al 2013)[99]	External Validation	1	Prospective	Stable	Death Adverse outcome	In-hospital	41.8 (38.5-45.1) 58.2 (54.9-61.5)	8.8 (6.3-12.2) 3.2 (2-5.1)
(Becattini, Casazza et al 2013)[99]	External Validation	1	Prospective	Stable	PE-related death Adverse outcome	In-hospital	41.8 (38.5-45.1) 58.2 (54.9-61.5)	5 (3.2-7.7) 2.4 (1.4-4.1)
(Becattini, Agnelli et al. 2016)[178]	External Validation	1	Retrospective	Stable	PE-related death	30-day	38.3 (35-41.7) 61.7 (58.3-65)	4.2 (2.5-7.1) 1.6 (0.8-3.2)
2008 ESC Intermediate								
(Vanni, Nazerian et al. 2011)[168]	External Validation	1	Retrospective	Stable	PE-related death	In-hospital	57.6 (53.1 – 62.1) 42.4 (37.9 – 46.9)	6.4 (4.1 – 10.1) 1.0 (0.3 – 3.7)
(Labyk, Ciurzynski, et al. 2012)[183]	External Validation	1	Retrospective	Stable	PE-related death	In-hospital	44.2 (39-49.6) 55.8 (50.4-61)	4.1 (1.9-8.7) 1.6 (0.6-4.7)
(Becattini, Casazza et al 2013)[99]	External Validation	1	Retrospective	Stable	PE-related death	In-hospital	78.3 (75.4 – 80.9) 21.7 (19.1 - 24.6)	1.8 (1.0 – 3.1) 0 (0 – 2)
	Overall	3	Retrospective	Stable	PE-related death	In-hospital	60.6 (39.5-79.9) 39.4 (20.1-60.5)	3.7 (1.1-7.6) **0.7 (0-2.1)**

(Becattini, Casazza et al 2013)[99]	External Validation	1	Retrospective	Stable	Death Adverse outcome	In-hospital	78.3 (75.4-80.9) 21.7 (19.1-24.6)	6.9 (5.2-9.1) **0.5 (0.1-3.7)**
(Becattini, Casazza et al 2013)[99]	External Validation	1	Retrospective	Stable	PE-related death Adverse outcome	In-hospital	78.3 (75.4-80.9) 21.7 (19.1-24.6)	4.3 (3-6.1) **0.5 (0.1-3.7)**
(Dellas, Tschepe et al 2014)[110]	External Validation	1	Prospective	Stable	Adverse outcome	30-day	78.1 (72.2-83.1) 21.9 (16.9-27.8)	10.9 (7-16.4) **1 (0.1-14.1)**
(Becattini, Agnelli et al. 2016)[178]	External validation	1	Retrospective	Stable	PE-related death	30-day	72.2 (69-75.2) 27.8 (24.8-31)	3.6 (2.4-5.5) **0.2 (0-3.5)**
2014 ESC Intermediate High (Vanni, Nazerian et al. 2016)[186]	External Validation	1	Retrospective	Stable	PE-related complications	In-hospital	11.6 (9.7-13.7) 88.4 (86.3-90.3)	13 (8-20.5) 5.5 (4.1-7.2)
(Becattini, Agnelli et al. 2016)[178]	External Validation	1	Retrospective	Stable	PE-related death	30-day	34 (30.8-37.3) 66 (62.7-69.2)	4.8 (2.8-8) 1.5 (0.8-3)
(Jimenez, Lobo et al. 2016)[122]	External Validation	1	Retrospective	Stable	Death Adverse outcome	30-day	6.7 (5.2-8.6) 93.3 (91.4-94.8)	17.5 (9.7-29.6) 6.7 (5.2-8.7)
2014 ESC Intermediate (Becattini, Agnelli et al. 2016)[178]	External Validation	1	Retrospective	Stable	PE-related death	30-day	75.5 (72.4-78.4) 24.5 (21.6-27.6)	3.3 (2.1-5.1) **0.5 (0.1-3.5)**
(Jimenez, Lobo et al. 2016)[122]	External Validation	1	Retrospective	Stable	Death Adverse outcome	30-day	63.1 (59.8-66.3) 36.9 (33.7-40.2)	10.8 (8.5-13.8) 1.6 (0.7-3.8)
eStiMaTe High								
(Jiménez, Kopecna et al 2014)[121]	Derivation	1	Prospective	Stable	Death Adverse outcome VTE	30-day	3.7 (2.6-5.1) 96.3 (94.9-97.4)	25.8 (13.7-43.2) 6.7 (5.2-8.7)
(Jiménez, Kopecna et al 2014)[121]	External validation	1	Prospective	Stable	Death Adverse outcome	30-day	6.2 (4.5-8.6) 93.8 (91.4-95.5)	21.2 (10.7-37.8) 3.4 (2.2-5.4)
(Jiménez, Kopecna et al 2014)[121]	Overall	2	Prospective	Stable	Death Adverse outcome VTE	30-day	4.6 (3.5-5.7) 95.4 (94.3-96.5)	**23.4 (13.6-34.8)** 5.4 (4.2-6.7)
eStiMaTe High Intermediate								
(Jiménez, Kopecna et al 2014)[121]	Derivation	1	Prospective	Stable	Death Adverse outcome VTE	30-day	74.5 (71.5-77.3) 25.5 (22.7-28.5)	9.7 (7.6-12.2) 0.9 (0.3-3.3)

(Jiménez, Kopecna et al 2014)[121]	External validation	1	Retrospective	Stable	Death Adverse outcome	30-day	63.5 (59.3-67.5) 36.5 (32.5-40.7)	7.1 (4.8-10.4) 0 (0-2)
(Jiménez, Kopecna et al 2014)[121]	Overall	2	Both	Stable	Death Adverse outcome VTE	30-day	70.4 (68-72.8) 29.6 (27.2-32)	8.7 (7-10.6) **0.3 (0-1.2)**
FAST = 3 (Dellas, Tschepe et al 2014)[110]	External validation	1	Prospective	Stable	Adverse outcome	30-day	28.4 (23.4-34.1) 71.6 (65.9-76.6)	**22.1 (14.2-32.7)** 1.5 (0.5-4.7)
GPS ≥ 3 (Bova, Pesavento et al. 2009)[101]	External validation	1	Prospective	Stable	PE-related death	In-hospital	18.9 (14.1-24.9) 81.1 (75.1-85.9)	2.6 (0.4-16.5) 0.3 (0.0-4.7)
(Kabrhel, Okechukwu et al. 2014)[125]	External validation	1	Prospective	Stable	Severe clinical deterioration	In-hospital	23.8 (19.3-29) 76.2 (71-80.7)	**54.9 (43.3-66)** 27.3 (21.9-33.5)
(Kabrhel, Okechukwu et al. 2014)[125]	External validation	1	Prospective	Stable	Death Adverse outcome	In-hospital	23.8 (19.3-29) 76.2 (71-80.7)	**16.9 (9.9-27.3)** 6.6 (4-10.6)
Hestia and CT-RVD (Zondag, Vingerhoets et al. 2013)[176]	External validation	1	Prospective	Stable	Death Adverse outcome	30-day		
Hestia							41.5 (37.1-46) 58.5 (54-62.9)	10.3 (6.7-15.4) **0.7 (0.2-2.9)**
Hestia – CT-RVD							61.7 (57.2-66) 38.3 (34-42.8)	7.2 (4.8-10.9) **0.6 (0.1-3.8)**
Kostrubiec et al (NT-proBNP – cTnT) (Kostrubiec, Pruszczyk et al. 2005)[128]	Derivation	1	Prospective	Stable				
Intermediate					Death	30-day	72.0 (62.4-79.9) 28.0 (20.1-37.6)	**20.8 (13.0-31.7)** 1.7 (0.1-22.3)
Intermediate					PE-related death	30-day	69.9 (59.8-78.3) 30.1 (21.7-40.2)	12.3 (6.3-22.7) 1.7 (0.1-22.3)
Intermediate High					Death	30-day	18.0 (11.6-26.8) 82.0 (73.2-88.4)	**50.0 (28.4-71.6)** 7.3 (3.3-15.3)
Intermediate High					PE-related death	30-day	16.1 (1.0-25.0) 83.9 (75.0-90.0)	**40.0 (19.2-65.2)** 2.6 (0.6-9.7)
Modified (m) models (Hobohm, Hellenkamp et al. 2016)[118]	External validation Update	1	Retrospective	Stable	Adverse outcome	30-day		

m-Bova ≥ III							16.2 (12.9-20.2) 83.8 (79.8-87.1)	**19 (11.1-30.6)** 4 (2.3-6.8)
m-"2008 ESC" Intermediate High							73.2 (68.6-77.4) 26.8 (22.6-31.4)	8.8 (6-12.7) 0.5 (0-7.1)
m-"2014 ESC" Intermediate High							34.3 (29.7-39.1) 65.7 (60.9-70.3)	**15 (9.9-22.2)** 2 (0.8-4.6)
m-FAST							28.6 (24.3-33.3) 71.4 (66.7-75.7)	**18.9 (12.7-27.3)** 1.4 (0.5-3.8)
PESI ≥ II (Sanchez, Trinquart et al 2013)[158]	External validation	1	Retrospective (for PESI)	Stable	Adverse outcome	30-day	75.2 (71.4-78.7) 24.8 (21.3-28.6)	6 (4.1-8.8) **0.8 (0-5.2)**
PESI ≥ III (Palmieri, Gallota et al 2008)[150]	External validation	1	Prospective	Stable	Death Adverse outcome	In-hospital	69.7 (59.5-78.2) 30.3 (21.8-40.5)	**53.2 (41-65.1)** 11.1 (3.9-28.1)
(Kabrhel, Okechukwu et al. 2014)[125]	External validation	1	Prospective	Stable	Death Adverse outcome	In-hospital	51.7 (46-57.3) 48.3 (42.7-54)	13.6 (9.1-19.9) 4.2 (1.9-8.8)
	Overall	2					55.9 (50.9-60.9) 44.1 (39.1-49.1)	**23.3 (17.8-29.2)** 4.6 (1.7-8.5)
(Vanni, Nazerian et al. 2011)[168]	External validation	1	Retrospective	Stable	PE-related death	In-hospital	67 (62.3-71.3) 33 (28.7-37.7)	6.1 (3.8-9.5) **0.7 (0.1-4)**
(Kabrhel, Okechukwu et al. 2014)[125]	External validation	1	Prospective	Stable	Severe clinical deterioration	In-hospital	51.7 (46-57.3) 48.3 (42.7-54)	**46.8 (39-54.6)** 20.1 (14.4-27.4)
(Sanchez, Trinquart et al 2013)[158]	External validation	1	Retrospective (for PESI)	Stable	Adverse outcome	30-day	37.8 (33.8-42) 62.2 (58-66.2)	9 (5.7-13.8) 2.1 (1-4.4)
PESI ≥ IV (Sanchez, Trinquart et al 2013)[158]	External validation	1	Retrospective (for PESI)	Stable	Adverse outcome	30-day	17.2 (14.2-20.7) 82.8 (79.3-85.8)	8.8 (4.5-16.6) 3.9 (2.4-6.2)
PESI = V (Sanchez, Trinquart et al 2013)[158]	External validation	1	Retrospective (for PESI)	Stable	Adverse outcome	30-day	4 (2.6-6) 96 (94-97.4)	14.3 (4.7-36.1) 4.3 (2.9-6.5)
(Vanni, Nazerian et al. 2011)[168]	External validation	1	Retrospective	Stable	PE-related death	In-hospital	16.5 (13.3-20.4) 83.5 (79.6-86.7)	11.6 (6-21.2) 2.9 (1.6-5.2)
PESI + biomarkers (Sanchez, Trinquart et al 2013)[158]	External validation	1	Retrospective (for PESI)	Stable	Adverse outcome	30-day		

PESI I-II - BNP							32.7 (27.8 – 38.0) 67.3 (62.0 – 72.2)	4.7 (2.0 – 10.8) **0.9 (0.2 – 3.6)**
PESI I-II - cTnI							13.7 (10.3 – 17.9) 86.3 (82.1 – 89.7)	9.1 (3.5 – 21.8) **1.1 (0.3 – 3.3)**
PESI I-II - TTE-RVD							12.3 (9.0 – 16.5) 87.7 (83.5 – 91.0)	10.8 (4.1 – 25.5) **1.1 (0.4 – 3.5)**
PESI III-IV - BNP							56.3 (48.8 – 63.4) 43.8 (36.6 – 51.2)	10.1 (5.5 – 17.8) 6.5 (2.7 – 14.7)
PESI III-IV - cTnI							24.0 (18.2 – 30.9) 76.0 (69.1 – 81.8)	**16.7 (8.2 – 31.0)** 5.3 (2.5 – 10.6)
PESI III-IV - TTE-RVD							22.8 (17.0 – 29.9) 77.2 (70.1 – 83.0)	10.8 (4.1 – 25.5) 8.8 (4.9 – 15.2)
PESI V - BNP							76.2 (54.0 – 89.7) 23.8 (10.3 – 46.0)	**18.8 (6.2 – 44.7)** 8.3 (0.5 – 62.2)
PESI V - cTnI							30.0 (14.1 – 52.7) 70.0 (47.3 – 85.9)	**16.7 (2.3 – 63.1)** 14.3 (3.6 – 42.7)
PESI V - TTE-RVD							23.8 (10.3 – 46.0) 76.2 (54.0 – 89.7)	**20.0 (2.7 – 69.1)** 12.5 (3.1 – 38.6)
PESI + biomarkers (Jimenez, Aujesky et al. 2011)[120]	Update	1	Unclear Prospective	Stable	PE-related death	30-day		
cTnI							32.1 (28.5-36.0) 67.9 (64.0-71.5)	10.5 (6.9-15.8) 4.2 (2.7-6.7)
TTE-RVD							20.3 (17.3-23.7) 79.7 (76.3-82.7)	11.7 (7.0-18.7) 4.9 (3.3-7.2)
US-DVT							38.6 (34.7-42.6) 61.4 (57.4-65.3)	9.6 (6.4-14.2) 4.1 (2.5-6.7)
TTE- RVD – cTnI							10.0 (7.8-12.7) 90.0 (87.3-92.2)	**15.3 (8.1-26.8)** 5.3 (3.7-7.5)
PESI ≥ IV - TTE-RVD – cTnI							12.7 (9.0-17.7) 87.3 (82.3-91.0)	**20.7 (9.6-39.0)** 8.0 (5.0-12.7)
cTnI - US-DVT							13.9 (11.3-16.9)	**17.1 (10.4-26.8)**

							86.1 (83.1-88.7) 18.0 (13.5-23.5) 82.0 (76.5-86.5) 8.6 (6.6-11.2) 91.4 (88.8-93.4) 4.1 (2.7-6.0) 95.9 (94.0-97.3) 10.5 (7.2-15.2) 89.5 (84.8-92.8)	4.5 (3.0-6.7) **24.4 (13.7-39.7)** 6.4 (3.7-11.0) **19.6 (10.9-32.7)** 5.0 (3.5-7.2) **20.8 (8.9-41.3)** 5.6 (4.0-7.9) **25.0 (11.7-45.6)** 7.8 (4.9-12.4)
PESI ≥ IV - cTnI - US-DVT TTE-RVD - US-DVT TTE-RVD - cTnI - US-DVT PESI ≥ IV - TTE-RVD - US-DVT								
PREP - Clin ≥ II (Sanchez, Trinquart et al. 2010)[157]	Derivation	1	Prospective	Stable	Death VTE	30-day	32.3 (28.2-36.6) 67.7 (63.4-71.8)	12.3 (8-18.5) 1.9 (0.9-4)
PREP - Clin ≥ III (Sanchez, Trinquart et al. 2010)[157]	Derivation	1	Prospective	stable	Death VTE	30-day	1.9 (1-3.5) 98.1 (96.5-99)	**22.2 (6.3-54.7)** 4.9 (3.3-7.3)
sPESI ≥ 1 (Kabrhel, Okechukwu et al. 2014)[125]	External validation	1	Prospective	Stable	Severe clinical deterioration	In-hospital	65.8 (60.2-70.9) 34.2 (29.1-39.8)	**41.3 (34.7-48.3)** 19.6 (13.1-28.4)
(Kabrhel, Okechukwu et al. 2014)[125]	External validation	1	Prospective	Stable	Death Adverse outcome	In-hospital	65.8 (60.2-70.9) 34.2 (29.1-39.8)	11.2 (7.5-16.4) 4.9 (2.1-11)
(Dellas, Tschepe et al 2014)[110]	External validation	1	Prospective	Stable	Adverse outcome	30-day	66.1 (60.2-71.4) 33.9 (28.6-39.8)	11.2 (7.4-16.6) **0 (0-4)**
sPESI ≥ 1- hscTnT (Lankeit, Jimenez et al. 2011)[133] hs-cTnT sPESI ≥ 1 sPESI ≥ 1- hscTnT	External validation	1	Prospective	Stable	Death Adverse outcome	30-day	 59.3 (55.1-63.4) 40.7 (36.6-44.9) 62.4 (58.1-66.4) 37.6 (33.6-41.9) 75.9 (72.0-79.3) 24.1 (20.7-28.0)	 8.7 (6.0-12.3) 1.9 (0.7-4.9) 8.8 (6.2-12.4) **1 (0.3-3.9)** 7.8 (5.5-10.8) **0.4 (0.0-5.9)**
sPESI ≥ 1 - Lactate (Vanni, Jimenez et al. 2015)[185] **sPESI ≥ 1**	External validation	1	Prospective	Stable	PE-related complications	In-hospital	 72.8 (68.7-76.5) 27.2 (23.5-31.3)	 4.7 (2.9-74) 2.2 (0.7-6.7)

sPESI ≥ 1 - Lactate							21.8 (18.4-25.6) 78.2 (74.4-81.6)	11.1 (6.4-18.6) 2.1 (1-4.1)
TELOS (Vanni, Jimenez et al. 2015)[185]	Derivation	1	Prospective	Stable	PE-related complications	In-hospital	5.6 (3.9-8) 94.4 (92-96.1)	17.9 (7.9-35.6) 3.2 (2-5.2)
(Vanni, Nazerian et al. 2016)[186]	External validation	1	Retrospective	Stable	PE-related complications	In-hospital	5.7 (4.5-7.4) 94.3 (92.6-95.5)	21.1 (12.5-33.3) 5.4 (4.2-7.1)
	Overall	2	Both	Stable	PE-related complications	In-hospital	5.7 (4.6-7) 94.3 (93-95.4)	**20 (12.8-29.9)** 4.4 (2.6-7.2)

In the first column, the cut-off is indicated by the corresponding higher risk group for the cut-off except for the Bova et al 2014 and Sanchez et al 2013 (PESI + biomarkers) studies which are displayed in risk categories. Bova's study combined individual patient data (IPD) from 6 studies. Event rates for models with cut-offs suitable for low-risk PE in blue and for high-risk PE in red.

Table 4.5: Outcomes in studies reporting on type 2 models (originally not specific to the prognosis or to the domain of PE) and on type 3 models (hospital criteria checklists).

Risk cut-off (Author, year)	Development phase	N studies	Type of study	Haemodynamic status	Outcome	Timepoint	Proportion (95% CI) High Risk Group Low Risk Group	Event rate(95% CI) High Risk Group Low Risk Group
Revised Geneva score (RGS) (Bertoletti, Le Gal et al 2013)[100]	External validation	1	Prospective for RGS	Not reported	All-cause death	3-month		
RGS High							11.8 (8.8-15.5) 88.2 (84.5-91.2)	14.3 (6.6-28.3) 4.8 (2.9-7.7)
RGS High Intermediate							84.0 (79.9-87.5) 16.0 (12.5-20.1)	7.0 (4.6-10.5) **0.9 (0.1-12.3)**
Simplified Geneva score (SGS) (Bertoletti, Le Gal et al 2013) [100]	External validation	1	Retrospective for SGS	Not reported	All-cause death	3-month		
SGS High							7.8 (5.5-11.1) 92.2 (88.9-94.5)	**17.9 (7.6-36.4)** 4.9 (3.0-7.8)
SGS High Intermediate							84.0 (79.9-87.5) 16.0 (12.5-20.1)	7.0 (4.6-10.5) **0.9 (0.1-12.3)**
GRACE - ACS Risk score (Paiva, Providencia et al 2013) [149]	External validation	1	Retrospective	Both stable and unstable	All-cause death	30-day		
GRACE - ACS High							56.8 (49.9-63.4) 43.2 (36.6-50.1)	**25.6 (18.5-34.3)** 10.1 (5.3-18.3)
GRACE - ACS High Intermediate							81.1 (75.1-85.9) 18.9 (14.1-24.9)	**23.4 (17.6-30.4)** **1.3 (0.1-17.1)**
GRACE - PE Risk score (Paiva, Providencia et al 2013)[149]	External validation	1	Retrospective	Both stable and unstable	All-cause death	30-day		
GRACE - PE High							49.0 (42.3-55.8) 51.0 (44.2-57.7)	**29.7 (21.6-39.3)** 8.6 (4.5-15.7)
GRACE - PE High Intermediate							78.2 (72.0-83.3) 21.8 (16.7-28.0)	**24.2 (18.2-31.4)** **1.1 (0.1-15.1)**
sCRB-65 (Keller, Coldewey et al. 2015)[127]	External validation	1	Retrospective	Both stable and unstable	All-cause death	In-hospital	Not reported	Not reported

APACHE ≥ 19 (Bach, Taute et al. 2016)[98]	External validation	1		Not reported	All-cause death	30-day	20 (16.2-24.4) 80 (75.6-83.8)	**37 (26.7-48.6)** 4.1 (2.3-7.1)
GLASGOW COMA SCALE ≤ 10 (Bach, Taute et al. 2016)[98]	External validation	1		Not reported	All-cause death	30-day	14.8 (11.5-18.8) 85.2 (81.2-88.5)	**44.4 (31.9-57.8)** 4.8 (2.9-7.8)
EUROSCOREII ≥ 5.9 (Bach, Taute et al. 2016)[98]	External validation	1		Not reported	All-cause death	30-day	30.1 (25.6-35) 69.9 (65-74.4)	**22.7 (15.8-31.5)** 5.5 (3.3-9.1)
Davies checklist (Davies, Wimperis et al 2007)[109] Unsuitable versus suitable	Derivation	1	Prospective	Not reported	All-cause death	3-month	 57.9 (51.0-64.5) 42.1 (35.5-49.0)	 5.1 (2.3-10.9) 3.5 (1.1-10.4)
Davies checklist* (Davies, Wimperis et al 2007)[109]	External validation and Impact (management study)	1	Prospective	Stable meeting inclusion criteria (suitable) for home treatment	All-cause death PE-related VTE Major/ Fatal bleeding	3-month	Not reported	1.9 (0.4-5.5) None None None
Hestia checklist* (Zondag, den Exter et al 2013)[175]	External validation	1	Prospective	Both stable and unstable	All-cause death	7-day 30-day 3-month	46.9 (42.4-51.4) 53.1 (48.6-57.6) 46.9 (42.4-51.4) 53.1 (48.6-57.6) 46.9 (42.4-51.4) 53.1 (48.6-57.6)	1.8 (0.7-4.8) **0.2 (0.0-3.1)** 4.1 (2.2-7.7) **0.8 (0.2-3.2)** 9.6 (6.4-14.3) **1.2 (0.4-3.7)**
Hestia checklist (Zondag, Vingerhoets et al 2013)[176]	External validation (and update)	1	Prospective	Both stable and unstable Both stable and unstable Stable Stable	All-cause death Death Adverse outcome All-cause death Death Adverse outcome	30-day 30-day 30-day 30-day	44.6 (40.2-49.0) 55.4 (51.0-59.8) 44.6 (40.2-49.0) 55.4 (51.0-59.8) 41.5 (37.1-46.0) 58.5 (54.0-62.9) 41.5 (37.1-46.0) 58.5 (54.0-62.9)	4.1 (2.1-7.6) **0.7 (0.2-2.9)** **19.9 (15.2-25.7)** **0.7 (0.2-2.9)** 3.6 (1.7-7.3) **0.7 (0.2-2.9)** 10.3 (6.7-15.4) **0.7 (0.2-2.9)**

Hestia – NT-proBNP versus Hestia (den Exter, Zondag et al. 2016)[180] **Hestia – NT-proBNP** **Hestia**	Impact - Low-risk Outpatient management	1	Prospective (RCT)	Stable	Adverse outcome	30-day	 Not applicable Not applicable	 0/275 **0 (0-1.3)** 3/275 **1.09 (0.2-3.1)**
Hestia checklist (Weeda, Kohn et al. 2016)[188]	External validation	1	Retrospective	Both stable and unstable	All-cause death	In-hospital 30-day	74.2 (70.4-77.6) 25.8 (22.4-29.6) 74.2 (70.4-77.6) 25.8 (22.4-29.6)	4.4 (2.8-6.9) **0.3 (0-5.1)** 8.2 (5.9-11.2) **0.3 (0-5.1)**

In the first column, the cut-off is indicated by the corresponding higher risk group for the cut-off. Event rates for models with cut-offs suitable for low-risk PE in blue and for high-risk PE in red. * In the original publication[189], the 3-month event rates were the following: all-cause death 1% (0.2-2.9), VTE 2% (0.8-4.3), PE 1.68% (0.5-3.9), DVT 0.3% (0-1.9), major bleeding 0.7% (0.08-2.4). There was no PE-related death.

Quantitative analysis - Prognostic accuracy

Summary estimates are displayed (table 4.6) for different cut-offs as identified in the studies to discriminate between low-risk and high-risk groups. They are provided when at least four studies were identified for a specific cut-off, and a specific outcome and time point. The highest overall sensitivity estimates were obtained with the Prognostic Algorithm (4 studies) for predicting in-hospital mortality (97% [95% CI: 96 – 98]) and 30-day mortality (98% [96 – 99], then with PESI (94% [89 – 97]) for 3-month mortality (6 external validation studies) and sPESI (93% [90 – 95]) for 30-day (15 studies) and for 3-month mortality (13 external validation studies) (table 4.6). All results are consistent and similar in external validation studies. The same applies for LR negative estimates. The specificity at suggested cut-offs is at best 54% [51 - 58] for PESI $\geq$ III cut-off for 3-month mortality. Shifting the cut-off along the risk scale provides higher values for sensitivity or for specificity (table 4.6). In figure 4.3a and figure 4.3b, summary receiver-operating characteristic (sROC) plots show test accuracy of the two most validated models at relevant cut-offs PESI $\geq$ III and sPESI $\geq$ 1 associated with 30-day all-cause death for all studies and for external validation studies separately.

Table 4.6: Accuracy of prognostic models for different cut-offs.

	Outcome Time-point	Model Risk cut-off (n of studies)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	LR positive (95% CI)	LR negative (95% CI)
All studies	Mortality In-hospital	Algorithm (n=4)[95 182]	**97 (96 – 98)**	23 (22 – 25)	11.05 (6.91 – 17.65)	1.27 (1.24 – 1.30)	**0.11 (0.07 – 0.18)**
		PESI : ≥ III vs ≤ II (n=7)[94 112 143 150 168]	90 (88 – 92)	42 (36 – 48)	6.90 (5.04 – 9.46)	1.56 (1.41 – 1.73)	0.23 (0.18 – 0.29)
		PESI V vs ≤ IV (n=5)[94 143 168]	51 (41 – 61)	**83 (80 – 86)**	5.21 (3.80 – 7.14)	3.07 (2.62 – 3.59)	0.59 (0.49 – 0.71)
		sPESI (n=4)[112 130 144 175]	99 (20 – 100)	49 (35 – 63)	100.82 (0.30 - 34262.83)	1.94 (1.49 – 2.51)	0.02 (0.00 – 6.88)
	Mortality 30-day	Algorithm (n=4)[95 182]	**98 (96 – 99)**	24 (19 – 30)	15.26 (6.47 – 35.99)	1.29 (1.20 – 1.39)	**0.08 (0.04 – 0.19)**
		PESI: ≥ II vs I (n=9)[94 104 119 123 126 139 159 160]	**97 (96 – 98)**	19 (18 – 20)	9.00 (6.49 – 12.48)	1.20 (1.18 – 1.23)	**0.13 (0.10 – 0.18)**
		PESI : ≥ III vs ≤ II (n=13)[94 104 112 119 123-126 139 154 159 160]	90 (88 – 91)	44 (41 – 48)	7.14 (5.75 – 8.88)	1.61 (1.52 – 1.72)	0.23 (0.19 – 0.27)
		PESI : ≥ IV vs ≤ III (n=9)[94 104 119 123 126 139 159 160]	72 (64 – 78)	68 (63 – 73)	5.44 (4.55 – 6.49)	2.26 (2.12 – 2.41)	0.42 (0.34 – 0.51)
		PESI : V vs ≤ IV (n=9)[94 104 119 123 126 139 159 160]	49 (39 - 59)	**85 (81 - 89)**	5.54 (4.72 – 6.50)	3.32 (3.00 – 3.67)	0.60 (0. 51 – 0.70)

		sPESI (n=15)[108 112 115 119 125 134 139 146 148 149 152 154 169 175]	93 (90 – 95)	39 (35 – 43)	8.27 (5.69 – 12.01)	1.52 (1.42 – 1.61)	0.18 (0.13 – 0.26)
	Mortality 3-month	PESI: ≥ II vs I (n=4)[94 104 111 161]	**99 (82 – 100)**	28 (17 – 42)	50.04 (1.47 – 1706.14)	1.37 (1.14 – 1.65)	**0.03 (0.00 – 0.86)**
		PESI : ≥ III vs ≤ II (n=6)[94 100 104 111 112 161]	**94 (89 – 97)**	54 (51 – 58)	18.73 (9.21 – 38.06)	2.06 (1.88 – 2.26)	**0.11 (0.06 – 0.21)**
		PESI : ≥ IV vs ≤ III (n=4)[94 105 111 161]	78 (47 - 93)	**76 (65 – 84)**	11.02 (4.05 – 30.02)	3.20 (2.62 – 3.91)	0.29 (0.11 – 0.77)
		PESI : V vs ≤ IV (n=4)[94 104 111 161]	40 (23 – 60)	**90 (82 – 95)**	6.37 (4.05 – 10.02)	4.2 (2.89 – 6.11)	0.66 (0.50 – 0.86)
External validation studies	Mortality In-hospital	PESI : ≥ III vs ≤ II (n=5)[112 143 150 168]	90 (82 – 95)	42 (33 – 50)	6.65 (3.02 – 14.68)	1.55 (1.32 – 1.81)	0.23 (0.12 – 0.46)
		2008 ESC High (n=4)[103 129 168 183]	51 (32 – 70)	**93 (85 – 97)**	13.65 (7.37 – 25.27)	**7.18 (4.13 – 12.49)**	0.53 (0.36- 0.76)
		2008 ESC Intermediate (n=4)[99 129 168 183]	**95 (66 – 99)**	35 (22 – 51)	9.51 (1.63 – 55.31)	1.46 (1.25 – 1.71)	**0.15 (0.03 – 0.92)**
		sPESI (n=4)[112 130 144 175]	**99 (20 – 100)**	49 (35 – 63)	100.82 (0.30 - 34262.83)	1.94 (1.49 – 2.51)	**0.02 (0.00 – 6.88)**
	Mortality 30-day	PESI: ≥ II vs I (n=6)[104 119 123 126 139 160]	**99 (84 – 100)**	17 (14– 21)	16.86 (1.06 – 266.91)	1.19 (1.12 – 1.27)	**0.07 (0.00 – 1.07)**
		PESI : ≥ III vs ≤ II (n=9)[104 112 119 123 125 126 139 154 160]	**95 (89– 98)**	44 (39 – 48)	14.52 (5.54 – 38.05)	1.69 (1.52 – 1.88)	**0.12 (0.05 – 0.28)**
		PESI : ≥ IV vs ≤ III	74	67	5.88	2.26	0.38

		(n=6)[104 119 123 126 139 160]	(60 – 85)	(60 – 73)	(3.72 – 9.33)	(2.00 – 2.55)	(0.25 – 0.58)
		PESI : V vs ≤ IV (n=6)[104 119 123 126 139 160]	52 (33 – 71)	**85 (79 – 90)**	6.27 (3.77 – 10.42)	3.51 (2.85 – 4.32)	0.56 (0.39 – 0.81)
		2008 ESC High (n=4)[132 148 149 178]	29 (21 – 37)	**91 (89 – 93)**	4.14 (2.36 – 7.27)	3.24 (2.08 – 5.05)	0.78 (0.69 – 0.89)
		2008 ESC High Intermediate (n=4)[132 148 149 178]	92 (85 – 96)	33 (28 – 39)	6.12 (3.26 – 11.5)	1.39 (1.31 – 1.48)	0.23 (0.12 – 0.42)
		sPESI (n=13)[108 112 119 125 139 146 148 149 152 154 169 175]	93 (89 – 95)	39 (35 – 44)	8.13 (5.43 – 12.18)	1.52 (1.42 – 1.64)	0.19 (0.13 – 0.27)
	Mortality 3-month	PESI: ≥ II vs I (n=4)[94 104 111 161]	**99 (82 – 100)**	28 (17 – 42)	50.04 (1.47 – 1706.14)	1.37 (1.14 – 1.65)	**0.03 (0.00 – 0.86)**
		PESI : ≥ III vs ≤ II (n=6)[94 100 104 111 112 161]	**94 (89 – 97)**	54 (51 – 58)	18.73 (9.21 – 38.06)	2.06 (1.88 – 2.26)	**0.11 (0.06 – 0.21)**
		PESI : ≥ IV vs ≤ III (n=4)[94 105 111 161]	78 (47 - 93)	**76 (65 – 84)**	11.02 (4.05 – 30.02)	3.20 (2.62 – 3.91)	0.29 (0.11 – 0.77)
		PESI : V vs ≤ IV (n=4)[94 104 111 161]	40 (23 – 60)	**90 (82 – 95)**	6.37 (4.05 – 10.02)	4.2 (2.89 – 6.11)	0.66 (0.50 – 0.86)

Summary estimates of sensitivity and specificity in analyses including at least four studies. DOR = Diagnostic odds ratio, LR = likelihood ratio. All subgroups (studies with "Stable" or "Both stable and unstable" patients, prospective and retrospective studies) included. "All studies" corresponds to summary results of derivation, internal validation and external validation studies all combined as available, as opposed to summary results of "External validation studies" separately. In bold characters the most clinically significant results.

Figure 4.3a: Summary receiver-operating characteristic (sROC) plots showing test accuracy of PESI ≥ III cut-off associated with 30-day all-cause death: all studies (left) and external validation studies (right)

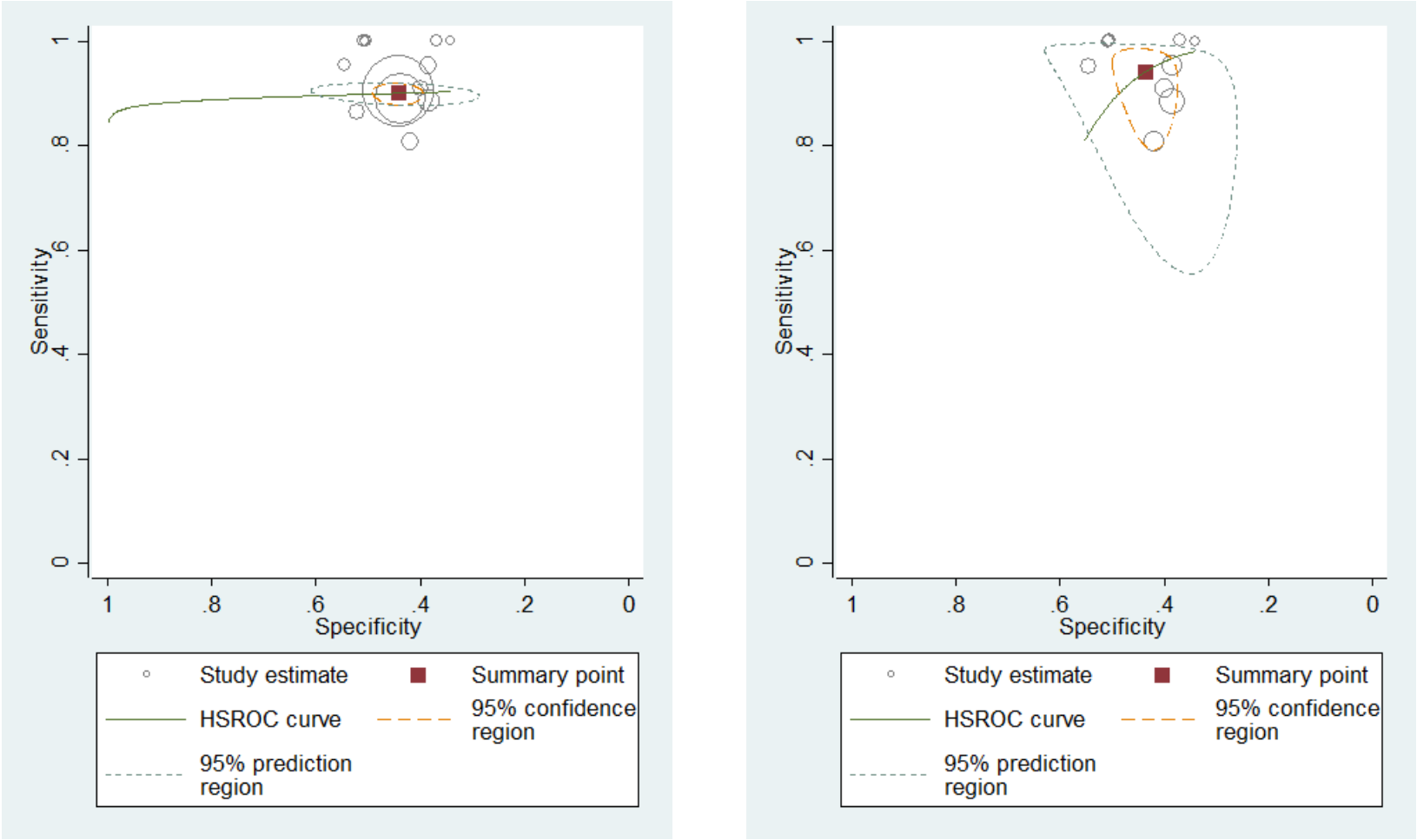
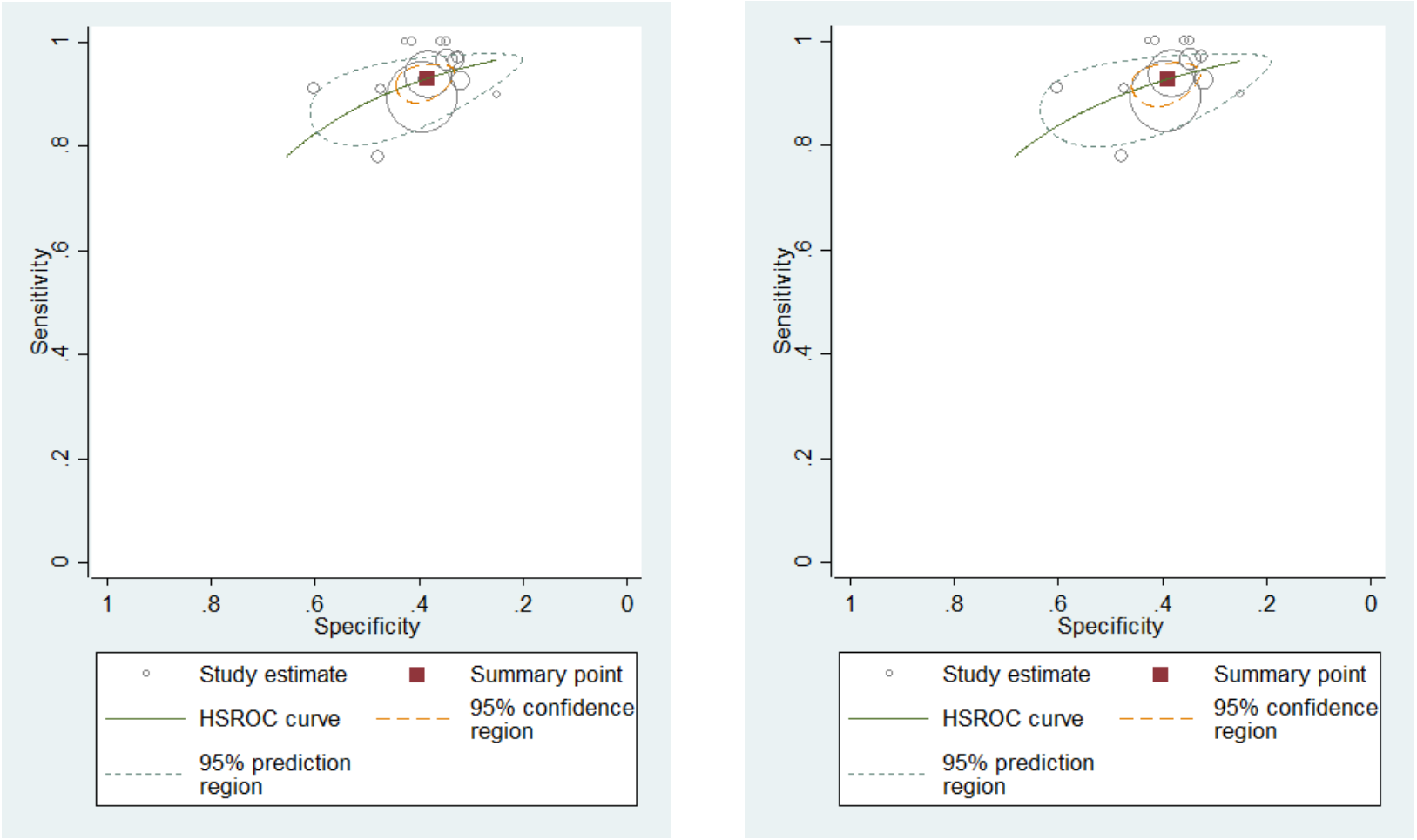


Figure 4.3b: Summary receiver-operating characteristic (sROC) plots showing test accuracy of sPESI ≥ 1 cut-off associated with 30-day all-cause death: all studies (left) and external validation studies (right)



Model updating

For better identification of lower and higher risk groups, some studies assessed the effect on outcomes of adding one or more prognostic variables to an existing model. There is increasing evidence about the greater effectiveness of these "new models", even though existing ones such as PESI, sPESI and Hestia are already highly effective.

In the study of Moores, the addition of non-elevated cTnI to low-risk PESI did not improve the negative predictive value compared with either test alone[140]. In the Lankeit study[133], the combination of a negative highly sensitive cTnT (hscTnT<14 pg/mL) and a sPESI value of 0 at baseline improved risk classification and identified a group at lower risk of mortality. The same applies for the combination of NT-proBNP (< 600 pg·mL−1) and low-risk sPESI[134]. In the study of Ozsu, hs-cTnT combined with sPESI provided better predictive information than cTnT[146]. Adding cTn to the PESI[160] and the sPESI[162] models resulted in a higher AUC value with no additive value for Ddimer to PESI and cTn[160]**.** To sum-up, there is an increased value in identifying lower risk patients by adding NT-proBNP and hs-cTnT to PESI or sPESI.

Other update studies tried to improve the identification of high-risk patients. Adding BNP and TTE-RVD to the PREP clinical model resulted in a significant difference in AUC[157]. A significant increase in "NRI: Net Reclassification Improvement", as defined by Pencina & al[190], was obtained in the original study which updated PREP model by adding BNP and TTE-RVD to the clinical model[157]. Using the PREP cohort in patients with normotensive PE, Sanchez et al showed that biomarkers (cTnI, BNP) and echocardiography provided additional prognostic information to PESI[158]. In the Palmieri study[150] which included highly selected "non-massive central PE", increased cTnI contributed to identifying patients with raised risk of development of haemodynamic instability, which was independent of, and in addition, to PESI.

Novel models[102 110 121 131 185] specifically developed for normotensive PE patients and integrating biomarkers (cTn, NT-proBNP, H-FABP, lactates), CT or TTE-RVD and US-detected DVT with clinical

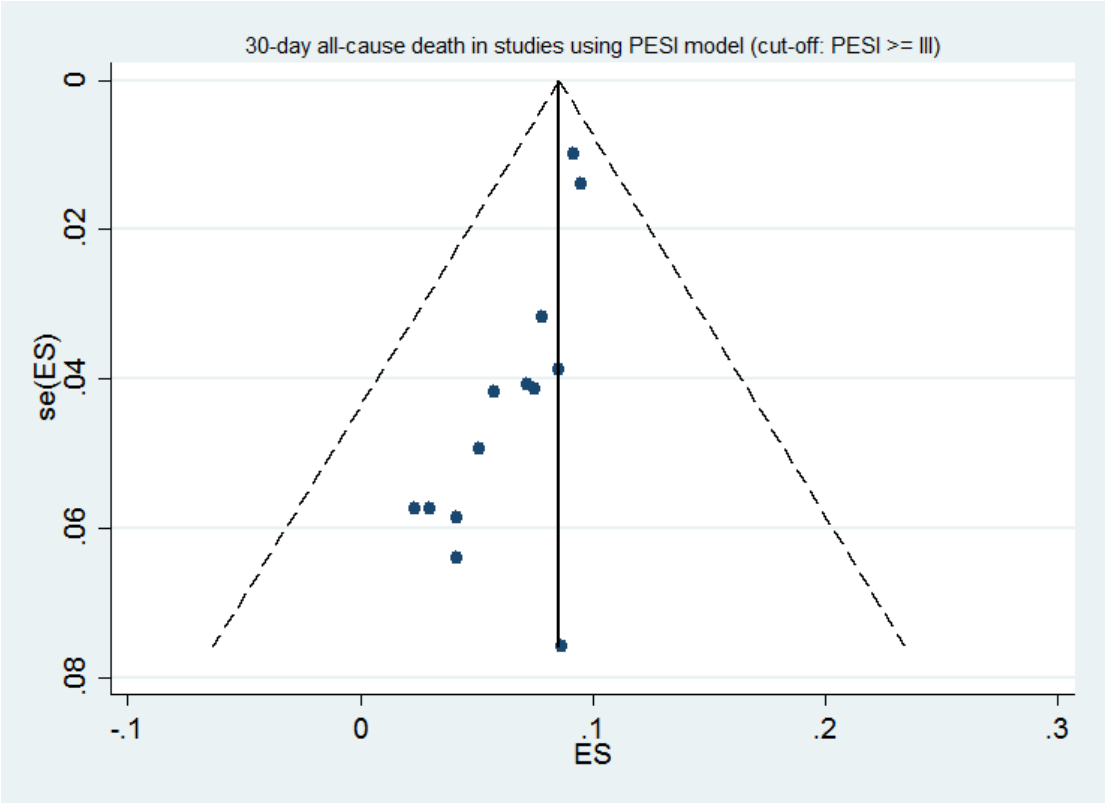
variables (SBP, HR), or with Bova, PESI or sPESI, showed a high ability to identify not only patients at lower risk but also thoseat higher risk of early death or adverse outcome at the expense of a lower proportion of patients in these risk groups (table 4.3, table 4.4).

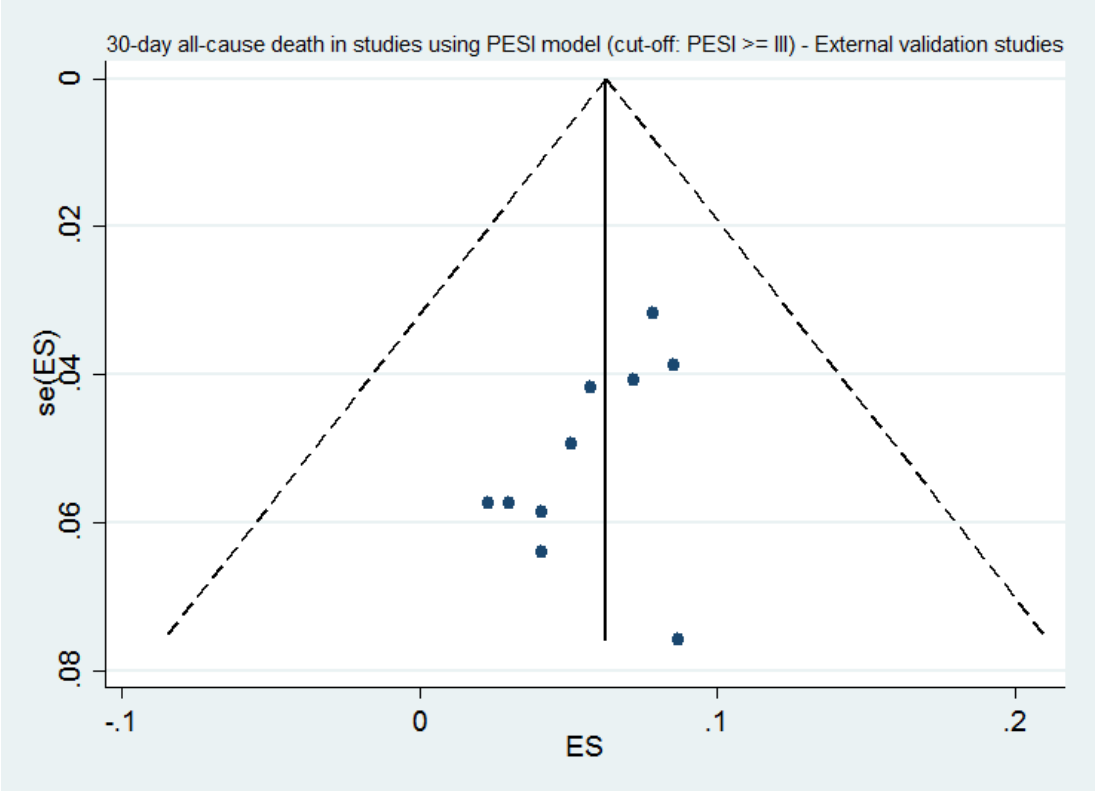
Tests for heterogeneity, investigation for publication bias, sensitivity analysis and subgroup analysis.

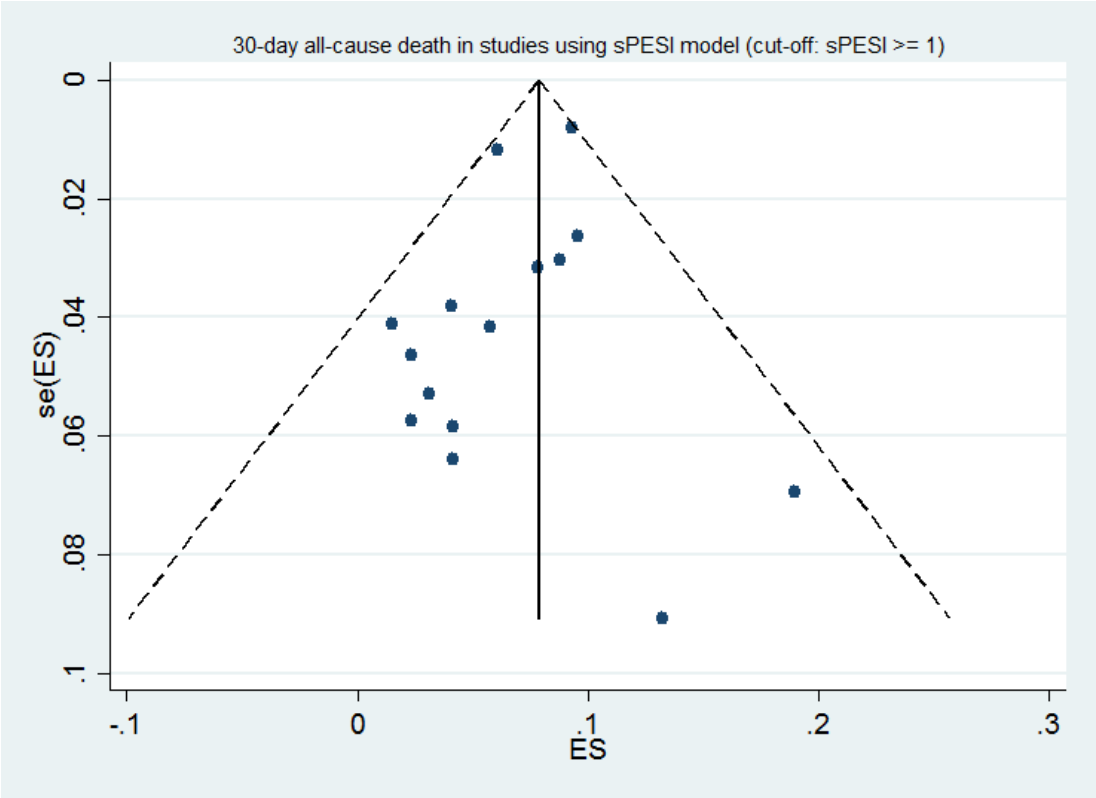
Results of tests for heterogeneity using the I^2 statistic (i.e. variation in effect size attributable to heterogeneity), and of subgroup analyses show major problems due to heterogeneity. For instance, comparing results between studies that reported 30-day all-cause death in the low-risk group for PESI optimal cut-offs (PESI $\geq$ III, sPESI $\geq$ 1), I found important between-study heterogeneity for sPESI if all studies are included (I^2 = 75.844, p<0.0001) or if only external validation studies are included (I^2 = 77.155, p<0.0001). Heterogeneity remains important (I^2>50%) in studies that combined stable and unstable PE (I^2=76.667, p<0.0001), but not in studies of stable PE alone (I^2=0, p=0.95). Heterogeneity might be related to patient selection in some studies. If a high proportion of patients at low-risk are included in the study population (or a lower proportion of patients at high risk), this results in lower event rates in the population sample (prevalence) and within risk groups. For PESI, significant heterogeneity was found when including all studies (I^2=64.900, p=0.001) or only external validation studies (I^2=63.894, p=0.003) (Figure 4.2).

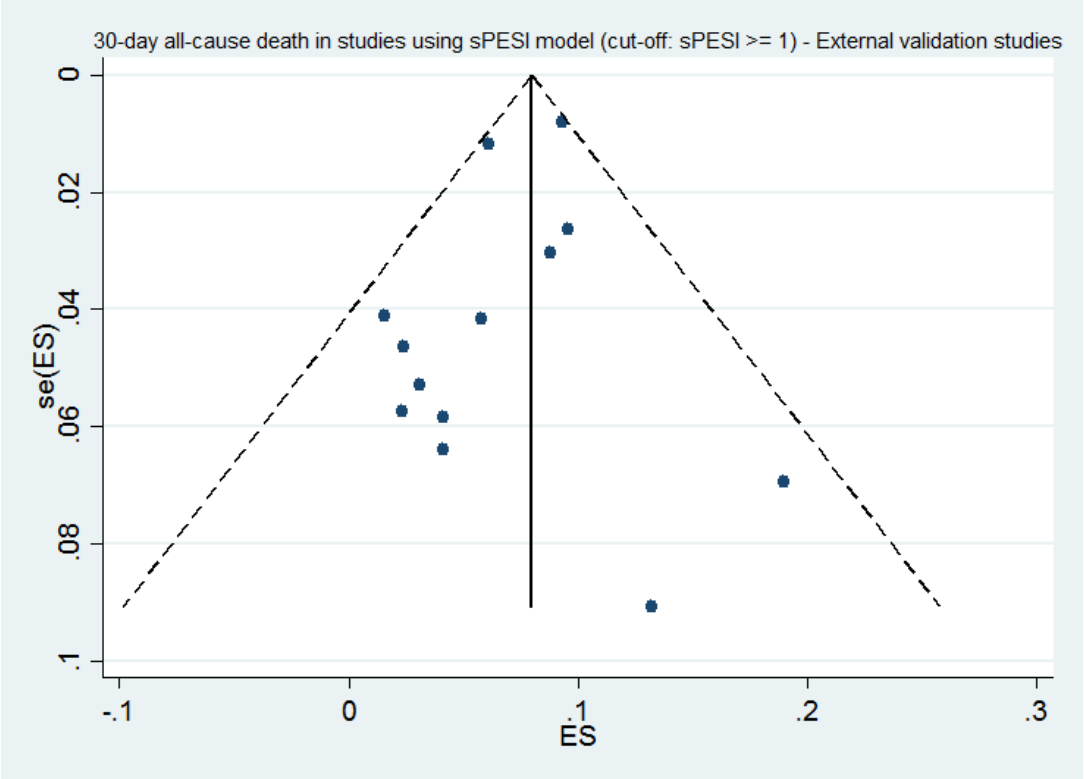
Investigations for publication bias for instance for 30-day all-cause death with PESI and sPESI models at optimal cut-offs (PESI $\geq$ III, sPESI $\geq$ 1) showed evidence of publication bias mainly for PESI (Figures 4) whether with the funnel plot or with the Egger's test (p=0.001) and Begg's test (p=0.023 and p=0.028). Publication bias was still present after sensitivity analysis and for subgroup of patients (haemodynamic status), type of studies (prospective or retrospective) but not for external validation studies at 5% significance level (Figures 4) (p=0.058 for Egger's test, and p=0.151 and p=0.178 for Begg's test).

Figure 4.4: Funnel plots with pseudo 95% confidence limits






30-day all-cause death in studies using sPESI model (cut-off: sPESI >= 1)
se(ES)
0
.02
.04
.06
.08
.1
-.1
0
.1
.2
.3
ES


30-day all-cause death in studies using sPESI model (cut-off: sPESI >= 1) - External validation studies
se(ES)
0
.02
.04
.06
.08
.1
-.1
0
.1
.2
.3
ES

Model impact

The clinical utility of a model is assessed by its effect on clinical decision making and subsequent patient outcomes. However, there are few studies that directly assess for the PE models (table A4.4.5).

The safety of treating low-risk PE patients as outpatients was examined in three management studies[91 147 179] and in two randomized trials[97 145]. The first management study[179] was a feasibility study among low-risk patients based on the GPS model in a very small number of patients. It showed the use of the GPS model to be safe. In another one-group management study[91], stable PE patients with NT-proBNP <500 pg mL^{-1} were treated at home. Seven (4.6%) patients were readmitted within the first 10 days but there were no deaths, no VTE events, and no clinically relevant or major bleeding at 3-month follow-up. In a prospective single centre study[147] among 31 patients with negative cTn and low-risk sPESI (not including cancer item) who were treated at home, one patient (3.2%) had died by a 3-month follow-up. The first of the two randomized trials[145] did not demonstrate the clinical utility of Uresandi's model[167] for outpatient management. The rate of short-term mortality was unexpectedly high in both management groups, as was the rate of VTE events and major bleeding. The second randomized trial[97] was a non-inferiority study in highly selected low-risk PE patients. It showed that outpatient care based on the PESI model can safely and effectively be used in place of inpatient care: 1 (0.6%) death in each group, with 1 (0.6%) VTE and 2 (1.2%) major bleeding events in the outpatient group at a 3-month follow-up. In a Cochrane Review[191], this randomized trial was ranked as very low quality evidence due to the lack of blinding of outcome assessors, small number of events with imprecision in the confidence interval (CI) and indirectness, and small sample size. Because of other eligibility criteria for outpatient-management and study design, only 56% (152/271) of patients with low NT-proBNP level[91], 15% (31/206) with negative cTn and low-risk sPESI, 13% (132/1016) with low-risk

Uresandi's model[145], 18% (43/244) with low-risk GPS[179] and 44% (344/783) with PESI I-II[97] could be treated as outpatients.

Three other studies assessed the safety of treating low-risk PE patients as outpatients based on hospital checklists. Using Davies criteria[109], 157 patients with PE recruited from 10 centres with established nurse-led outpatient DVT services in the UK received outpatient anticoagulation therapy. There were no deaths, bleeding or recurrent thromboembolic events by the time of a 3-month follow-up. Using the Hestia criteria[189], 297 patients were managed as outpatients with low event rates at 3 months: all-cause death 1% (0.2-2.9), VTE 2% (0.8-4.3) and major bleeding 0.7% (0.08-2.4). There was no PE-related death. In a randomized non-inferiority trial in 17 Dutch hospitals[180], outpatient treatment of PE patients selected by the Hestia criteria was associated with a low risk of 30-day adverse outcome (3/275 patients: 1.1%; 95%CI 0.2-3.2%) in the direct discharge group (Hestia alone) as compared to no adverse outcomes in the 275 patients (0%; 95%CI: 0-1.3%) subjected to NT-proBNP (Hestia and NT-proBNP group). The proportion of eligible patients for outpatient management is higher when using hospital checklists: 44% and 51% with Davies and Hestia criteria respectively.

The PEITHO study[184] randomized normotensive PE patients at "intermediate-high" risk (with RVD and myocardial injury) to receive Tenecteplase (fibrinolytics) or placebo. Death or hemodynamic decompensation occurred in 13/506 patients (2.6%) in the tenecteplase group as compared with 28/499 (5.6%) in the placebo group. Fibrinolytic therapy did not prevent in-hospital death and increased the risk of major haemorrhage and stroke. Models are less specific for predicting poor outcome in normotensive high-risk patients and there might be benefit from combining prognostic variables for better selection of patients, in particular those at risk of death from PE, as long as patients who are likely to respond to therapy are identified.

Finally, risk stratification was found to be frequently performed in patients admitted with acute PE and found to be stable during a 5-year period[163]. Its use was associated with assignment to higher levels of care and more intense treatment, but did not improve the outcome [163].

DISCUSSION

Summary of main results

This systematic review identified 26 prognostic models in acute PE and 11 other types of models that were not originally specific to PE or exclusively used for its prognosis.

Of the 26 models specific to PE, three (2008 ESC, 2014 ESC and Shock index) were assessed in validation studies with one of them assessed in an impact study[184] without having been assessed in a derivation study, and thirteen[90 92 93 124 128 130 136 144 170 172-174 181] underwent only the derivation process. Ten other models[94 95 102 119 121 131 157 167 171 185] were validated or updated, four[94 119 167 171] of which were assessed in impact studies.

The 11 other types of models were only validated (without derivation) and two of them (Davies and Hestia) were assessed in impact studies[109 180 189].

The event rates in the populations studies is high: around 6% to 7% for in-hospital or 30-day all-cause death, or in-hospital "Death and Adverse outcome". Subgroup analysis did not help to find any difference in prevalence between subgroups but interpretation is made difficult because of high statistical heterogeneity and the small number of studies.

PESI and sPESI are the most widely validated and updated models. PESI has also been assessed in an impact study that compared outpatient to inpatient treatment for low-risk PE patients. However, the authors of the relevant Cochrane review[191] rated this study as "very low quality of

evidence" and it has many limitations related to the small number of events and the small smple size. As expected, the event rates for different outcomes and time-points increase along the risk scale in the PESI model and this may help select patients at lower and higher risks. The attempt to simplify PESI is attractive. sPESI has been assessed in more validation studies than PESI and has shown lower event rates in patients at low-risk regardless of some issues related to heterogeneity and publication bias that are encountered for both the original and the simplified PESI versions. However, the proportion of patients in this risk category is lower for sPESI than for PESI and, unlike PESI, no impact study was found for sPESI. Agreement between the simplified PESI and the original PESI is fair[152]. PESI and sPESI are both included in the risk stratification of PE patients in the 2014 ESC guidelines[3].

Different models/ strategies for identifying low-risk PE seem highly competitive with the PESI and sPESI models. Favourable results are obtained with Davies[109] and Hestia[88 175 180 188] hospital checklists for treating low-risk PE patients as outpatients. Both checklists help clinicians to assess the need for hospital admission. A lower to similar event rate in the low-risk category[175 188] and likely a higher proportion of patients at low-risk[175] are obtained with Hestia than with sPESI. Hestia has been assessed in impact studies[88 180] but the same comments as for PESI apply to Hestia regarding the quality of evidence from these studies. Large validation and impact studies that compare hospital checklists with prognostic models like sPESI are needed to assess patient selection and safety for out-of-hospital management according to each strategy. I did not find any study that assessed adequately clinical intuition or compared it to a prognostic model or strategy. In a retrospective study[82], nearly two thirds of patients presenting to the emergency department with low-risk PESI were potentially eligible for outpatient therapy because of relative contraindications to outpatient management. These contraindications are associated with an increased frequency of adverse events at 30 days and not at 5 days.

Other prognostic models have shown improvement in identifying low-risk and high-risk groups either on their own (algorithm for the low-risk - Shock index, 2008 ESC high, PREP-Clin III, PESI≥IV , PESI V, eStiMaTe high, FAST 3, Bova stage III, TELOS for the high-risk), or by the addition of one or more clinical, biological and imaging-based markers of RVD and myocardial injury to the existing models or by incorporating these markers into new models (NT-proBNP and hs-cTn for the low-risk - SBP, BNP, cTN, H-FABP, venous US and imaging-based RVD for the high-risk). For the identification of low-risk PE, it does not seem worth using them instead of PESI models because of lack of validation and impact studies of these models and inconsistency in findings (see direct comparison in Chapter 5). Applying the ESC guidelines to identifying intermediate-high-risk PE in normotensive patients[184] who may benefit from thrombolytic therapy does not help to prevent early death from PE. In comparison of original and updated models with the ESC model, it is difficult to determine which is preferable for identifying the high-risk category although the new and updated models provide evidence of higher accuracy (better positive predictive value). Large validation and impact studies are needed to assess these new and updated models before their use in clinical practice.

Summary of models' characteristics, performances and utility are displayed in table 4.7

Table 4.7: Summary of the characteristics and the performances of most relevant models.

Model	Derivation studies	External validation studies (N)	Updating studies (N)	Impact studies (N)	Proportion of patients at low-risk (%)	Event rate within low-risk group (%)	Event rate within high-risk group (%)	Utility from impact study results	Ease of use - generalisability
Algorithm	Yes	2	0	0	22 - 24	1.1 – 1.6	7.9 – 11.6	NA	N of variables not memorable
Bova (risk scale)	Yes	2	1	0	84 - 96	3.8 – 4.4	5.4 – 8.1	NA	**Yes**
Davies	Yes	0	0	1	44	0	NA	**Yes** (but small sample size)	Checklist
2008-ESC (risk scale)	No	4	0	1	28.2 – 61.7	2.3 – 4.3	6.8 - 12.7	No (adequate sample size)	**Yes**
2014-ESC (risk scale)	No	2	0	0	30.4 – 83.8	0.4 – 4.2	6.8 – 7.4	NA	**Yes** (2008-ESC + PESI/ sPESI)
eStiMaTe (risk scale)	Yes	1	0	0	30.7 - 95.2	0.7 - 5	8.6 – 23.5	NA	**Yes** (sPESI + other markers)
FAST	Yes	1	0	0	71.6	1.5	22.1	NA	No (HFABP not available)
GPS (risk scale)	Yes	2	1	1	79.7	6.1	17.1	No (very small sample size)	No (Venous US generally not available)
Hestia	No	1	2	1	38.6 – 55.4	0.3 – 1.2	6.2 – 19.9	**Yes** (but small sample size)	Checklist

PESI (risk scale)	Yes	10	Many	1	41.2	2.2	10.8	**Yes** (but small sample size)	No (N of variables and weights)
sPESI	Yes	14	Many	1 (without cancer item)	34.9	1.3	9.1	No (very small sample size)	**Yes**
PREP - clinical variables (risk scale)	Yes	1	1	0	62.7 - 92.8	1.9 - 5.4	17.7 – 43.2	NA	**Yes**
Shock Index	No	2	0	0	80.3	10.7	24.1	NA	**Yes**
RIETE	Yes	0	0	0	24.4	0.6	4.6	NA	No (N of variables and weights)
TELOS	Yes	1	0	0	94.3	2.5	15.8	NA	**Yes**
Spanish	Yes	1	0	1	47.8 - 62	2.7 - 4.2	11.4 - 18	No (high event rate)	No (weights)

N is number of external validation, updating or impact studies assessing a model for a specific outcome and time point, mostly 30-day all-cause death. Results corresponding to models with a risk scale are reported for the lowest and the highest cut-offs.

Overall completeness and applicability of evidence

This systematic review reports findings for several outcomes and timepoints. Analyses were not only restricted to 30-day all-cause mortality, although this was the most common in publications. They included assessment of outcomes occurring earlier at the initial phase ("in-hospital" outcomes i.e. outcomes within the first 5 to 14 days depending on publications), and later at 3 months. Although outcome at the initial phase is now what is required, it seems important to consider later events too, at least to 1 month[82 125]. Indeed, initial management may have a later impact on 30-day and even 3-month outcomes, as has been shown in various old studies according to Hull et al[192-196] and Brandjes et al[197], and even in a more recent one[197]. Failure to achieve an adequate anticoagulant effect early in the course of treatment can lead to later recurrences[197], and early and adequate anticoagulation is associated with reduced in-hospital and 30-day mortality[197]. In randomized non-inferiority trials, VTE events seem to occur in similar time periods with DOACs and conventional therapy (LMWH + Warfarin) and mostly within the first month (Chapter 2 provides results from systematic reviews on DOACs).

I also considered outcomes other than all-cause mortality in this systematic review, such as PE-related death, adverse outcome (death, clinical deterioration or haemodynamic collapse), VTE, major bleeding and their combinations, whether in "both stable and unstable" or in "stable" PE patient risk groups. Clinical deterioration, not a rare condition[125], is usually not assessed when a patient is treated out-of-the-hospital, but this might happen to a patient while in the hospital or at home. They may be rescued in the hospital but may be not at home. Given the impact of clinical deterioration on other outcomes such as death, and unscheduled rehospitalisation or visit, it seems worthwhile assessing these events rather than clinical deterioration directly if the aim would be to compare two groups in a randomized trial. PE-related death is dependent on both the risk of death from PE and from other causes (cancer, etc …), and, consequently, risk of dying from PE is overestimated when the mortality rate from other causes is high. Therefore, special

statistical analyses need be used to estimate the (cumulative) incidence of PE-related death in the presence of competing risk of death from other causes. PE-related death should be assessed adequately using predefined criteria (Chapter 3) but it is particularly difficult to relate death to PE when death occurs at home.

The systematic review considered mostly event rates in the low-risk group. But, as a comprehensive and evidence-based approach, I also considered event rates in the whole population and in the high-risk, although the results in the high-risk groups provide less evidence than for the low-risk groups. A difference in outcome may be due to a difference in risk profile, or to a difference in type of treatment and type of management. For a same risk profile and a same type of treatment, the difference may be related to only the type of management. In agreement with the review of Vinson et al[198], careful selection is needed for low-risk patients with acute PE who will be managed as outpatients. Of note, broad implementation of management strategies is controversial and varies by country and across different organisations of patient care and patient pathways. Furthermore, future decisions about management might be modified by the simplification of anticoagulant treatment thanks to the availability of (new) direct oral anticoagulants.

Most of the models assessed in my review are effective and provide a low event-rate in low-risk groups, and appear reproducible and robust. However, using a model for identifying patients at low risk may not be worthwhile if the aim is to make a choice to send patients home; because the patients might still have an unacceptablly high risk of a serious adverse outcome or might need hospitalization for other medical or for social reasons. It is important to define the incidence limit for a specific outcome, which should be clinically relevant and if models go beyond this they should not be viewed as of high performance. This limit remains an arbitrary choice and it is difficult to set a formal threshold that would be used for all patients. Although a threshold may apply in general, it may need to be adjusted on the basis of the patient's or physician's attitudes

to risk (e.g. risk averse, risk neutral, risk prone), conditions for out-of-hospital management, and any other medical, psychological or social problems of the patient. Patient's preference and quality of life issues, a higher baseline (population) risk level and the potential impact of the intervention on the outcome may also influence physician's decision to send the patient home. For instance, a cancer patient might prefer to be treated at home rather than in the hospital despite a higher risk of event rate (because of the poor prognosis related to the cancer). It is also important to determine how the most relevant and well-performing models (like sPESI) could be used in clinical practice to identify patient suitable for home management in comparison to judgements based on clinical intuition, and I return to this topic later in this thesis.

Differences in predictive performance of the models may be due to differences in prognostic criteria and thresholds for risk groups regardless of study design, development phase, population, outcome and time-point. In two model construction studies[94 95] using the same cohort and the same outcome, a change in criteria and threshold changed risk group proportions and event rates within these risk groups. Shifting the cut-off to reduce the incidence of events in the low-risk group led to a smaller proportion of patients in the low-risk group: selecting lower risk PE patients makes the model more effective but less efficient. This also applies to the high-risk patient groups: the greater the proportion of patients classified as high-risk, the lower the incidence of outcomes in this group and vice versa. Adding biomarker data may help to identify higher or lower risk patients, but my review shows that findings on the additive value of biomarkers are inconsistent across studies. This may be due to the higher predictive performance of some models, heterogeneity in the populations arising from study design[91 97 145] or a higher sensitivity of some biomarkers[133].

I separated checklists from prognostic models because of differences related to the clinical question, the criteria and the outcome/ timepoint used for their assessment. *The clinical question* is about whether the patient needs be managed in the hospital or not and about how good

checklists are at selecting patients for hospital admission or outpatient management. This is different to prognostic models, where the question is about the risk for an individual patient (drawn from studies) to have a poor outcome and the ability of the models to predict that risk and influence management. *The criteria* to be used are different. Prognostic models may use demographic criteria, comorbidities, clinical findings, and additional markers of right ventricular dysfunction; while checklists use some medical criteria that are not included in prognostic models as well as social criteria. These criteria are related to factors such as VTE and bleeding risks, the need for hospitalisation and the presence of medical or social contra-indications to outpatient management. They are close to those used by clinician's intuition but do not include all the variables that are evaluated by clinical judgment. *The outcomes and time-points* assessed are different. The question for prognostic models is about predicting an adverse outcome, such as death or PE complications, which might be assessed as all-cause mortality (and PE complications) at optimal time-points of 1 and 3 months. Because haemodynamic deterioration is hardly directly measurable if the patient is at home, and because a differential assessment may result when comparing patients at home and patients in the hospital, the consequences (death, unscheduled hospitalisations/ visits) need be measured. When the question to be answered with a checklist is whether to send a patient home or not, the outcome will be a composite of death, recurrence and major bleeding, unscheduled hospitalisation/ visit with the same comments for haemodynamic deterioration as above. The most relevant time-point for assessment will be 5 days or 10 ± 2 days (median [interquartile range] for the duration of hospitalisation 8 [5–12]) [82 125 199]. Therefore, for comparing prognostic models and checklists, both 5-day and 30-day time-points need be assessed. [82 125]

Quality of the evidence

My review used a comprehensive search strategy, assessed the quality of the included studies to allow a focus on those of good quality, and used statistical techniques to analyze their results and

combine and compare the findings. However, the included studies contain methodological flaws in the design, conduct and reporting. Many are retrospective or use prospectively collected data for diagnosis purposes, and one of the most common limitations is the lack of reporting of the case-ascertainment strategy used in the study. These problems might lead to selection bias that could affect the event rates and influence the variables included in the final model. The time of inception of the cohorts (ie whether it was at diagnosis or on admission) was ill-defined and patient selection may have been different across studies. Other common methodological issues are the lack of a justification for the sample size, the absence of a full definition of prognostic variables and the lack of standardisation of treatments which might have been dictated by the prognostic variables that were assessed (and, therefore, may have affected the likelihood of certain outcomes), the lack of blinded assessment of the outcomes (to the prognostic variables), and possible problems with data analysis related to the statistical methods for missing data.

Potential biases in the review process

I believe there are no biases in the searches within the search period or in decisions on study eligibility. Although I used a highly sensitive search to minimise the influence of reporting biases related to duplicate and cumulative full publication, time-lag, language, location, and reference list citation[17], it is not possible to know how a study's findings might influence decisions to publish it; unlike the circumstance of randomised trials where positive results for new treatments are more likely to lead to full publication. To assess publication bias for proportion and event rates, I tested for funnel plot asymmetry but the presence of funnel plot asymmetry should not be automativelly interpreted as publication bias[200] since heterogeneity and consequently patient and study characteristics may be associated with study size as well as effect size.

I used the Freeman-Tukey double arcsine transformation for the meta-analyses. This is recommended when the number of observations is small or the observed proportion is near the margins. By using the Freeman-Tukey double arcsine transformation, all the studies are retained,

with admissible confidence intervals for each individual study as well as for the pooled proportion[20].

Data extraction was performed by two reviewers. The second reviewer was not blinded to the data extracted. To ensure quality, data were rechecked by the first reviewer. Study quality was assessed using a domain approach[17] rather than a numeric scale. The domain approach, as recommended by Cochrane, is more transparent to the reader, showing how each study performed in each aspect of conduct. As shown by Juni & al[19], "the use of summary scores to identify trials of high quality is problematic and relevant methodological aspects should be assessed individually and their influence on effect sizes explored".

The analyses were done for distinct models, outomes/time-points, with subgroup and sensitivity analyses to deal with heterogeneity. I used multiple statistical techniques, which could introduce bias in the selection of results to present but no discrepancies were found across the results and all analyses are available. I used absolute risk rather than relative risk because this is more appropriate for estimating the risks for individual patients.

Comparison with other reviews

This study was not limited to clinical prediction rules and to my knowledge and that of the others who worked on it, it is the first broad systematic review and meta-analysis of prognostic models in acute PE patients. There are two published systematic reviews on clinical prediction rules[201 202] and a meta-analysis of PESI models[203], but, as discussed below, my systematic review has important differences to all of these, expands their scope considerably and provides more comprehensive and up-to-date data (table 8).

The key strengths of my review are the well-defined selection criteria, broad search strategy, and presentation of results of all available predictive models with full details on study characteristics, population and prognostic information and study quality. Quantitative analyses are provided to

answer each aspect of model development in accordance with the recommendations of recently published guidelines for prognostic model research[204], for different outcomes and time-points in "both stable and unstable" as well as in "stable" PE, and at various cut-offs, with the aim of improving management of acute PE patients who are either at low-risk or at high-risk. For the analysis of performance, I provide not only a summary estimate of sensitivity and specificity but also a summary estimate of event rates ("absolute risk"[204]) within risk groups that is more meaningful for clinicians and seems more appropriate for the study of prognosis.

Table 4.8: Comparison of my review with other systematic reviews and meta-analyses of clinical prediction rules.

Author, year	**Squizatto et al, 2012**[201]	**Zhou et al, 2012**[203]	**Kohn et al, 2015**[202]	**This study**[205]
Study design	Systematic review and meta-analysis	Meta-analysis	Systematic review and meta-analysis	Systematic review and meta-analysis
Years of search	Untill August 2011	Up to June 2012	January 2000 to March 2014	Inception to July 2014 (updated August 2016)
Databases for search	MEDLINE, Embase	MEDLINE, Embase	MEDLINE, Embase	MEDLINE, Embase, The Cochrane Library
Language included	No langauge restriction	English	English	No langauge restriction
Number of studies in review	33	21	40	99
Type of studies included	Derivation, Validation	Validation (external)	Derivation, Validation	Derivation, Validation, Update and Impact
Number of models in review	9	2	11	26 (+ 11 other types of models*)
Type of models included	Clinical prediction rules	PESI and sPESI	Clinical prediction rules	All prognostic models
Quality appraisal method used	3-point score for cohort studies	Newcastle–Ottawa Scale	QUADAS2 (diagnostic tool) Domain approach	Prognostic criteria Domain approach
Analysis of stable PE patients separately	No	No	No	Yes
Outcome	All-cause mortality, Adverse outcomes	All-cause mortality, PE-related mortality, Adverse outcomes	All-cause mortality	All-cause mortality, PE-related mortality, Adverse outcomes, VTE, Major bleeding
Analysis of different outcomes separately	Yes	Yes	Not applicable	Yes
Time-point	14-day, 30-day, 3-month	Not reported	In-hospital, 7-day, 30-day, 3-month	In-hospital/ 7-day, 30-day, 3-month
Analysis of different time-points separately	No	No	No	Yes
Risk groups	Low-risk group	Low-risk group versus High-risk group	Low-risk group	Low-risk group and High-risk group
Number of cut-offs accounted for	Single cut-off	Single cut-off	Single cut-off	All available cut-offs (analysis along the risk scale)

Summary estimate in meta-analysis	Event rate in patients at low-risk for all models combined	Prognostic accuracy**, Odds ratio	Prognostic accuracy**	Prognostic accuracy**, Proportion of patients in each risk group, Event rates within each risk group (Absolute risk), Population event rate
Overall summary estimate from combined derivation and validation studies	Yes	No	Yes	Yes
Summary estimate from external validation studies	No	Yes	No	Yes
Analysis of update studies	No	No	No	Yes
Analysis of impact studies	No	No	No	Yes
Conclusion of the review	"Prognostic CPRs efficiently identify PE patients at a low risk of mortality".	"PESI has discriminative power to predict the short-term death and adverse outcome events in patients with acute pulmonary embolism, the PESI and the sPESI have similar accuracy"	"Numerous clinical prediction rules for prognosticating early mortality in patients with aPE are available, but not all demonstrate the high sensitivity needed to reassure clinicians"	"We provide evidence-based information about the validity and utility of the existing prognostic models in acute PE that may be helpful for identifying patients at low-risk. Novel models seem attractive for the high-risk normotensive PE but need to be externally validated then be assessed in impact studies".

* 11 other types of models include 9 models which variables are originally not specific to PE or to its prognosis and 2 Hospital criteria checklists, ** Prognostic accuracy (summary sensitivity, summary specificity and summary Receiver Operating Characteristic).

CONCLUSIONS

The extensive systematic review reported in this chapter provides useful information on the prediction ability and the utility of existing prognostic models in acute PE that might help clinicians and researchers to identify patients at low-risk of events who would be suitable for early discharge or outpatient management and those at high-risk who may need closer monitoring or more aggressive therapy. It shows the potential for improving the selection of lower risk and higher risk groups in normotensive PE patients with novel and updated models that integrate biomarkers (cTn, BNP, NT-proBNP, H-FABP, lactates), computed tomography or transthoracic echocardiography right ventricular dysfunction, and ultrasound-detected DVT, into existing models or with other clinical variables (systolic blood pressure, heart rate). These findings provide a good basis for planning future research in validation and impact studies.

The following chapters build on this with the objectives:

- To assess whether it is worth using competing models/ strategies and updated models as compared to the original and the simplified PESI models for identifying patients at low-risk. This is investigated with a decision-analytic approach with sensitivity analysis in direct comparison studies in Chapter 5.

- To explore how physicians assess prognosis and manage acute PE patients, and how they rely on prognostic strategies and clinical intuition in Chapter 6.

- To explain the extreme variability of event rates in population (prevalence) and in risk groups, including the variation in patient selection in studies to date, which is evaluated in Chapter 7.

- To present the protocol for a future study that would assess the value of additional information that may be provided by clinician's intuition combined to sPESI, with sPESI in Chapter 8.

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Chapter 5 - Net Benefit of Prognostic Models in Acute Pulmonary Embolism in Direct Comparison Studies

INTRODUCTION

My systematic review of prognostic models in acute PE in the previous chapter showed the scarcity of model impact studies, which has led to a reliance on external validation or updating studies for assessing the benefits of these models to patient management. PESI and sPESI were found to be the most validated models, and the collected evidence showed their high predictive performance. However, conventional performance measures used in the systematic review may suffer from limitations related to the following: 1/ study results may come from indirect comparisons of individual studies or from meta-analyses; which are likely to be less reliable than those from direct comparison between models that share the same cohort and assesses the same outcome and time-point, 2/ differences between models in the observed outcome (event rate in risk groups, sensitivity or specificity) may be too small to help when choosing one model, 3/ methods of assessment that account for only sensitivity or only specificity, or alternatively for only negative predictive value or only positive predictive value, and ignore the counterpart of these paired measures do not account for both harm and benefit, and 4/ performance measures that assign a similar weight for true positive (TP) and false positive (FP) results do not account for the relative cost of misclassification and their clinical consequences, because it sets the harm from false positive results as equal to the harm from false negative results which is not the case in clinical practice and provides inadequate information for decision making. Models need to be compared using a decision-analytic approach based on weighted comparison measures[1 2] in relation to risk threshold[3 4] such as the net benefit (NB), and direct comparison studies. NB allows classification of FP values in terms of TPs (Chapter 3) and direct comparison is possible through

head-to-head paired-data comparisons of a competing model with a reference model (such as PESI or sPESI) or other models, or comparisons of an updated model with its baseline version.

Therefore, the further analysis of my systematic review presented in this chapter expresses the consequences of using prediction models as NB in terms of identifying low-risk categories for serious outcomes in acute PE. This will inform choices between models because those providing the higher NB best identify low-risk PE patients for whom early discharge and out-of-hospital management are likely to be safe.

METHODS

Data

Bibliographic search, data collection and data analysis: The methods I used to search, extract and analyze data and assess quality are reported in Chapter 4. To compare models' predictive performance, data analysis in this chapter focus on results from studies that used direct comparison.

Study selection

Models and study design: I included data from individual studies that shared the same cohort of patients in the analysis. These data were extracted from validation or updating studies, and from derivation and internal validation studies when compared with data from external validation or updating studies. Model impact studies were not included as their outcomes have direct clinical implication, and their populations are different from those in validation studies because patients would have been selected because they belonged to a risk group and according to variables not strictly related to a model, such as the eligibility criteria for the clinical trial. Prospective and retrospective studies were included and defined according to the analysis performed, not simply

the study design. For example, studies that were initially designed for a prospective evaluation of a type of model but used later to assess another model were considered as retrospective for this second model (post-hoc analysis).

Population/patients/settings: Patients included in studies had an acute PE whether stable or unstable. Studies that provided separate results on stable PE patients (defined by a systolic blood pressure $\geq$ 90 mmHG) contribute more than 95% of PE patients and address the selection of patients for home treatment or for hospitalization or other types of management according to their risk profile. Unstable PE (as defined in Chapter 2) was not included separately because this life-threatening condition needs to be treated in the hospital.

Outcomes and time-points: The same outcomes and time-points were assessed for a specific comparison. The most relevant were in-hospital and 30-day all-cause death, and in-hospital and 30-day PE-related death. When these outcomes were not available, composites outcomes were used that incorporate all-cause death and adverse outcomes, or PE-related death and adverse outcomes, and composites that include VTE events but not bleeding. Later outcome time-points (such as 3-month all-cause death or 3-month PE-related death) were not used in the analysis. These are less clinically relevant because of the long period between when the clinical decision is usually made (on admission or during the patient's stay in hospital) and the event; and no survival data (time-to-event) were available from individual studies.

Study classification: To enable paired-data comparisons between competing models or between updated and baseline models, studies were selected when a head-to-head comparison between models was available. The following were considered as clinically relevant and sound methodology criteria: models assessed in external validation or updating study, with prospective design and analysis, separate data available on stable normotensive PE patients and reporting of in-hospital or 30-day outcomes.

***Defining model cut-offs and risk-groups*:** A model's cut-off between high-risk group(s) and lower risk group(s) is indicated by its corresponding high-risk group(s) and this holds for all models in the text and tables that follow. For the ESC models, when both "Unstable and Stable PE" are assessed, the cut-off "High Intermediate High" means that both High and Intermediate-High classes are included in the higher risk group, and the cut-off "High Intermediate" means that the High, Intermediate-High and the Intermediate-Low classes are included in the higher risk group. When "stable only" PE is assessed, the cut-offs are denoted as "Intermediate High" (intermediate Low and Low classes included in the lower risk group), or "Intermediate" (both Intermediate-High and Intermediate-Low included in the higher risk group). The eStiMaTe model (PROTECT study) is a multimarker combination that includes s-PESI, *BNP, cTnI and US-DVT*. For the low-risk group, both s-PESI and BNP are negative, for the Intermediate-risk group either s-PESI or BNP is positive, and for the high-risk group all markers (s-PESI, cTnI, BNP and US-DVT) are positive.

Analysis

Types of comparison: I performed a between-model comparison for models that shared the same cohort (paired-data analysis). This concerned the comparison of two or more original prognostic models (PESI, s-PESI, GPS, PREP, eStiMaTe, Prognostic Algorithm…) whether they were assessed within the same article or in different articles (because, in some cases, two models were applied to the same cohort of patients but the results for each model were published in separate articles). This concerned also the comparison of updated models with original models for the assessment of the incremental values of markers added to prognostic models, such as markers of RVD (BNP, NT-proBNP, TTE-RVD, CT-RVD) or myocardial injury (troponin, h-FABP), markers of haemodynamic concern (Lactate), markers of coagulation (D-dimer), and markers of thrombosis (ultrasonography-detected DVT). Results are separated for comparisons of competing models and updating of models. As PESI and sPESI are the most validated models (Chapter 4) and are

recommended by the 2014 ESC guidelines[5], I used them as the reference models for comparison with competing and updated models.

Measure of performance: Because they express clinical utility, decision-analytic measures were used to assess performance and were preferred to the other measures[6-8] based on classification only (sensitivity and specificity), discrimination between risk groups (area under the receiver operating characteristics curve AUC with the concordance C-statistic, and the differences in AUC between two models), reclassification (net reclassification improvement NRI)[9-13] and other methods. Net benefit (NB) as a simple and commonly used decision-analytic measure was selected ahead of other utility measures such as "Weighted Comparison Index"[14 15] , difference in Net Benefit (ΔNB)[1 16], difference in Relative Utility (ΔRU)[17 18] and difference in Event Free Life Year (EFLY)[19 20]. NB incorporates and weighs the clinical consequences (outcomes) of FP against TP results for a model (and vice versa) and accounts for harm/benefit ratio[1] directly related to decision threshold[3 4].

$$\boldsymbol{NB} = \left[TP - \left(\frac{p_T}{1 - p_T}\right) * FP\right] * \left[\frac{1}{N}\right]$$

where N is the total sample size, T the decision threshold (risk threshold), pT the treatment threshold probability, and weight the odds of [threshold probability][3 4], a decision trade depending on how expert clinicians valued FP against TP that corresponds to the weight of FP relative to TP, or cost (FP/TP).

$$\boldsymbol{Weight} = \frac{Harm}{Benefit} = \frac{p_T}{1 - p_T}$$

In other terms, NB translates FP in TP terms (or vice versa) according to threshold probability for a specific population event rate.

The unit of NB is true positives[**2**]. A NB of 0.090 means that the model is equivalent to a strategy that led to hospital admission for 90 patients per 1000 at risk with all of them being positive for

the outcome events during the follow-up time period. The strategy with the highest net benefit at a particular threshold probability has the highest clinical value[2].

Sensitivity analysis: As threshold probability is subjective, my sensitivity analyses provide values for NB along a range of acceptable threshold probabilities for identifying patients at low-risk for a model (without changing event rate). This method is more common when analysing baseline original patient data, with different types of performance measures[14 21] and to display NB against thresholds values in "Decision Curve Analysis"[1], or to display Relative Utility against risk threshold in "Relative Utility Curve" analysis[17 18]. As sensitivity and specificity change with threshold probability (and with population event rate i.e. the prevalence)[22 23], varying the threshold probability was done carefully within a limited and narrow range of values to keep them closer to the original values of the study.

Threshold values were defined for only one treatment choice: early discharge versus in-hospital management for patients considered at low-risk by a model. Values were varied with increments of 0.5% from 0.5 to 4% (harm-to-benefit ratio from [0.005/ (1-0.005)] to [0.04/ (1-0.04)], that is from 0.005 to 0.0417). Threshold values were obtained through my survey among emergency and expert physicians reported in Chapter 6 (Survey question 21) and among 10 physicians from the departments of Cardiology and Vascular Medicine in my workplace (Toulon hospital)[12] and according to the definition of low-risk patient groups in the ESC guidelines[5 24]. Sensitivity analysis was not performed for identifying "high-risk" and "very-high-risk" groups because of the uncertainty around the acceptable threshold probability values for intensive monitoring or for administering thrombolytic therapy or other more "aggressive therapy" (Chapter 6 – Survey question 22).

The assumptions were that TP and FP results remain rather constant for small variations of threshold values when comparing two models. For out-of-hospital management or early

[12] The median risk threshold obtained was 1 - 2% (3 - 4% with implemented health care system), and the range of variation was from 0.5 to 4%.

discharge, decision was based on the assumptions that out-of-hospital and in-hospital quality of care are not different (with an implemented healthcare system), and that there are no comorbidities or other conditions that require the patient to be managed in hospital.

RESULTS

Results are displayed by the type of comparison performed: between competing models versus reference models or other models (Table 5.1), or between updated models versus baseline models (Table 5.2). The results are separated according to the type of PE prognostic model they were compared to (PESI, s-PESI or other model). Detailed results on study and patient characteristics, prognostic information and study quality are provided previously (Chapter 4).

Two examples show how Net Benefit was calculated (Table 5.3 and Table 5.4)

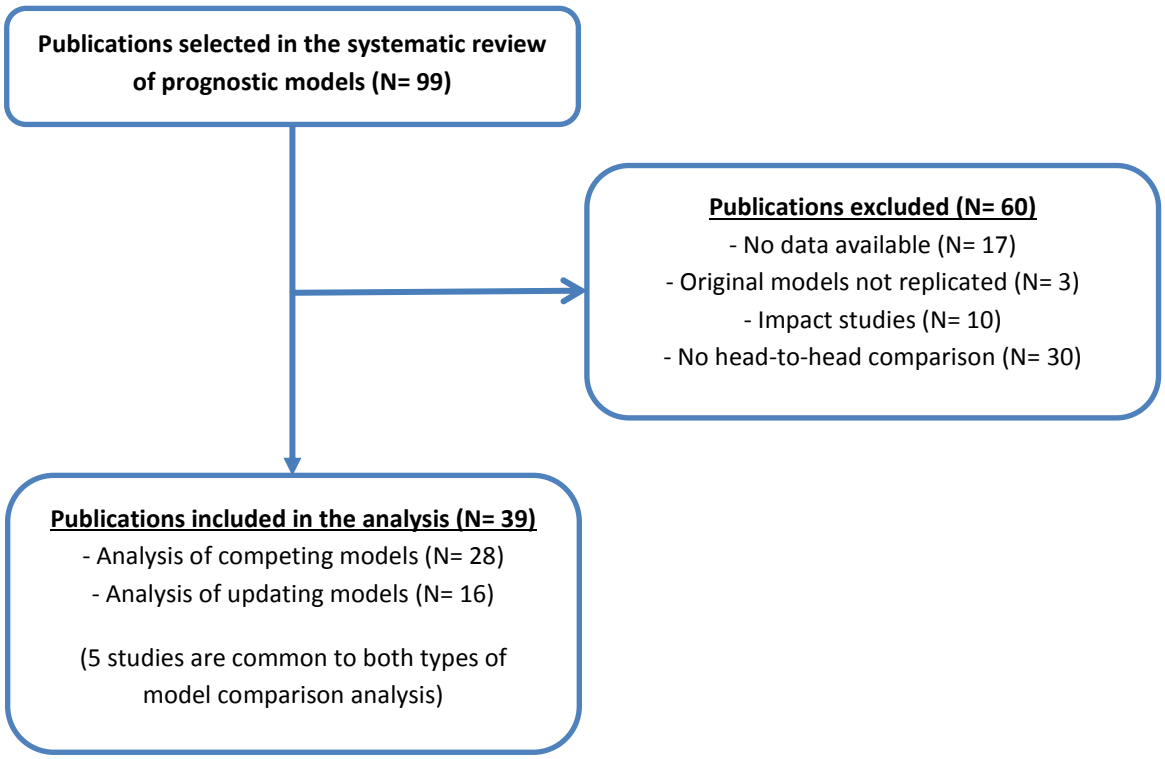
Results of NB are displayed in figures together with the corresponding tables for each comparison in the appendices (A.5.1 to A5.23 for competing models and A5.24 to A5.39 for updated models). Main study characteristics (models, phase of development, type of study, patients, time-point, outcome and sample size), distribution of risk groups and event rates, and overall NRI are also presented in these tables.

Study selection

Among the 99 studies in the systematic review, 17 studies were excluded because data comparison were not completely reported in the original papers and could not be obtained from authors. Eight studies[25-32] were excluded from the competing models analysis and nine studies[33-41] from the model updating analysis. Three other studies[42-44] reported on modified models and were excluded as these models were not any more consistent with the original models they were expected to represent. All other studies that were evaluated in impact studies or did not include a

head-to-head comparison assessment were also excluded (Figure 5.1). This left 39 studies for these analyses: 23 groups of comparisons of competing models and 16 groups of comparisons of updating models (5 studies were common to both types of model comparison analysis).

Figure 5.1: Flow chart for study selection



Competing models

Competing models were assessed against PESI in 4 between-model comparison studies (7 publications). PESI provides a higher NB than 2008 ESC, GPS and PREP ("Facteurs **PR**onostiques de l'**E**mbolie **P**ulmonaire" i.e. "Prognostic factors for pulmonary embolism") models but a lower NB than eStiMaTe and PREP (PREP cohort).

Competing models were assessed against sPESI in 9 between-model comparison studies. This shows a higher NB for sPESI than for 2008 ESC, 2014 ESC, FAST, Hestia, Shock Index, the Spanish model and TELOS, and an equal NB for sPESI and 2008 ESC but a lower NB for sPESI than for GRACE-PE (GRACE-PE cohort).

In seven direct comparison studies between PESI and sPESI, NB was higher for PESI in 3 studies, for sPESI in 3 other studies (one of them in sPESI cohort), and equal for PESI and sPESI in one study (PESI cohort).

Finally, 2014 ESC was superior to Bova, equal to 2008 ESC but inferior to TELOS.

Updated models

All studies updating a model by adding a marker to PESI have a higher NB than PESI alone (4 studies by adding TTE-RVD, CT-RVD, H-FABP or WBC/ SIRS) except when the added marker was cTn (1 study).

NB is higher with sPESI than with the updated model including CT-RVD, BNP or TTE-RVD (4 studies) but lower than the updated model (3 studies), two of which included hs-cTn or NT-proBNP in the model.

Finally, the Hestia and PREP models provide in their proper cohorts a higher NB than the updated model, as opposed to Bova and Shock Index which provide a higher NB with the updated model (Bova-Lactate, Shock Index-TTE-RVD).

Whether in the competing model (A.5.1 to A5.23) or the updating model (A5.24 to A5.39) analyses, contrasting results are found when using overall NRI as opposed to NB (see first example on comparison of competing models "A5.1: PESI - 2008 ESC" in Appendices). NRI (Chapter 3) is a measure that assigns the same weight to TP as to FP findings (it does not account for threshold value) and depends on the choice of risk categories and risk cut-offs. NRI is useful for an overall test evaluation. Discrepancies between NRI and NB may also occur because the number of patients in the cohort where the models are applied is different for each model. For example, in the FAST cohort, the ESC model was not feasible in all patients as shown in example A5.8: sPESI - FAST - ESC (FAST cohort) in the Appendices.

Table 5.1: Competing models

Author	**Competing models**		**Cohort where model applied**	**Higher NB** (range of threshold values)
Vanni, Nazerian et al. 2011[45]	PESI	2008 ESC Intermediate		PESI
Jimenez, Yusen et al. 2007[46]	PESI	GPS		PESI
Sanchez, Trinquart et al. 2010[47-49]	PESI	PREP, eStiMaTe	PREP	eStiMaTe & PREP (> PESI)
Chan CM, Woods C, Shorr AF. 2010[50] and 2012[51]	PESI	PREP		PESI (< 2%)
Lankeit, Gomez et al. 2012[52]	sPESI	2008 ESC		sPESI
Ozsu, Ozlu et a 2014[53]	sPESI	2008 ESC		sPESI = 2008 ESC
Cordeanu, Gartner et al 2016[54]	sPESI	2014 ESC		sPESI (< 4%)
Dellas, Tschepe et al 2014[55]	sPESI	FAST, (2008 ESC)	FAST	sPESI (< 3%)
Zondag, den Exter et al 2013[56]	sPESI	Hestia	Hestia	sPESI
Sam, Sanchez et al. 2011[57]	sPESI	Shock Index		sPESI
Ferrer, Morillo et al 2013[58]	sPESI	Spanish		sPESI
Vanni, Jimenez et al 2015[59]	sPESI	TELOS	TELOS	sPESI
Paiva, Providencia et al 2013[60]	sPESI	GPS, ESC, SI		2008 ESC and sPESI
Paiva, Providencia et al 2013[60]	sPESI	GRACE-ACS, GRACE-PE	GRACE-PE	GRACE-PE
Aujesky, Obrosky et al. 2005[61-63]	PESI	sPESI, PE-Algorithm	PESI, PE-Algorithm	PE-Algorithm (PESI = sPESI)
Jimenez, Aujesky et al. 2010[64]	PESI	sPESI	sPESI	sPESI
Erkens, Gandara et al. 2011[65]	PESI	sPESI		PESI
Kabrhel, Okechukwu et al 2014[66]	PESI	sPESI, GPS		PESI
Mizuno, Yamamoto et al 2015[67]	PESI	sPESI		PESI
Maestre, Trujillo-Santos et al 2015[68]	PESI	sPESI, RIETE	RIETE	sPESI, RIETE (< 2.5%)
Rozjabek, Coleman et al 2016[69]	PESI	sPESI		sPESI
Becattini, Agnelli et al 2016[70]	2014 ESC	2008 ESC		2008 ESC = 2014 ESC
Jimenez, Lobo et al 2016[71]	2014 ESC	Bova		2014 ESC
Vanni, Nazerian et al 2016[72]	2014 ESC	Bova, TELOS		TELOS

Table 5.2: Updated models

Author	**Updated model**	**Original model**	**Cohort where model applied**	**Higher NB** (range of threshold values)
Moores, Aujesky et al. 2010[73]	PESI - cTn	PESI		PESI
Sanchez, Trinquart et al 2013[48]	PESI-BNP, PESI-cTn, PESI-TTE-RVD	PESI	PREP	PESI-TTE-RVD (lower NB PESI)
Singanayagam, Chalmers et al 2010[74]	PESI - CT-RVD	PESI		PESI - CT-RVD
Lauque, Maupas-Schwalm et al 2014[75]	PESI - H-FABP	PESI		PESI - H-FABP
Jo, J., Lee M., et al. 2013[76]	PESI-WBC, PESI-SIRS	PESI		PESI-WBC, PESI-SIRS
Spirk, Aujesky et al. 2011[77]	sPESI - cTn	sPESI		sPESI
Lankeit, Jimenez et al 2011[78]	sPESI - hs-cTnT	sPESI		sPESI - hs-cTnT (< 2.5%)
Ozsu, Abul et al 2013[79]	sPESI - hs-cTnT	sPESI		sPESI
Lankeit, Jiménez et al 2014[80]	sPESI - NT-proBNP	sPESI		sPESI - NT-proBNP (< 2.5%)
Vanni, Jimenez et al 2015[59]	sPESI - Lactate	sPESI	TELOS	sPESI (< 2%)
Ozsu, Ozlu et al 2014[53]	sPESI - 2008 ESC	sPESI		sPESI - 2008 ESC
Ostovan, Ghaffari et al 2016[81]	modified-sPESI	sPESI	modified-sPESI	sPESI
Vanni, Nazerian et al 2016[72]	Bova - Lactate	Bova		Bova - Lactate
Zondag, Vingerhoets et al 2013[82]	Hestia - CT-RVD	Hestia	Hestia	Hestia
Sanchez, Trinquart et al. 2010[47]	PREP - BNP - TTE-RVD	PREP	PREP	PREP
Toosi, Merlino et al. 2008[83]	Shock Index - TTE-RVD	Shock Index		Shock Index - TTE-RVD

Table 5.3: Net Benefit of PESI, sPESI and GPS models in the Kabrhel et al study[66] with sensitivity analysis. Study: Prospective - External validation - Patients: Stable PE - Outcome assessed: 30-day all-cause death. Corresponding figure is displayed below.

Risk cut-off	TP	FP	FN	TN	N	Threshold probability	P	NB
PESI ≥ III	12	137	0	142	291	0.005	0.04	0.039
sPESI	12	179	0	100	291	0.005	0.04	0.038
GPS ≥ 3	8	62	4	217	291	0.005	0.04	0.026
PESI ≥ III	12	137	0	142	291	0.01	0.04	0.036
sPESI	12	179	0	100	291	0.01	0.04	0.035
GPS ≥ 3	8	62	4	217	291	0.01	0.04	0.025
PESI ≥ III	12	137	0	142	291	0.015	0.04	0.034
sPESI	12	179	0	100	291	0.015	0.04	0.032
GPS ≥ 3	8	62	4	217	291	0.015	0.04	0.024
PESI ≥ III	12	137	0	142	291	0.02	0.04	0.032
sPESI	12	179	0	100	291	0.02	0.04	0.029
GPS ≥ 3	8	62	4	217	291	0.02	0.04	0.023
PESI ≥ III	12	137	0	142	291	0.025	0.04	0.029
sPESI	12	179	0	100	291	0.025	0.04	0.025

GPS ≥ 3	8	62	4	217	291	0.025	0.04	0.022
PESI ≥ III	12	137	0	142	291	0.03	0.04	0.027
sPESI	12	179	0	100	291	0.03	0.04	0.022
GPS ≥ 3	8	62	4	217	291	0.03	0.04	0.021
PESI ≥ III	12	137	0	142	291	0.035	0.04	0.024
sPESI	12	179	0	100	291	0.035	0.04	0.019
GPS ≥ 3	8	62	4	217	291	0.035	0.04	0.020
PESI ≥ III	12	137	0	142	291	0.04	0.04	0.022
sPESI	12	179	0	100	291	0.04	0.04	0.016
GPS ≥ 3	8	62	4	217	291	0.04	0.04	0.019

TP: true positive, FP: false positive, FN: false negative, TN: true negative, N: number of patients, P: prevalence (population event rate), NB: net benefit

Threshold (%)	PESI	sPESI	GPS
0.5	0.038871	0.038146	0.026421
1	0.036482	0.035024	0.025339
1.5	0.034068	0.03187	0.024247
2	0.031629	0.028684	0.023143
2.5	0.029166	0.025465	0.022028
3	0.026677	0.022213	0.020902
3.5	0.024162	0.018927	0.019764
4	0.021621	0.015607	0.018614

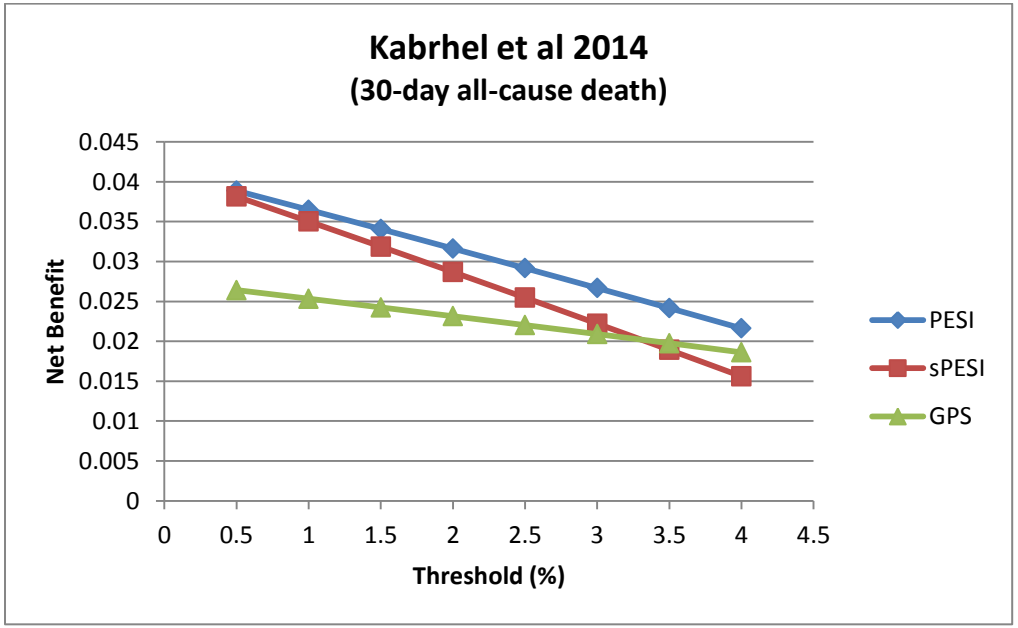


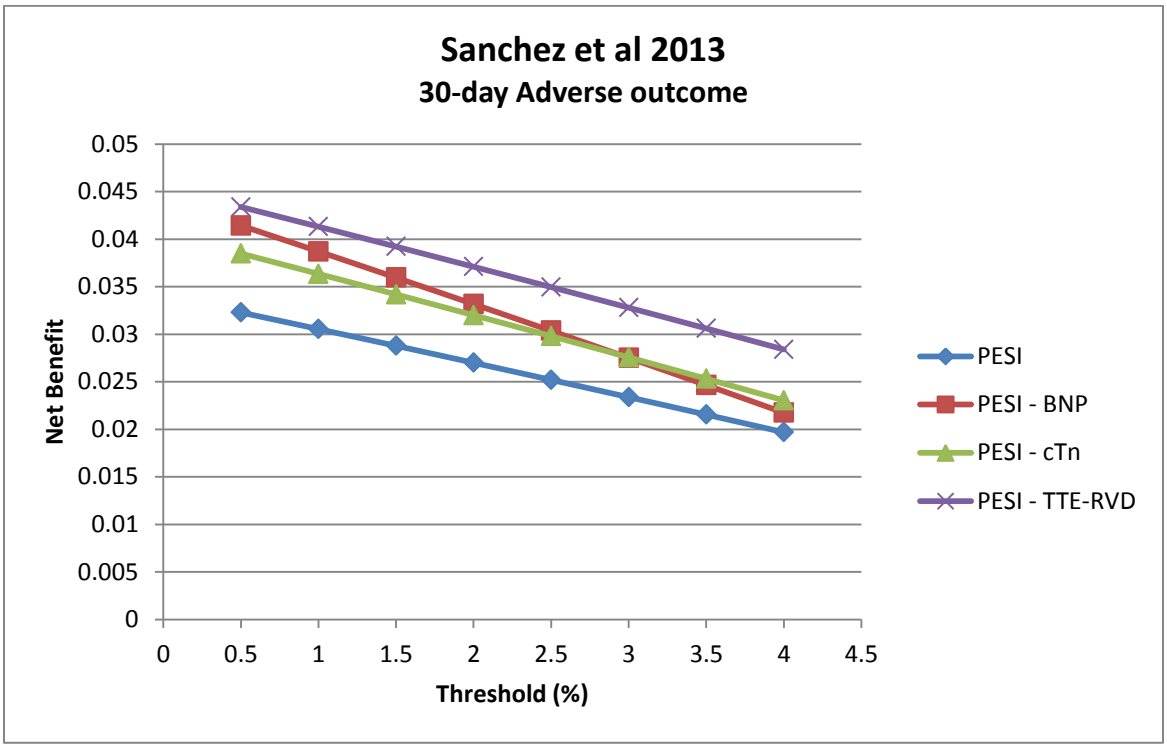
Table 5.4: Net Benefit of PESI and updated PESI models in the Sanchez et al study[48] with sensitivity analysis. Study: Prospective - External validation - Patients: Stable PE - Outcome assessed: 30-day Adverse outcome. Corresponding figure is displayed below.

Risk cut-off	**TP**	**FP**	**FN**	**TN**	**N**	**Threshold probability**	P	**NB**
PESI ≥ III	18	182	7	322	529	0.005	0.05	0.032
PESI ≥ III or BNP pos	23	280	2	216	521	0.005	0.05	0.041
PESI ≥ III or cTnI pos	21	218	3	275	517	0.005	0.05	0.039
PESI ≥ III or TTE-RVD pos	22	198	3	261	484	0.005	0.05	0.043
PESI ≥ III	18	182	7	322	529	0.01	0.05	0.031
PESI ≥ III or BNP pos	23	280	2	216	521	0.01	0.05	0.039
PESI ≥ III or cTnI pos	21	218	3	275	517	0.01	0.05	0.036
PESI ≥ III or TTE-RVD pos	22	198	3	261	484	0.01	0.05	0.041
PESI ≥ III	18	182	7	322	529	0.015	0.05	0.029
PESI ≥ III or BNP pos	23	280	2	216	521	0.015	0.05	0.036
PESI ≥ III or cTnI pos	21	218	3	275	517	0.015	0.05	0.034
PESI ≥ III or TTE-RVD pos	22	198	3	261	484	0.015	0.05	0.039
PESI ≥ III	18	182	7	322	529	0.02	0.05	0.027
PESI ≥ III or BNP pos	23	280	2	216	521	0.02	0.05	0.033
PESI ≥ III or cTnI pos	21	218	3	275	517	0.02	0.05	0.032

PESI ≥ III or TTE-RVD pos	22	198	3	261	484	0.02	0.05	0.037
PESI ≥ III	18	182	7	322	529	0.025	0.05	0.025
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PESI ≥ III or BNP pos	23	280	2	216	521	0.04	0.05	0.022
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PESI ≥ III or TTE-RVD pos	22	198	3	261	484	0.04	0.05	0.028

TP: true positive, FP: false positive, FN: false negative, TN: true negative, N: number of patients, P: prevalence (population event rate), NB: net benefit

Threshold (%)	PESI	PESI - BNP	PESI - cTn	PESI - TTE-RVD
0.5	0.032298	0.041445	0.0385	0.043399
1	0.030551	0.038717	0.03636	0.041322
1.5	0.028787	0.035962	0.034198	0.039225
2	0.027005	0.033178	0.032014	0.037106
2.5	0.025205	0.030366	0.029807	0.034965
3	0.023386	0.027524	0.027578	0.032802
3.5	0.021548	0.024654	0.025325	0.030617
4	0.019691	0.021753	0.02305	0.028409



DISCUSSION

Summary of main results

This is the first study to assess the difference in performance between prognostic models in acute PE using a decision-analytic measure in head-to-head paired data comparison studies. The analysis included 23 groups of comparisons of competing models and 16 groups of comparisons of updating models. I used the NB based on threshold probability values that weighs the clinical consequences of FP against TP results for a model. It sets the limits where it is worth using one model instead of another one given a population event rate.

The included studies mostly compared alternative prognostic models to PESI and s-PESI. NB is higher with PESI than with other competing models in 3 of 5 comparisons, but lower than the updated models in 4 of 5. NB is higher with sPESI than with 7 other competing models, equal to NB for 2 other models, lower than NB for only one model that was evaluated in its proper cohort, and higher for sPESI than the updated models in 4 of 7 studies. When compared to each other in NB, PESI and sPESI present an equal number of studies in which either one is better than the other. For the remaining competing or updated models, there are too few studies to draw firm conclusions.

Whether for the assessment of competing or updating models, the difference in NB between two models may be too small to support the selection of one model rather than the other. However, the research findings I present here help to define the range of assigned threshold values at which one model is shown to be of higher performance and more benefit than the other model; the limit being determined by the cut-off for which two models are equivalent (ΔNB= 0).

To sum-up, at low risk thresholds, reference models PESI and s-PESI perform better than the other competing models, but similarly when compared to each other, in terms of NB. The incremental

value of adding a prognostic marker is higher for PESI than for sPESI, thus suggesting the strength and robustness of sPESI.

Overall completeness and applicability of evidence

Models were compared for their ability to help clinicians to manage low-risk PE patients. No comparison was done for high-risk patients because of the uncertainty about risk cut-offs and the wide variation in acceptable risk for physicians and patients, and the nature of the available data (aggregate results). This would have been better done by using individual patient data analysis.

Competitive models are usually compared against one of the reference models, PESI or s-PESI, which are recommended by the 2014 ESC guidelines[5] for the identification of patients at low-risk. Although PESI has shown an impact on patient management in a randomized trial[84], most comparisons and updating of models are now assessed using the simplified version (s-PESI) as a reference model. sPESI provides a simple, memorable and readily available score, and has shown a high predictive performance in external validation studies at least equivalent to that of PESI (see Chapter 4). Models that are compared to PESI or s-PESI are already selected among the best and are usually highly competitive, which might explain the small difference in NB.

Study results may depend not only on the baseline model and the added predictor performances but also on threshold probability (risk threshold) and the population event rate (prevalence, also called mean risk), the reason why a sensitivity analysis was performed by varying risk threshold at a specific event rate[14]. No variation in event rate was induced on these data because this would change all results due to the large range of values needed for this analysis. Many observations show evidence of higher NB and population event rate simultaneously (Tables and Figures in Appendices).

The analysis shows some inconsistent results across studies that might be explained by the strength of model performance and strength of additive markers, and the differences in study

quality (study design, development set), sample size and precision, and other factors linked to population/ patient selection, type of outcome and time-point. Outcomes and time-points selected for inclusion in comparison studies are clinically relevant but models were rarely compared in prospective and in external validation / updating studies, and in stable only PE. Stable PE data were not reported separately in some studies; hence the need to include results from studies that combined both stable and unstable PE. Access to individual patient data (rather than the raw estimates from aggregate data) might have helped to overcome this but it was not possible to obtain such data. However, it should not change the main results because I only used studies that provided stable PE patient results separately to assess stable PE, and as the proportion of patients with unstable PE is low (< 3-5% of all population sample), the value of NB for the models would have been slightly different but the models' ranking according to NB would have been unchanged (Tables and Figures A5.21 (1) and (2), and A5.37).

Quality of the evidence

NB was chosen because it is a simple and commonly used utility measure and accounts for thresholds and event rates and allows assessing variation in sensitivity analysis. It is known that these results based on decision analytic measures may differ to findings based on other performance measures, as was the case when comparing both overall NRI and NB analyses (Appendices A5). This is inherent to the way each type of performance measure is used and the objective it is intended to achieve (Chapter 3). The additive value of the NB analysis to event rate in a risk group is that it provides a range of threshold values for a specific population event rate for which one model is supposed to be better than another one.

The clinical decision that these findings might impact on is a model-based therapeutic decision on patient management and more precisely on type and intensity of treatment. Only health values outcomes from the physician viewpoint were considered. Quality of life or patient's preference, or the economic or the opportunity costs were not accounted for. The threshold probability at

which a physician decides to provide specific treatment for a patient informs on how he/she weighs harms (false positive results) against benefit (true positive results) and vice versa[1].

Most studies in my analyses were rarely intended for comparison or for updating of models, and I found many methodological flaws (Appendices A5). Not surprisingly, models developed in a derivation set have higher performance power than other models they are compared to within that same set, leading to contradictory results across studies for the comparison between PESI and s-PESI for instance. PESI has a higher performance value when PESI derivation sample is used as a validation set for the other model(s)[61-63] and conversely s-PESI[64] is better when its derivation sample is used. This over-optimism or overfitting leads to an overestimate of the overall prognostic ability of a model (optimism bias) and may apply to comparisons between competing models, or between an adjusted/updated model and an original model. Furthermore, differences may exist between validation/update studies and derivation studies that are not related to the performance of the model but to differences in population/ patients/ settings or to the way the model has been used.

Potential biases in the review process

Although it seems there are no important missing studies in this analysis, one cannot exclude the possibility of publication bias despite the comprehensive search performed.

The analysis of aggregate study data rather than individual patient data did not allow the measuring confidence intervals and a sensitivity analysis with adequate precision. The sensitivity analysis was performed with caution by using consistent threshold values with small variations around the original values of the studies. TP and FP values were kept unchanged. The assumption is that small variations would not have influenced so much sensitivity and specificity (examples in Table 5.3 and Table 5.4). As diagnostic test accuracy may change with event rate[22 23], no sensitivity analysis was performed using this variable.

Finally, my results may have been affected by population event rate, because a low population event rate may result in a low event rate in risk groups. Variation of proportion of patients at specific risk is inversely related to event rates within that specific risk group (Chapter 4)

Agreements and disagreements with other studies or reviews

This analysis is supplementary to the analysis in Chapter 4, by providing between-model comparative results when paired data were available. Despite the extensive searches done for the systematic review, I am not aware of any similar analysis on prognostic models in acute PE using decision-analytic performance measures.

CONCLUSIONS

Implications for practice

In the absence of model assessment in impact studies, we need a model that helps inform clinical decisions and is easy to use in clinical practice. The model should have high predictive performance for identifying low-risk groups based mainly on decision-analytic measures that account for clinical consequence. The analyses in this chapter allow clinicians to select which model to use in comparison to another model for a range of decision threshold probability values, provided that the models were assessed in high quality studies. At low thresholds values, PESI and mostly s-PESI has a higher NB than the other models and this meets the recommendations of the 2014 ESC guidelines. NB seems to increase with the addition of prognostic markers to PESI more often than it does with the addition of prognostic markers to s-PESI.

Implications for research

There is an ongoing need for a well-conducted large prospective external validation multicenter study with head-to-head comparison, using this decision-analytic approach, of the best prognostic models identified through the systematic review. The study should use an inception cohort of stable PE patients and assess short-term outcomes like in-hospital and 30-day death and PE-related death/adverse events. Decision-analytic measures from the patient data could help to assess various threshold treatment probability values and risk stratify patients into three risk groups (low, intermediate, high) for a better clinical decision. The use of a reliable case ascertainment strategy is also needed to overcome selection biases shown by the wide variation of population event rates in studies to date and the research I present in chapter 7 helps identify such a strategy.

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Chapter 6 - Opinion and Practice Survey about the Use of Prognostic Models in Acute Pulmonary Embolism (OPSUM-PE)

INTRODUCTION

Many PE prognostic tools have been suggested for use in clinical practice apart from or in addition to clinical judgment. These are based on individual prognostic factors or indicators, prognostic models or hospital checklists **(Chapter 2 and Chapter 4)**. The implementation of these tools[1-8] seems inconsistent and controversial across countries[9-12] and across organisations[13 14]. This raises the question of whether these tools are clinically useful and, if so, which of them should be used.

In light of this uncertainty about the use of risk prediction for PE patients, I conducted an online survey of opinion and practice among both physicians from emergency departments (ED) and those specifically involved in the management of PE patients. I sought information on the assessment of prognosis when treating patients with acute PE to determine attitudes on the use of prognostic models and barriers to uptake, and to gather expert opinion on prognosis and management of acute PE patients.

OBJECTIVE

To assess and to compare opinion and practices among emergency physicians and expert physicians involved in the diagnosis and management of patients with acute PE.

Knowledge on why one prognostic tool for PE is preferred over another and the barriers to applying prediction rules in clinical practice may be helpful for the development and the implementation of a knowledge translation plan and of strategies to improve the assessment of prognosis in patients with acute PE, including the use of prognostic models (if ever) with the objective of improving patient management and outcome. The information would also contribute to the evidence base for future research into PE prognosis and treatment.

METHODS

Study design

A cross-sectional survey using an e-questionnaire administered online, using SurveyMonkey (https://www.surveymonkey.com/). The survey was available online for approximately nine months from September 2014. This coincided with the release of the 2014 ESC guidelines, which were launched at the ESC congress in August/September 2014 and published in print in November 2014[10].

Population

Physicians who work in emergency rooms and physicians from specialties who are involved in the diagnosis and management of patients with acute PE were invited to participate via emails. The target population was identified and reached through (1) lists of emergency physicians registered as members of the French Society for Emergency Medicine (SFMU or Société Française de Médecine d'Urgence) or as members of the European Society for Emergency Medicine (EuSEM), and (2) a list of expert physicians who were members of the "INvestigation Network On Venous ThromboEmbolism" (INNOVTE), a French research group.

Questionnaire

The questionnaire was designed with information from the systematic review of prognostic models in acute PE. It was written in English and in French. The English version was intended for the EuSEM group and the French version for the SFMU and the INNOVTE groups. The French version included one more question about management in high-risk patients. A draft of the questionnaire was sent to a small number of physicians who work in emergency departments or other medical departments who are familiar with PE and experts in the diagnosis and management of PE for feedback. It was discussed with them individually or in groups, to assess face validity (appropriateness of phrasing and response options), content validity and reliability (between-question consistency). The final questionnaire was then tested before it was used for the full survey.

This self-completion questionnaire (Table A6.1) was a mixture of close-ended (Yes – No questions, and multiple choice questions) and a few open-ended questions. It included physician's personal (Q1-Q5) and centre (workplace: Q6-Q8, PE activity: Q9-Q11) information, their personal assessment of prognosis in patients with acute PE (attitudes: Q12-Q16, reasons for using a model: Q17, barriers to the use of prognostic models: Q18), and their personal management of patients with acute PE in relation to prognosis assessment (opinions/beliefs: Q19 – Q20, management: Q21 – Q22). The questionnaire was centered on the use of prognostic models to find out whether they are used and how often, without or with single prognostic factors, without or with clinical judgment; and whether they are preferred to clinical judgment or hospital checklists. It also gathered physicians' opinions and beliefs about which criteria they considered optimal for a prognostic model to be accepted and about the barriers to its uptake; and on how best to manage PE patients at low-risk and at high-risk.

The administration of the questionnaire was approved by the corresponding scientific societies.

Outcome

My aim was to assess and compare attitudes towards the use of prognostic models and the barriers to their uptake in patients with acute PE, and to identify physicians' preferred methods for assessing prognosis and guiding clinical decisions and their opinions about management according to risk level in patients with acute PE. The primary outcome was the frequency of use of prognostic models (Q14). Secondary outcomes were also assessed: most used prognostic tools (Q12), physician preferences for "Clinical Judgment" (Q19) or for "Hospital Checklist" against "Prognostic Models" (Q20).

Data analysis

Analyses were performed for the sample as a whole and for each affiliation group (EuSEM, SFMU and INNOVTE). Different cut-offs were considered for the primary and secondary outcomes. The respondent characteristics and the response rates were also assessed. The SFMU group responses were compared with those of the EuSEM group to compare findings between French and (mainly) European emergency physicians (same specialty, different countries) and with those of the INNOVTE group of non-emergency PE-expert physicians (different specialties, same country).

Results for categorical variables were provided in frequency and proportion with 95% confidence interval (95% CI), and those for continuous variables in median, interquartile range, mean and standard deviation. A two-sample t-test was used for continuous variables and a chi-squared (chi^2) or Fischer exact test for categorical variables to analyse differences between affiliation groups. When needed (for skewed variables and small numbers), analysis was done on log-transformed data or a two-sample rank-sum Wilcoxon Mann-Whitney U test was used. Results were considered statistically significant at p-value less than 0.05.

Univariate and multivariate analyses were performed for the primary outcome (and also for the secondary outcomes). Variables included in the analysis were affiliation group, age, age groups ($\geq$35 versus <35 years), gender, training level (whether physician was an attending or not), activity duration (>3 years versus $\leq$3 years), type of hospital (university or non-university), and activity

volume (number of PE per year, and PE per year > 25 versus ≤ 25). Multivariate logistic regression was used to investigate the association between affiliation groups and main outcomes response categories. A stepwise selection with backward elimination was used as follows: 1- All variables were included in the model. 2- The variable with the largest p-value (least statistically significant) is removed. 3- The procedure continues until stopping rule is reached (i.e. only variables with p< 0.05 are included). Results are presented as non-adjusted and adjusted odds ratio with 95% CI. Statistical analyses were performed for available case analysis (pairwise deletion) using Stata/SE (StataCorp LP) version 13.1.

Sample size

Sample size was calculated using a two-sample proportions chi^2 test and applying the normal approximation correction for continuity (power analysis with Stata software – Stata/SE 13.1). For a difference of 25% in the frequency of the use of a prognostic model, the calculated sample size was 41 (40 – 42) respondents for the French sample and 177 (166 - 199) for the European sample (Table A6.2).

Confidentiality

The physician did not need to identify themselves. Answers were collected once, recorded anonymously and kept undisclosed.

RESULTS

Response rate

The questionnaire was available online from September 28, 2014 to June 16, 2015 and members of all three affiliation groups were invited twice to participate via email. The response rate was

13.2% (287/2183) for EuSEM, 26.6% (133/500) for SFMU and 63.1% (41/65) for INNOVTE. A total of 233 respondents (51%) reached the end of the questionnaire.

Respondent characteristics

Respondents' characteristics are displayed on table 6.1 regarding demographics, expertise, affiliation group, country, workplace, PE activity volume and PE out-of-hospital management**.**

There were several differences in the respondents' characteristics between the three affiliation groups (Table 6.2). Comparing the SFMU French emergency group physicians with the EUSEM group physicians shows a significant difference in the proportion of males (80% versus 64%, p= 0.001) and of attending physicians (91% versus 55%, p< 0.001), in PE activity volume (median number of PE per year is 40 in the SFMU group versus 100 in the EuSEM group, p< 0.001) and in the proportion of PE completely managed as outpatients or discharged within 72 hours (much lower in the SFMU group: median 10 versus 47.5, p< 0.001). In comparison with the INNOVTE group, SFMU physicians are younger (median 41 versus 50 years, p= 0.002), and have a shorter duration of activity as attending (median 10 versus 17 years, p= 0.022). Significantly fewer physicians in the SFMU group work in university hospitals (40% versus 83%, p< 0.001) and PE activity volume is significantly lower in the SFMU group than in the INNOVTE group (median number of PE per year: 40 in the SFMU group versus 80 in the INNOVTE group, p< 0.001).

Table 6.1 - Respondents' characteristics in the whole sample

Respondent characteristics	**Values**
Age (years)	N= 461 41.8 ± 9.7 40 [34, 50]
Gender (Male)	N= 461 317 (68.8: 64.3, 73)
Level of training - Attending - Fellow - Resident - Medical students - Other - Missing	N= 461 312 (67.7: 63.2, 71.9) 48 (10.4: 7.8, 13.6) 74 (16: 12.8, 19.7) 3 (0.6: 0.1, 1.9) 23 (5 : 3.2, 7.4) 1 (0.2: 0, 1.2)
Duration of professional activity as attending physician (years)	N= 461 10.2 ± 8.4 8 [3, 15]
Affiliation - EuSEM - SFMU - INNOVTE	N= 461 287 (62.3: 57.6, 66.7) 133 (28.8: 24.7, 33.2) 41 (8.9: 6.5, 11.9)
Country N (%) - France - Netherlands - United Kingdom - United States - Belgium - Canada - Romania - Germany - Italy - Spain - Turkey - Australia - Missing - Other countries[1]	N= 461 182 (39.5) 31 (6.7) 24 (5.2) 15 (3.2) 12 (2.6) 11 (2.4) 10 (2.2) 9 (1.9) 9 (1.9) 9 (1.9) 9 (1.9) 8 (1.7) 69 (15) 63 (13.7)
Type of hospital - University - Non-university - Other	N= 354 174 (49.1: 43.8, 54.5) 177 (50: 44.7, 55.3) 3 (0.8: 0.2, 2.6)
Type of department/care unit - Emergency department - ICU - Internal medicine[2]	N= 334 296 (88.6: 84.7, 91.8) 6 (1.8: 0.7, 3.9) 32 (9.6: 6.6, 13.3)
PE activity volume (N of PE within a year)	N= 337 123.9 ± 163

	80 [25, 150]
Proportion of PE completely managed as outpatients	N= 337 11.6 ± 23 1 [0, 10]
Proportion of PE discharged within 72 hours	N= 337 36.1 ± 36.2 25 [5, 65]

[1]Other countries" includes participants from Northern and Eastern Europe, Middle East and Asia. Mean ± standard deviation, Median [IQR: interquartile range], (Proportion: 95% confidence interval). [2]Internal medicine includes cardiology, haematology, pneumology, vascular medicine, etc. ……]

Table 6.2: Respondent characteristics in the affiliation groups

Characteristics	**EuSEM** N= 287	**SFMU** N= 133	[1]**p value**	**INNOVTE** N= 41	[2]**p value**
Age (years)	40.8 ± 9.7 39 [34, 47]	42.1 ± 9.0 41 [34, 50]	0.126	47.4 ± 9.8 50 [38, 54]	**0.002**
Gender – Male	184 (64: 58, 70)	106 (80 : 72, 86)	**0.001**	27 (66 : 49, 80)	0.091
Level of training	N= 287	N=132		N= 41	
- Attending	157 (55: 49, 61)	120 (91: 85, 95)	**0.000**	35 (85: 71, 94)	0.379
- Fellow	34 (12: 8, 16)	10 (8: 4, 13)		4 (10: 3, 23)	
- Resident	73 (25: 21, 31)	1 (0.8: 0, 4)		0	
- Medical students	3 (1: 0.2, 3)	0		0	
- Other	20 (7 : 4, 11)	1 (0.8: 0, 4)		2 (5: 0.6, 17))	
- Missing	0	1 (0.8: 0, 4)		0	
Duration of professional activity as attending physician (years)	8.6 ± 7.5 7 [3, 13]	11.7 ± 8.9 10 [5, 18]	**0.000**	16.7 ± 8.7 17 [10, 23]	**0.022**
Type of hospital	N= 219	N= 94		N= 41	
- University	102 (47: 40, 53)	38 (40: 30, 51)	0.324	34 (83: 68, 93)	**0.000**
- Non-university	114 (52: 45, 59)	56 (60: 49, 70)		7 (17: 7, 32)	
- Other	3 (1: 0.3, 4)	0		0	
Type of department/care unit	N= 215	N= 82	NA	N= 37	NA
- Emergency department	215 (100: 98, 100)	81 (99: 93, 100)		0	
- ICU	0	1 (1: 0, 7)		5 (14: 5, 29)	
- Internal medicine[4]	0	0		32 (86: 71, 95)	
PE activity volume (N of PE within a year)	N= 218 133.5 ± 171.4	N= 82 92 ± 139.5	**0.000**	N= 37 138.6 ± 154.8	**0.000**

	100 [30, 150]	40 [15, 100]		80 [50, 180]	
Proportion of PE completely managed as outpatients	N= 215 16.3 ± 27 5 [0, 20]	N= 82 2.5 ± 5.2 0 [0, 2]	**0.000**	N= 37 4 ± 9.6 0 [0, 5]	0.553
Proportion of PE discharged within 72 hours	N= 215 44.6 ± 39 47.5 [10, 75]	N= 82 20.3 ± 25.7 10 [0, 30]	**0.000**	N= 37 21.2 ± 18.8 20 [10, 25]	0.090

[Key: the number of respondents to the specific question is shown for each group, unless otherwise specified. "p value": [1]p value for comparison between SFMU and EuSEM groups, [2]p value for comparison between SFMU and INNOVTE groups. [3"]Other countries" includes participants from Northern and Eastern Europe, Middle East and Asia. Mean ± standard deviation, Median [IQR: interquartile range], (Proportion: 95% confidence interval). [4]Internal medicine includes cardiology, haematology, pneumology, vascular medicine, etc. ….. NA= not applicable.]

Attitudes

Respondents' use of prognostic models is displayed on table 6.3. The most often used prognostic tools are clinical judgment (36%) and prognostic models (29.6%). Prognostic indicators and hospital checklists are equally used (14%). The most used prognostic models are the PESI model (25.8%), the ESC guidelines (25.4%) and the s-PESI model (21.2%).

The analysis of the frequency of use of prognostic models (Table 6.3, Table 6.4 and Figure 6.1) shows that more than half the respondents (57% from all groups, 55% from the EuSEM group, 63% from the SFMU group and 53% from the INNOVTE group) use a prognostic model in more than 50% of cases. Furthermore, 39% (36% from the EuSEM group, 48% from the SFMU group and 39% from the INNOVTE group) use a prognostic model in more than 75% of PE patients. There is no significant difference in the frequency of the reported use of prognostic models between affiliation groups (Table 6.4).

Many prognostic indicators are used. The most common in all three groups are comorbidities and clinical context (86%), and vital signs (89%), followed by demographic factors and markers of RVD as shown on computed tomography (CT), transthoracic echocardiography (TTE) or biomarkers, mainly cTn (Table 6.3). Almost two thirds of physicians (62%) report using the prognostic indicators in addition to the prognostic models.

Table 6.3 – Respondents' use of prognostic models in the whole sample

Use of prognostic tools	**Values**
Most used prognostic tools	N=264
- Prognostic models	78 (29.5: 24.1, 35.4)
- Prognostic indicators	37 (14 : 10, 18.8)
- Clinical judgment	95 (36 : 30.2, 42.1)
- Hospital checklist	37 (14 : 10, 18.8)
- None	12 (4.5 : 2.4, 7.8)
- NA	5 (1.9 : 0.6, 4.4)
Type of prognostic models used[3]	N=264
- PESI	68 (25.8 : 20.6, 31.5)
- Simplified PESI	56 (21.2:16.4, 26.6)
- PESI-derived algorithm	13(4.9: 2.6, 8.3)
- PREP	12 (4.5: 2.4, 7.8)
- Shock index	24 (9.1: 5.9, 13.2)
- ESC guidelines	67 (25.4: 20.2, 31.1)
- None	61 (23.1: 18.2, 28.7)
Frequency of use of prognostic models	N=264
- More than 75%	104 (39.4: 33.5, 45.6)
- 51-75%	46 (17.4: 13, 22.5)
- 26-50%	28 (10.6: 7.2, 15)
- 5-25%	33 (12.5: 8.8, 17.1)
- Less than 5%	53 (20.1: 15.4, 25.4)
Type of prognostic indicators used[3]	N= 237
- Demographic factors	147 (62: 55.5, 68.2)
- Comorbidities and context	203 (85.6: 80.5, 89.9)
- Vital signs	212 (89.4: 84.8, 93.1)
- Troponin	125 (52.7: 46.2, 59.2)
- Natriuretic peptides	75 (31.6: 25.8, 38)
- D-dimer	104 (43.9: 37.5, 50.4)
- Lower limb venous US	81 (34.2: 28.2, 40.6)
- Echocardiography	139 (58.6: 52.1, 65)
- CT scan	169 (71.3: 65.1, 77)
How are prognostic indicators used	N= 237
- With prognostic models	148 (62.4: 55.9, 68.6)
- Without prognostic models	73 (30.8: 25, 37.1)
- Not at all	16 (6.7: 3.9, 10.7)

Demographic factors (age, gender), Troponins (cTnT, cTnI, high sensitive cTnT), Natriuretic peptides (BNP, NT-proBNP), US (ultrasound)]. (Proportion: 95% confidence interval)

Most used prognostic tools: Physicians use mostly clinical judgment (36%), then prognostic models (30%).
Type of prognostic models used: Physicians may use many prognostic models.
Frequency of use of prognostic models: 39% of physicians use prognostic models more than 75% of cases. This is not inconsistent: 1- Prognostic models are used as an adjunct to other prognostic tools e.g. clinical judgment or the others. 2- More than 75% of use includes most used prognostic tools and use in conjunction with the other tools or models.

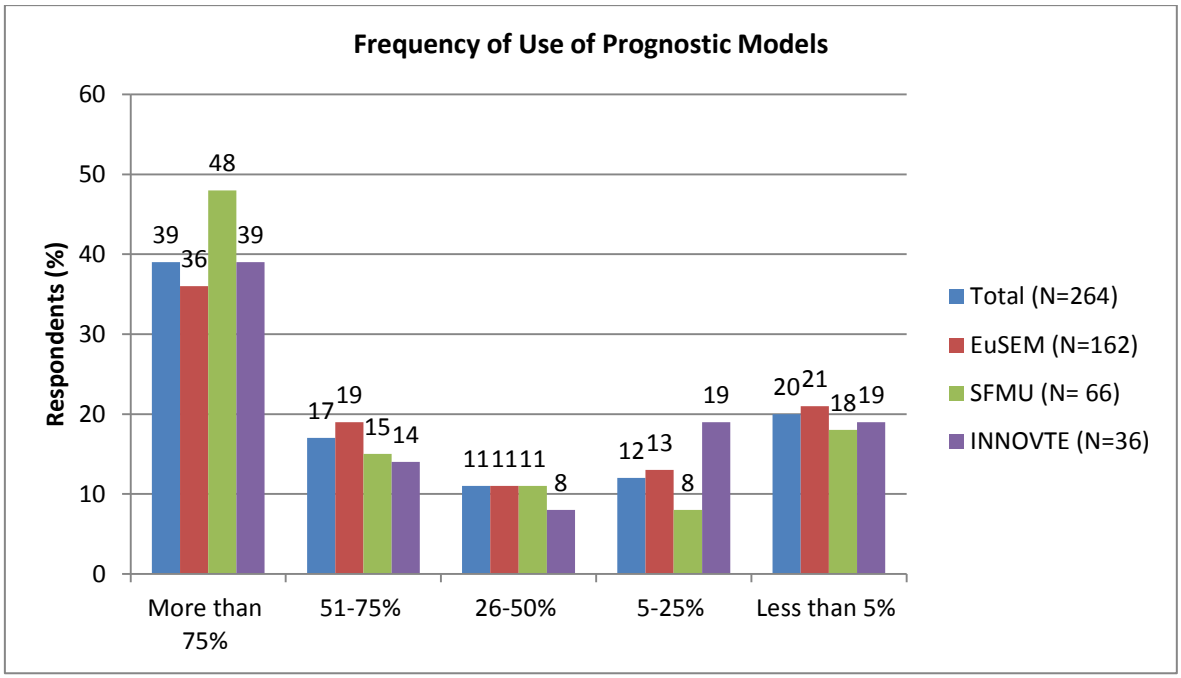
Table 6.4: Respondents' use of prognostic models in the affiliation groups

	EuSEM	SFMU	[1]p value	INNOVTE	[2]p value
Most used prognostic tools	N=162	N=66		N= 36	
- Prognostic models	38 (23: 17, 31)	27 (41 : 29, 54)	**0.010**	13 (36 : 21, 54)	0.676
- Prognostic indicators	24 (15 : 10, 21)	8 (12 : 5, 22)	0.678	5 (14 : 5, 29)	0.767
- Clinical judgment	60 (37 : 30, 45)	22 (33 : 22, 46)	0.650 0.064	13 (36 : 21, 54)	0.829
- Hospital checklist	29 (18 : 12, 25)	5 (8 : 3, 17)		3 (8 : 2, 22)	1.000
- None	6 (4 : 1, 8)	4 (6 : 2, 15)		2 (6: 1, 19)	
- NA	5 (3 : 1, 7)	0		0	
Type of prognostic models used[3]	N=162	N=66		N= 36	
- PESI	40 (25 : 18, 32)	21 (32: 21, 44)	0.322	7 (19 : 8, 36)	0.247
- Simplified PESI	26 (16:11, 23)	14 (21: 12,33)	0.345	16 (44: 28, 62)	**0.022**
- PESI-derived algorithm	12 (7: 4, 13)	0	**0.021**	1 (3: 0, 15)	0.353
- PREP	7 (4: 2, 9)	1 (2: 0, 8)	0.444	4 (11: 3, 26)	0.051
- Shock index	19 (12: 7, 18)	5 (8 : 3, 17)	0.477	0	0.158
- ESC guidelines	57 (35: 28, 43)	6 (9: 3, 19)	**0.000**	4 (11: 3, 26)	0.739
- None	41 (25: 19, 33)	11 (17: 9, 28)	0.169	9 (25: 12, 42)	0.312
Frequency of use of prognostic models	N=162	N=66		N= 36	
- More than 75%	58 (36: 28, 44)	32 (48: 36, 61)	0.100	14 (39: 23, 57)	0.408
- 51-75%	31 (19: 13, 26)	10 (15: 8, 26)	0.570	5 (14: 5, 29)	1.000
- 26-50%	18 (11: 7, 17)	7 (11: 4, 21)	1.000	3 (8: 2, 22)	1.000
- 5-25%	21 (13: 8, 19)	5 (8: 3, 17)	0.358	7 (19: 8, 36)	0.107
- Less than 5%	34 (21: 15, 28)	12 (18: 10, 30)	0.718	7 (19: 8, 36)	1.000
Type of prognostic indicators used[3]	N= 143	N= 59		N= 35	
- Demographic factors	83 (58: 50, 66)	37 (63: 49, 75)	0.637	27 (77: 60, 90)	0.174
- Comorbidities and context	115 (80: 73, 87)	55 (93, 84, 98)	**0.032**	33 (94: 81, 99)	1.000
- Vital signs	122 (85: 78, 91)	56 (95: 86, 99)	**0.059**	34 (97: 85, 100)	1.000
- Troponin	60 (42: 34, 50)	37 (63: 49, 75)	**0.009**	28 (80: 63, 92)	0.107
- Natriuretic peptides	23 (16: 10, 23)	27 (46: 33, 59)	**0.000**	25 (71: 54, 85)	**0.019**
- D-dimer	89 (62: 54, 70)	14 (24: 14, 37)	**0.000**	1 (3: 0, 15)	**0.008**

- Lower limb venous US	66 (46: 38, 55)	10 (17: 8, 29)	**0.000**	5 (14: 5, 30)	1.000
- Echocardiography	80 (56: 47, 64)	34 (58: 44, 70)	0.877	25 (71: 54, 85)	0.195
- CT scan	110 (77: 69, 84)	39 (66: 53, 78)	0.117	20 (57: 39, 74)	0.508
How are prognostic indicators used	N= 143	N= 59		N= 35	
- With prognostic models	93 (65: 57, 73)	38 (64: 51, 76)	0.786	17 (49: 31, 66)	**0.000**
- Without prognostic models	39 (27: 20, 35)	17 (29: 18, 42)		17 (49: 31, 66)	
- Not at all	11 (8: 4, 13)	4 (7: 2, 16)		1 (3: 0, 15)	

[Key: the number of respondents to the specific question is shown for each group, unless otherwise specified. "p value": [1]p value for comparison between SFMU and EuSEM groups, [2]p value for comparison between SFMU and INNOVTE groups. Demographic factors (age, gender), Troponins (cTnT, cTnl, high sensitive cTnT), Natriuretic peptides (BNP, NT-proBNP), US (ultrasound)]

Figure 6.1: Frequency of use of prognostic models



Prognostic models characteristics and barriers to their uptake

Table 6.5 shows that almost all characteristics in the questionnaire are suggested as good attributes for a good prognostic model. The following four characteristics were suggested by more than 90% of respondents: model is easy to use and has good predictive performance, variables in models are readily available, and model is reproducible.

The most important barriers (Table 6.6) are lack of awareness (52%), lack of practicality (34%), lack of training (31%), lack of time (31%), no guidelines in center or hospital (30%), lack of confidence in predictive performance (26%), and lack of perceived usefulness (22%).

Table 6.5 - Respondents' opinions on the characteristics for a good prognostic model

Characteristics	**N= 237**
Has good predictive performance - Yes - No - Don't know	 224 (**94.5** : 90.8, 97) 3 (1.3 : 0.3, 3.6) 10 (4.2 : 2, 7.6)
Easy to use - Yes - No - Don't know	 224 (**94.5** : 90.8, 97) 8 (3.4: 1.5, 6.5) 5 (2.1: 0.7, 4.8)
Variables in model readily available - Yes - No - Don't know	 217 (**91.6**: 87.3, 94.8) 10 (4.2: 2, 7.6) 10 (4.2: 2, 7.6)
Reproducible - Yes - No - Don't know	 215(**90.7**: 86.3, 94.1) 3 (1.3 : 0.3, 3.6) 19 (8: 4.9, 12.2)
Helps to inform medical decision - Yes - No - Don't know	 189 (79.7 : 74.1, 84.7) 22 (9.3: 5.9, 13.7) 26 (11: 7.3, 15.7)
Externally validated - Yes - No - Don't know	 189 (79.7 : 74.1, 84.7) 14 (5.9 : 3.3, 9.7) 34 (14.3 : 10.1, 19.5)
Well-constructed using a derivation set - Yes - No - Don't know	 173 (73 :66.9, 78.5) 26 (11 : 7.3, 15.7) 38 (16 : 11.6, 21.3)
Not costly - Yes - No - Don't know	 165 (69.6: 63.3, 75.4) 44 (18.6: 13.8, 24.1) 28 (11.8: 8, 16.6)
Was subjected to a study of impact - Yes - No - Don't know	 151 (63.7: 57.2, 69.8) 42 (17.7: 13.1, 23.2) 44 (18.6: 13.8, 24.1)

(Proportion: 95% confidence interval)

Table 6.6 - Respondents' opinions on the potential barriers to the use of prognostic models.

Potential barriers	**N= 237**
Lack of awareness or familiarity with the models	124 (**52.3**: 45.8, 58.8)
Lack of practicality	81 (**34.2**: 28.2, 40.6)
Lack of training (or workshop attendance)	74 (**31.2**: 25.4, 37.5)
Lack of time in general or in rush hours	74 (**31.2**: 25.4, 37.5)
No guidelines in center or hospital	72 (**30.4**: 24.6, 36.7)
Lack of confidence in predictive performance	61 (**25.7**: 20.3, 31.8)
Lack of perceived usefulness	53 (**22.4**: 17.2, 28.2)
Lack of resources (personnel, equipment)	48 (20.2: 15.3, 25.9)
Lack of relevance (not convinced in)	43 (18.1: 13.4, 23.6)
Lack of access to information	38 (16: 11.6, 21.3)
Beliefs that clinical judgment is sufficient	35 (14.8: 10.5, 19.9)
Individual barriers to change	31 (13.1: 9.1, 18)
Management not interested	30 (12.7: 8.7, 17.6)
No implementation strategies	50 (21.1: 16.1, 26.8)

Clinical judgment and hospital checklists versus prognostic models

Table 6.7, Table 6.8 and Figure 6.2 show that clinical judgment was considered to be “as good as” or “better than” prognostic model by 60% of the respondents (63% of the respondents for the EuSEM group, 50% for the SFMU group and 60% for the INNOVTE group). Hospital checklist was rated “as good” or “better” by 73% (67%, 88% and 74% respectively for the EuSEM, the SFMU and the INNOVTE groups).

Table 6.7 - Respondents' preferences for assessing prognosis and managing patients with acute PE in the whole sample.

Physicians' preferences for assessing prognosis and managing patients with acute PE	
Clinical judgment versus prognostic models for early discharge and out-of-hospital management	N= 233
- Clinical judgment better	40 (17.2: 12.6, 22.6)
- Clinical judgment as good	99 (42.5: 36.1, 49.1)
- Clinical judgment worse	62 (26.6: 21, 32.8)
- Don't know	32 (13.7: 9.6, 18.8)
Hospital checklist versus prognostic models for early discharge and out-of-hospital management	N= 233
- Checklist better	84 (36: 29.9, 42.6)
- Checklist as good	87 (37.3: 31.1, 43.9)
- Checklist worse	14 (6: 3.3, 9.9)
- Don't know	48 (20.6: 15.6, 26.4)
Highest acceptable 30-day mortality rate limit for early discharge or outpatient management	N= 233
- Less than 0.5%	46 (19.7: 14.8, 25.4)
- 0.5%	51 (21.9: 16.7, 27.7)
- 1%	81 (34.8: 28.7, 41.3)
- 2%	32(13.7: 9.6, 18.8)
- 3%	17 (7.3: 4.3, 11.4)
- Other	6 (2.6: 0.9, 5.5)

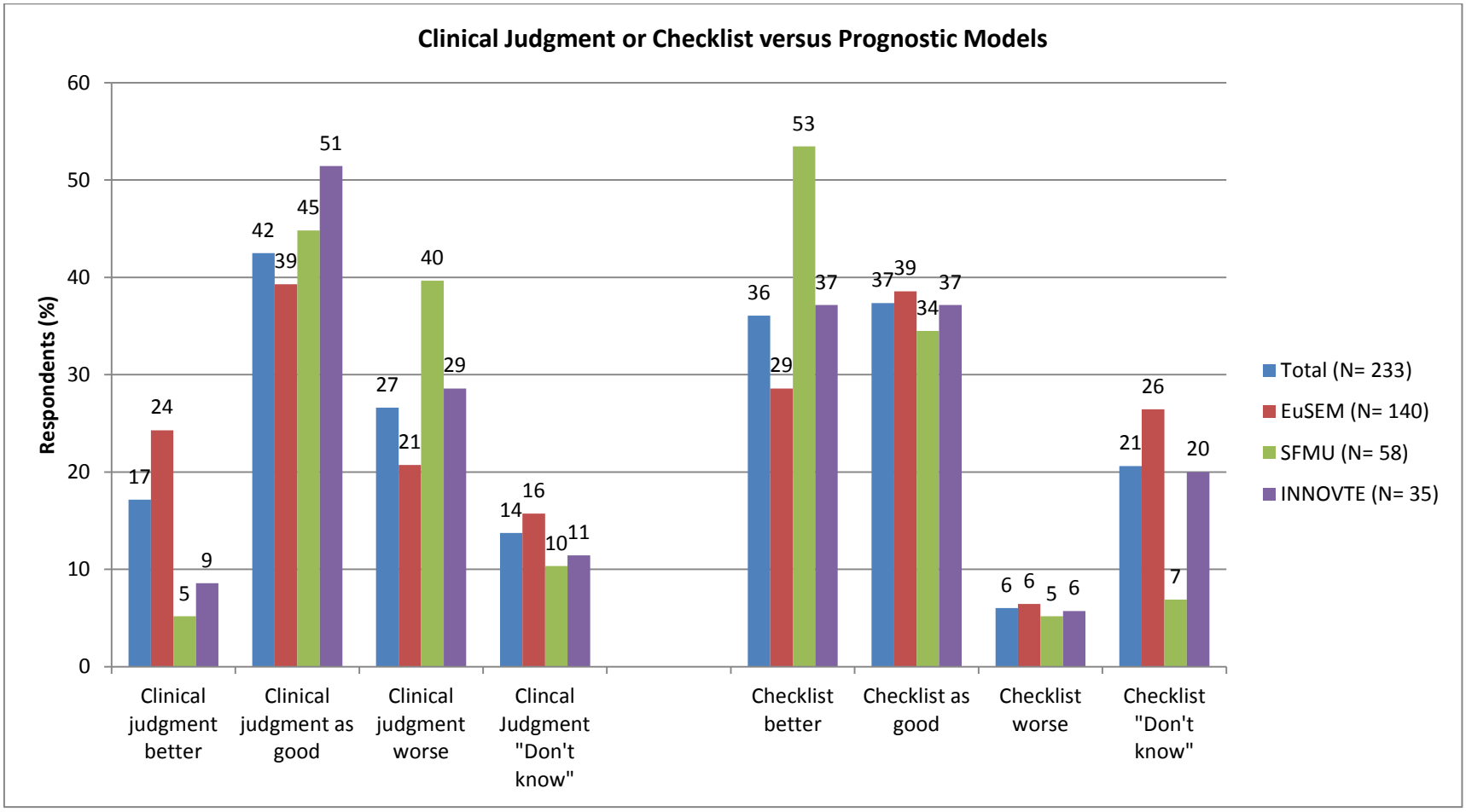
Table 6. 8: Respondents' preferences for assessing prognosis and managing patients with acute PE in the affiliation groups.

Physicians' preferences for assessing prognosis and managing patients with acute PE	**EuSEM** N=140	**SFMU** N= 58	**INNOVTE** N= 35
Clinical judgment versus prognostic models for early discharge and out-of-hospital management			
Clinical judgment better	34 (24: 17, 32)	3 (5: 1, 14)	3 (9: 2, 23)
Clinical judgment as good	55 (39: 31, 48)	26 (45: 32, 58)	18 (51: 34, 69)
Clinical judgment worse	29 (21: 14, 28)	23 (40: 27, 53)	10 (29: 15, 46)
Don't know	22 (16: 10, 23)	6 (10: 4, 21)	4 (11: 3, 27)
Hospital checklist versus prognostic models for early discharge and out-of-hospital management			
Checklist better	40 (29: 21, 37)	31 (53: 40, 67)	13 (37: 21, 55)
Checklist as good	54 (39: 30, 47)	20 (34: 22, 48)	13 (37: 21, 55)
Checklist worse	9 (6: 3, 12)	3 (5: 1, 14)	2 (6: 1, 19)
Don't know	37 (26: 19, 35)	4 (7: 2, 17)	7 (20: 8, 37)
Highest acceptable 30-day mortality rate limit for early discharge or outpatient management	30 (21: 15, 29)	13 (22: 13, 35)	3 (9: 2, 23)
Less than 0.5%	26 (19: 13, 26)	17 (29: 18, 43)	8 (23: 10, 40)
0.5%	51 (36: 28, 45)	15 (26: 15, 39)	15 (43: 26, 61)
1%	21(15: 10, 22)	7 (12: 5, 23)	4 (11: 3, 27)
2%	12 (9: 5, 14)	2 (3: 0.4, 12)	3 (9: 2, 23)

3% Other	0	4 (7: 2, 17)	2 (6: 1, 19)
Lowest acceptable 30-day mortality rate limit for administering thrombolytics[1]	NA	N= 19	N= 34
Less than or equal to 5%		2 (11: 1, 33)	2 (6: 1, 20)
Between 6% and 10%		7 (37: 16, 62)	9 (27: 13, 44)
Between 11% and 15%		2 (11: 1, 33)	6 (18: 7, 35)
Between 16% and 20%		3 (16: 3, 40)	7 (21: 9, 38)
Between 21% and 30%		2 (11: 1, 33)	4 (12: 3, 27)
More than 30%		2 (11: 1, 33)	3 (9: 2, 24)
Other value		1 (5: 0.1, 26)	3 (9: 2, 24)

[Key: the number of respondents to the specific question is shown for each group, unless otherwise specified. [1]This question was administered to 66 physicians (41 from the INNOVTE group and 25 at random from the SFMU group) with 80% response rate (34 respondents within the INNOVTE group and 19 within the SFMU group)]

Figure 6.2: Clinical judgment or checklist versus prognostic models



Risk levels and management

The highest acceptable 30-day mortality rate limit for early discharge or outpatient management is 1% for 35% of the respondents, 0.5% for 22% of respondents and less than 0.5% for 20% (Table 6.7, Table 6.8 and Figure 6.3). The lowest acceptable 30-day mortality rate limit for administering thrombolytic ranges mainly between 6 and 20% but more respondents (30%) adhere to 6 to 10% mortality risk limit to start thrombolytic therapy (Table 6.7, Table 6.8 and Figure 6.4). This last question was asked to a random sample of the SFMU group (19 respondents) and to all the respondents in the INNOVTE group (39 respondents).

Figure 6.3: Highest acceptable 30-day mortality rate limit for early discharge or outpatient management

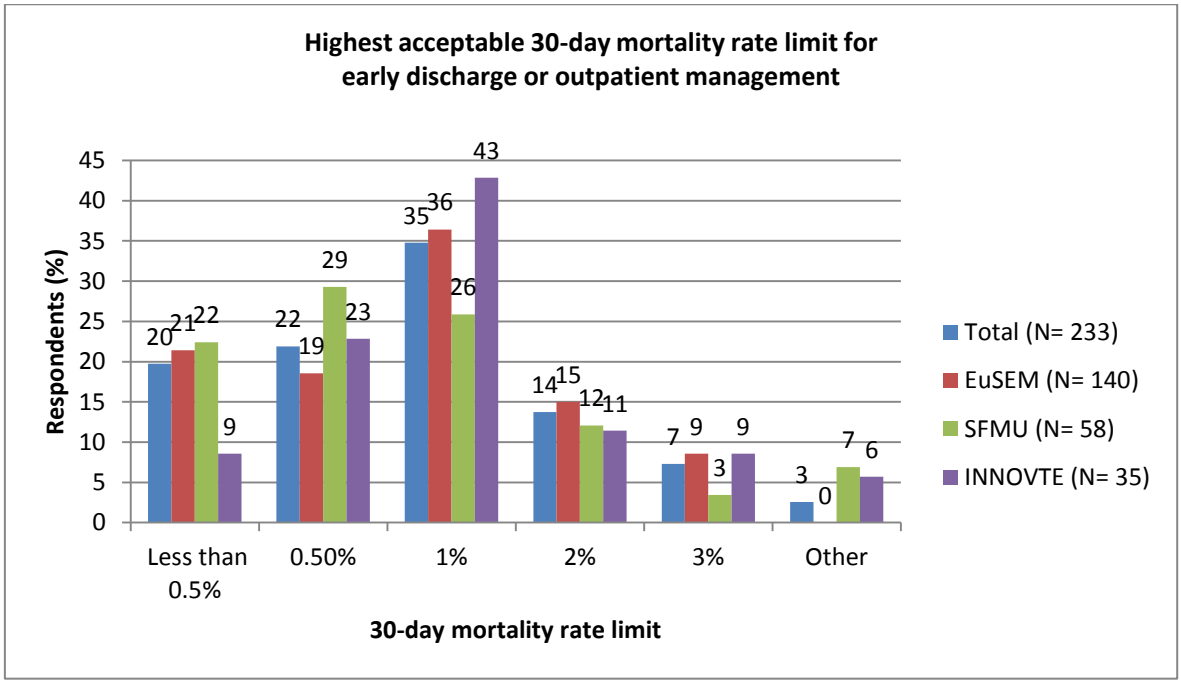
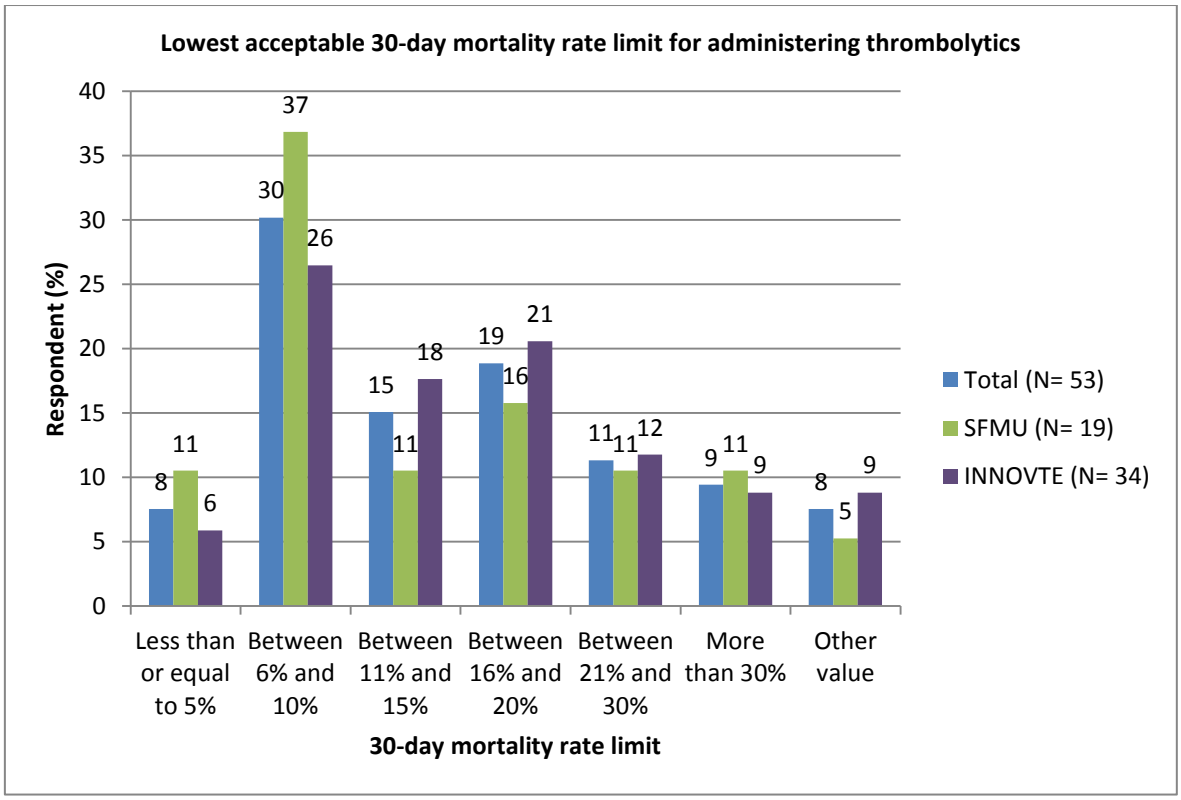


Figure 6.4: Lowest acceptable 30-day mortality rate limit for administering thrombolytics



Univariable and multivariable analyses

Results are displayed on Table 6.9. For the outcome “Prognostic models as the most often used prognostic tools”, two predictors were significant in univariable and multivariable analyses: affiliation to the EuSEM versus the SFMU group (adjusted odds ratio: 0.43 (0.23 - 0.81)) and university versus non university hospital (adjusted odds ratio: 2.48 (1.37 - 4.47)). For the outcome “Prognostic model used in 51-75% or more than 75%”, only the type of hospital (university versus non university hospital) was an independent predictor: adjusted odds ratio 1.78 (1.09 - 2.92).

For the outcomes “Clinical judgment as the most often used prognostic tool” and “Clinical judgment as good as or better than prognostic models”, no variable was a statistically significant predictor in univariable and multivariable analyses.

Finally, for the outcome “Checklist as good as or better than prognostic models”, significant predictors were affiliation group (EuSEM versus SFMU adjusted odds ratio 0.28 (0.12 - 0.67)) and years of professional activity duration (>3 years versus ≤3 years: adjusted odds ratio 1.04 (1.001 - 1.08)).

Table 6.9: Results of univariate and multivariate analyses

Outcome	Predictor	**Unadjusted odds ratio (95% CI)**	**Adjusted odds ratio (95% CI)**
Prognostic models are the most often used prognostic tools	Affiliation	0.78 (0.50 - 1.20)	
	EuSEM vs SFMU	**0.44 (0.24 - 0.82)**	**0.43 (0.23 - 0.81)**
	INNOVTE versus SFMU	0.82 (0.35 - 1.89)	
	INNOVTE versus EuSEM	1.84 (0.85 - 3.99)	
	Age ≥ 35 versus age < 35	1.22 (0.65 - 2.30)	
	Age	1.01 (0.99 - 1.04)	
	Gender: Male versus female	1.05 (0.59 - 1.88)	
	Activity duration: > 3 years versus ≤ 3 years	1.05 (0.55 - 1.98)	
	Activity duration	1.02 (0.99 - 1.05)	
	Training level : Attending versus other	1.79 (0.97 - 3.33)	
	Type of hospital: University versus other	**2.37 (1.36 - 4.13)**	**2.48 (1.37 - 4.47)**
	Activity volume: PE per year > 25 versus ≤ 25	0.98 (0.53 - 1.80)	
	Activity volume: N of PE per year	1.00 (1.00 - 1.00)	
Clinical judgment is the most often used prognostic tool	Affiliation	1.08 (0.72 - 1.63)	
	EuSEM vs SFMU	1.18 (0.64 - 2.15)	
	INNOVTE versus SFMU	1.13 (0.48 - 2.65)	
	INNOVTE versus EuSEM	0.96 (0.45 - 2.04)	
	Age ≥ 35 versus age < 35	0.78 (0.44 - 1.38)	
	Age	1.00 (0.98 - 1.03)	
	Gender : Male versus female	0.98 (0.57 - 1.70)	
	Activity duration: > 3 years versus ≤ 3 years	0.85 (0.47 - 1.54)	
	Activity duration	1.00 (0.98 - 1.04)	
	Training level : Attending versus other	1.43 (0.81 - 2.51)	
	Type of hospital: University versus other	0.81 (0.49 - 1.34)	
	Activity volume: PE per year > 25 versus ≤ 25	1.32 (0.73 - 2.38)	
	Activity volume: N of PE per year	1.00 (1.00 - 1.00)	

Prognostic model used in 51-75% or more than 75%	Affiliation EuSEM vs SFMU INNOVTE versus SFMU INNOVTE versus EuSEM Age ≥ 35 versus age < 35 Age Gender : Male versus female Activity duration: > 3 years versus ≤ 3 years Activity duration Training level: Attending versus other Type of hospital: University versus other Activity volume: PE per year > 25 versus ≤ 25 Activity volume: N of PE per year	0.78 (0.52 - 1.17) 0.70 (0.39 - 1.26) 0.64 (0.28 - 1.46) 0.92 (0.44 - 1.89) 0.86 (0.49 - 1.53) 1.01 (0.98 - 1.03) 0.96 (0.56 - 1.53) 1.14 (0.64 - 2.05) 1.02 (0.99 - 1.05) 1.15 (0.68 - 1.95) **1.78 (1.09 - 2.92)** 1.51 (0.86 - 2.63) 1.00 (1.00 - 1.00)	 **1.78 (1.09 - 2.92)**
Clinical judgment as good as or better than prognostic models	Affiliation EuSEM vs SFMU INNOVTE versus SFMU INNOVTE versus EuSEM Age ≥ 35 versus age < 35 Age Gender : Male versus female Activity duration: > 3 years versus ≤ 3 years Activity duration Training level : Attending versus other Type of hospital: University versus other Activity volume: PE per year > 25 versus ≤ 25 Activity volume: N of PE per year	1.30 (0.85 - 1.99) 1.74 (0.94 - 3.24) 1.50 (0.64 - 3.51) 0.86 (0.40 - 1.84) 1.07 (0.58 - 1.98) 1.01 (0.98 - 1.03) 0.67 (0.38 - 1.20) 1.18 (0.63 - 2.19) 1.02 (0.99 - 1.05) 1.18 (0.67 - 2.07) 1.42 (0.84 - 2.41) 0.89 (0.49 - 1.63) 1.00 (1.00 - 1.00)	

Checklist as good as or better than prognostic models	Affiliation EuSEM vs SFMU INNOVTE versus SFMU INNOVTE versus EuSEM Age ≥ 35 versus age < 35 Age Gender : Male versus female Activity duration: > 3 years versus ≤ 3 years Activity duration Training level: Attending versus other Type of hospital: University versus other Activity volume: PE per year > 25 versus ≤ 25 Activity volume: N of PE per year	0.63 (0.39 - 1.01) 0.28 (0.12 - 0.67) 0.40 (0.13 - 1.18) 1.41 (0.61 - 3.26) 0.81 (0.40 - 1.63) 1.01 (0.98 - 1.04) 0.82 (0.43 - 1.56) 1.26 (0.64 - 2.47) 1.03 (1.00 - 1.07) 1.33 (0.72 - 2.46) 1.33 (0.74 - 2.38) 1.40 (0.74 - 2.67) 1.00 (1.00 - 1.00)	**0.57 (0.35 - 0.94)** **0.28 (0.12 - 0.67)** **1.04 (1.001 - 1.08)**

Multivariate analysis: Strategy for inclusion. A stepwise selection with backward elimination was used as follows: 1- All variables were included in the model. 2- The variable with the largest p-value (least statistically significant) is removed. 3- The procedure continues until stopping rule is reached (i.e. only variables with p< 0.05 are included)

DISCUSSION

Summary of findings and comments

The most used prognostic tools by physicians managing patients with PE are prognostic models (30% of respondents) and clinical judgment (36%). This may be due to the large amount of evidence available on prognostic models and gains in their popularity in Europe. PESI, s-PESI and the "ESC guidelines" are reported as the most used prognostic models. Among physicians, 39% report using prognostic models for more than 75% of cases and 17% report using them for between 51-75% of cases. Respondents report using various prognostic indicators in addition to prognostic models in 62% of PE patients. Independent predictors for the frequency of use of prognostic models were affiliation to European versus French societies for emergency medicine (adjusted odds ratio: 0.43 (0.23 - 0.81)) and type of hospital (adjusted odds ratio for university versus non-university hospital: 2.48 (1.37 - 4.47)).

Physicians are aware of the importance of methodologically sound models and the characteristics of a good prognostic model, and prefer models with good performance that are highly reproducible, are easy to use and have variables already available for clinical practice. The most commonly reported barriers to the uptake of prognostic models are lack of awareness or familiarity with the models and lack of training, lack of perceived usefulness and practicality, lack of time, and lack of guidelines and implementation strategies. Many physicians report preferring clinical judgment and hospital checklists to prognostic models for assessing prognosis and managing patients with acute PE, with 60% describing clinical judgment and 73% describing hospital checklists as being as good as or better than models. The highest acceptable 30-day mortality rate limit for early discharge or outpatient management is less than or equal to 1%. However, despite a high volume of activity in management of acute PE patients, few (or no) patients are completely treated at home and few are discharged within 72 hours. This suggests a

low impact of prognostic tools on clinical decision making for early discharge or complete treatment at home. The lowest acceptable 30-day mortality rate limit for administering thrombolytic varies widely (from 6% to more than 20%) but is set between 6% and 10% by most of physicians. This wide range may be explained by the thrombolytic bleeding-related risk and the potential non-response to treatment, as shown in the PEITHO study[15].

There were some differences in respondents' characteristics between affiliation groups, mainly in the two emergency medicine groups. Regarding physicians' preferences for clinical judgment against prognostic models and its use, none of the variables (between-group potential heterogeneity factors) such as affiliation, age, gender, training level, activity duration, type of hospital, and activity volume had an impact on results in multivariate analysis. Affiliation group and type of hospital emerged as independent predictors for choosing prognostic models.

My survey provides important, original information on physicians' clinical practice and preferences for clinical management of acute PE patients. The findings are important for the identification and implementation of strategies in ED to improve prognostic risk assessment for patients with PE (education programme), and for planning future clinical research.

Comparison with other publications

To the best of my knowledge, and based on the extensive searching I did for research into prognostic models for PE, this is the first survey on the use of prognostic models in acute PE, although an earlier survey on the use of decision rules for the diagnosis of acute PE[16] by emergency medicine practitioners found that "57% of all respondents indicated use of unstructured or gestalt approach rather than a decision rule in more than half of cases, and one half of all clinicians reporting familiarity with the rules use them in more than 50% of applicable cases". Furthermore, my literature searches did not identify any studies that assessed clinical judgment as a prognostic tool in acute PE, but I did find some research into how a combination of contraindications to outpatient management might be used, with wide variation of these criteria

between studies[2 6 17-20]. This is further reported in Chapter 8. However, there is research into the use of clinical judgment as a diagnostic tool for suspicion of deep vein thrombosis (DVT) and for suspicion of PE; and a systematic review of studies comparing diagnostic clinical prediction rules with clinical judgment across a range of medical conditions, showed that none of the clinical prediction rules evaluated were superior to clinical judgment[21].

At least three checklists[4-6] are suggested for use as prognostic assessment tools for deciding whether a PE patient is not suitable for out-of-hospital management. The use of the Hestia checklist is associated with a low risk of adverse events[8 22-24] and seems as effective as sPESI[8] and more efficient. Even so, existing hospitalization checklists are different from clinical judgment because they do not include all clinical, biological and imaging variables that are usually available to the clinician and used for making a complete decision about managing patients with PE, i.e. deciding on an early discharge or complete home treatment. They also do not include all the variables to decide on an admission to a monitoring unit and aggressive therapy as is done by clinical judgment.

Limitations

My survey has some limitations. For example, the publication of the revised ESC guidelines in 2014 may have had a substantial subsequent impact on clinical practice. My survey was conducted from September 2014 to June 2015, and the ESC guidelines were launched at the ESC congress in August/September 2014 and published in print three months later[10]. This might raise questions about whether the same findings would be found if the survey was repeated now, a few years after the guidelines. However, although the guidelines differ from the 2008 ESC guidelines in that they incorporate the PESI and sPESI models, these models were already available to physicians through their original publications (PESI model published in 2005[1], sPESI model published in 2010[3]) and through a scientific statement from the American Heart Association published in 2011[11]. This means that both PESI models were incorporated into my

questionnaire and physicians should have been aware of these models for early discharge and complete outpatient management before the ESC guidelines became available at the end of 2014.

The findings from the Survey reflect real-world clinical practice regarding physicians' personal assessment of prognosis in patients with acute PE, and their personal management of patients in relation to this prognosis assessment. Physicians still rely on their clinical intuition and combine different tools for deciding about how to manage patients with acute PE. Many publications, including recent ones, report the underuse of PESI model[25 26] despite its clinical merits and report that home treatment is infrequently selected[27]. For instance, Stein et al[28] wrote "a large proportion of the patients in the future may not be chosen for outpatient treatment, irrespective of the availability of novel oral anticoagulants, because of the need for prolonged hospital stay". In their study, home treatment was selected for 6.0% of stable PE patients, and most of the patients treated at home were 30 years or younger or had no comorbid conditions. In a study by Vinson et al[17], nearly two-thirds of adults presenting to the ED with low-risk PE according to the PESI model were potentially eligible for outpatient therapy, and relative contraindications to outpatient management were associated with an increased frequency of adverse events at 30 days among patients with low-risk PE. This highlights the need for a new study to assess combinations of clinical intuition, prognostic models and hospitalization checklists (noting the comments above for the difference between checklists and clinical judgment).

Management of PE patients is clearly complex and, as noted earlier, many factors that are not incorporated in the suggested prognostic models or strategies may influence physician decisions. The need to investigate this further prompted my preparation of a protocol for a new study (Chapter 8). This was developed to assess whether clinical intuition is useful and to identify situations (if any) where it might provide a better answer than models or other strategies.

My survey of physicians working in routine practice has also validated the findings from earlier chapters. It shows that the low-risk threshold is arbitrary and that it is difficult to set a formal

threshold for all patients. However, the highest acceptable 30-day mortality rate limit for early discharge or outpatient management is 1% for 75% of respondents (total number of 233 respondents) and 2% for 86% of them. This finding was replicated among physicians from the department of cardiology and vascular medicine in my workplace (Chapter 5 - Net Benefit). As noticed in Chapter 4, a threshold may apply in general, but it may need to be adjusted on the basis of the patient's or physician's attitudes to risk, conditions for out-of-hospital management, and any other medical, psychological or social problems of the patient. Patient's preference and quality of life issues, a higher baseline (population) risk level and the potential impact of the intervention on the outcome may also influence physician's decision to send the patient home.

The response rate to my survey is low for all groups except the INNOVTE group, and few participants reached the end of the online questionnaire, which may be due to its length. The difference in the response rate between groups is not likely to be related to its administration because the administration was similar for all affiliation groups, but may be due to differences in the motivation of physicians in these groups and their levels of interest in venous thromboembolism and PE prognosis. The low response rate may have resulted in selection bias if respondents are not representative of their population, and the small sample sizes meant that definitive comparative analyses are not possible. A lack of group-level information on factors such as age, gender, training level and type of hospital means that I cannot check for representativeness or weight the results according to population. However, the results are consistent with observations in clinical practice and the comparisons between the affiliation groups are consistent with known differences between these three groups.

The problems with missing data in my survey mean that the analyses were performed on all available data for each question, in order to improve precision. Comparison analyses were performed only between groups of physicians having similar clinical practice (emergency physicians) to contrast findings between countries, or between groups of physicians within the

same country (French physicians) to contrast findings between specialties. I did not perform a comparison between groups that are different in both country and specialty.

Although the survey was administered online, it should not have suffered from the problems of under-coverage or self-selection that can occur for web surveys[13]. This is because all group members were reached and invited to participate via direct email from their scientific societies. Finally, the survey was a self-completion questionnaire that included mostly close-ended questions with multiple choice answers, but with other options for free-text. The responses are a mixture of declarative statements and opinions, and they do seem to reflect clinical practice.

CONCLUSIONS

To the best of my knowledge, this is the first survey on the use of prognostic models in acute PE. It reflects uncertainty among physicians about their use in clinical practice and provides new information that should be helpful for implementing strategies to improve prognostic risk assessment for the management of acute PE patients. It highlights the need for careful consideration of the use of clinical judgment and hospital checklists in future clinical research to improve the management of patients with acute PE.

[13] (http://www.applied-survey-methods.com/index.html)

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Chapter 7 - Development and Assessment of Ascertainment Strategy in Acute Pulmonary Embolism

INTRODUCTION

Rationale

Alongside the need for consideration of the use of clinical judgment and hospital checklists in research to improve the management of patients with acute PE highlighted by Chapter 6, my earlier chapters highlighted the need for careful consideration of how the sample of patients is obtained for such research. I have shown how the short-term outcome in patients treated for acute pulmonary embolism (PE) varies widely across cohort studies (Chapter 2) and studies used to construct and validate prognostic models (Chapter 4). This variability may be related to factors such as type, design and quality of studies, selection criteria in respect to population/patients and settings of interest, type of treatment and management, and type of outcome and duration of follow-up.

The extreme variability of event rate between studies used for the construction or the validation of prognostic models (same outcome and time-point, prospective cohorts) suggests that a potential explanation might be the type of patients included in the studies. Patients selected in prognosis studies may be not representative of all hospital cases and systematic differences between selected and non-selected patients due to ascertainment bias may result in differences in patient characteristics and risk stratification at baseline and in the incidence of clinical outcomes (death, VTE recurrence, major bleeding and other adverse events). Another explanation may be inadequate and unequal ascertainment of prognosis in relation to information bias, diagnostic bias or lost to follow-up bias that may lead to differences in the incidence and in the

assessment of prognostic models independently from any difference in the quality of treatment and patient care (inequality of management, compliance to treatment).

An appropriate ascertainment strategy that could help for case identification and for obtaining prognostic information appears a key element for an accurate estimation of event rate and for an adequate evaluation of prognostic models.

Objectives

I developed an ascertainment strategy to identify all incidental and recurrent acute events related to symptomatic PE in patients who were admitted for this condition or who developed it during hospitalization, in the initial phase and during a 3-month follow-up period, to monitor and improve the performance of case- ascertainment of PE in my hospital. An audit was then conducted to assess the validity of the existing method of case-identification of PE patients and the additional impact of "complete" case-ascertainment on recruitment rate, patient typology and event rates as compared with the usual method. Consequently, the ability for the strategy to obtain prognostic information at baseline and on follow-up was assessed.

Research questions

This audit primarily sought to answer two questions:

1. Is the usual hospital case-identification method finding all PE patients?
2. What differences are there between PE patients who are found and those who are missed by the usual method in terms of patient typology (case-mix: demographic, clinical, biological and imaging-based patient characteristics), risk-classification according to existing prognostic models and clinical outcomes?

METHODS

Study design

The study is an audit according to the definition of Health Research Authority National Health System[14] and was designed and conducted to assess and improve the performance of case-ascertainment of PE patients in the Toulon city hospital. Usual care in the hospital is to refer PE patients (outpatients, inpatients) to the department of vascular medicine involved in the diagnosis and management of DVT and PE. The audit was a single centre hospital-based prospective study, with an inception from day and time of hospital admission for outpatients and day and time of request for diagnostic tests for inpatients, and with a 3-month follow-up.

Local context

This audit was conducted in the Toulon city Hospital Centre, a teaching hospital. Toulon city has a population of approximately 165,000 people but its urban area has nearly 600,000 according to 2008 INSEE estimate[15]. About 70,000 patients are admitted each year to the emergency department (ED) referred from GPs or specialists and from other hospitals in Toulon, or in Hyères or Brignoles that are 20 km and 50 km from Toulon. Among them, approximately 700 patients present with clinically suspected pulmonary embolism (PE) or deep vein thrombosis (DVT). According to the local department of medical information, approximately 200 patients have an objectively confirmed diagnosis of PE and are treated in the hospital each year.

Development of ascertainment strategy

Ascertainment

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Ascertainment is the process of identifying and recording every PE-related event suffered by every patient admitted to the hospital[1]. The ascertainment strategy was based on case ascertainment (i.e. identifying and recording every patient admitted to the hospital with a clinically suspected PE either on admission (ER or services unit) or during hospitalisation), ascertainment of potential prognostic indicators in patients with confirmed PE early in the course of disease (inception cohort) within the first hours for clinical indicators and biomarkers and the first 24 hours for imaging tests, and ascertainment of events during follow-up (aiming to achieve complete follow-up of all study patients and obtain outcome information in each of them).

Evaluated case identification methods

I compared two methods to identify and recruit patients in the study: the "Passive" and the "Hot Pursuit" methods.

Passive method ("passive detection") is the routine method for the identification of patients with acute PE in the Toulon city hospital. Out-patients and in-patients are referred or notified to the vascular medicine department directly or from the ED or other medical services, within a very short time period following admission or clinical suspicion.

Hot pursuit method ("active detection") is the method developed for the identification of patients with acute PE and used by research personnel aiming at detecting under-ascertainment by screening for potential admissions and events and using different source documents. These additional patients were sought by daily ascertainment in medical units (departments of medicine, gynaecology and surgery, intensive care units, oncology, geriatrics, psychiatry, infection, rehabilitation) and diagnostic units (radiology, nuclear medicine, vascular ultrasound and clinical laboratories). The objective of daily ascertainment was to ensure that incidental and recurrent acute events related to PE were identified as soon as possible, ideally within the first hours after admission.

Data on source of patients, context and methods of case-identification, diagnostic methods and patient clinical pathways within the hospital were collected as well as the day and time these occur to measure the delay from time of admission and suspicion to time of notification to the vascular medicine group or to detection by the research team (appendices A7.3).

Details on sources of patients, potential pathways for out-patients and in-patients, and role of research team in case-identification and diagnostic confirmation, inclusion in the study and data collection of prognostic and outcome variables are given in appendices (A7.3).

Eligibility criteria

Case-definition: Consecutive patients with acute symptomatic PE ascertained prospectively from the hospital.

Inclusion criteria: Consecutive patients with a clinically suspected acute PE in whom the diagnosis was confirmed by objective testing and who could benefit from anticoagulant treatment (usual care). Both outpatients (patients admitted to the hospital) and inpatients (patients who develop PE during hospitalisation after acute medical conditions, surgical interventions, during pregnancy and in the post-partum period) were included, as well as both stable and unstable PE patients. Unstable PE patients were defined according to the 2008 ESC guidelines[2] as "a systolic blood pressure <90 mmHg or a pressure drop of $\geq$ 40 mmHg for > 15 min if not caused by new-onset arrhythmia, hypovolaemia or sepsis" (**Chapter 2**). The diagnosis of PE was confirmed by an objective method (CT pulmonary angiography (CTPA), ventilation perfusion (V/Q) scan, venous ultrasound (US), and if needed pulmonary angiography) according to PIOPED III[3] and 2008 ESC[2] predefined criteria (Appendices A7.3). Patients who had contra-indication to contrast injection[16]

[16] ACR manual on contrast media. Version 10.3/ May 31, 2017. ACR committee on drugs and contrast media. American College of Radiology; 2017 (Available at: https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast-Manual/Contrast_Media.pdf?la=en

(allergic reaction, renal failure) because they could benefit from other investigations than CT scan for the diagnosis of PE were included.

Exclusion criteria were: age < 18 years, asymptomatic PE detected by CT scan performed for other reasons, suspected PE not objectively confirmed because of incomplete diagnostic work-up, PE uncertain despite an adequate diagnostic strategy, patients under anticoagulant since at least 3 days, temporary or definitive contra-indication to anticoagulant treatment, patients referred directly for a specific diagnostic test for PE and managed out of the hospital by their physicians, patients transferred to another institute, refusal to participate by physician or by patient, patient having no trustworthy person and unable to understand information, patient living far from the centre and inability to contact the patient/ trustworthy person/ or physician by telephone or e mail.

Ascertainment and data collection of prognostic information at baseline

Data on demographic, clinical and prognostic variables were collected from patient records and from results of diagnostic test reports (CRF available upon request). This included demographic data (age, sex), clinical symptoms and signs related to PE and DVT, clinical context (unprovoked or provoked PE and cause, active and non-active cancer, previous history of PE/DVT, recent immobility, other risk factors for developing VTE), cell blood count, usual coagulation tests, creatinine and glomerular filtration rate, fibrinogen and C-reactive protein tests, electrocardiogram, chest X-ray, prognostic variables whether individual or integrated within prognostic models such as comorbidities (coronary heart disease, heart failure, COPD, other chronic pulmonary diseases, neurologic conditions, cognitive disorders, sleep apnea syndrome, chronic renal failure), vital signs (altered mental status, body temperature, heart rate, systolic and diastolic blood pressure, respiratory rate, oxygen haemoglobin saturation at room air and under oxygen), signs of hypercoagulable status (LiaTest D-dimer), signs of right ventricular dysfunction or ischemia as assessed by cardiac biomarkers (N terminal – ProBNP, troponins c-TnI) and

transthoracic echocardiography right ventricular dysfunction, ultrasound-detected vein thrombosis, and treatment at baseline.

The date and time that these variables were collected was recorded, which allows a check on which prognostic factors were assessed at inception. In order to ensure accurate, reliable and unbiased measurement strategies, clinical and prognostic variables were clearly defined if they were not standardized and a check was made as to whether the same blood tests were used throughout the study. Data collectors were trained and data collection was regularly assessed and was the same for both comparison groups. I also ensured that the detection method did not induce changes in management in the “Hot Pursuit" group and assumed that collection of data on the clinical variables, blood samples and imaging tests would not induce any changes to care because these tests were performed as usual.

Ascertainment and data collection of prognostic information on follow-up

For each patient, outcome variables were collected on the basis of a 3-month follow-up. These data concerned type of treatment and the date and time of its initiation at the early phase (anticoagulant, thrombolytic, filter insertion) and on follow-up, and the occurrence of adverse outcomes (i.e. death, non-fatal cardiogenic shock or cardio-respiratory arrest during hospitalisation, VTE events, bleeding, serious adverse events and any other adverse events).

Outcome variables were collected from inception during an 8-day, a 1-month and a 3-month follow-up, and at the time of occurrence of an adverse outcome. Follow-up visits to the centre were scheduled as usual. Patients who did not attend visits were telephoned and if no contact was made with the patient after consecutive calls over two days, contact was made with GP, trustworthy person or relatives. Multiple attempts to get outcome information were made to minimise loss to follow-up. Withdrawal (along with date and reasons) was recorded.

Data collectors were trained and used a standardised, short questionnaire in order not to induce any difference in observation between patients found and those not found by the "Passive" method. This questionnaire was used to detect adverse outcomes. In case of any event, documents concerning clinical symptoms and signs, diagnostic tests performed and management were stored for independent and unbiased review. I used blind adjudication of clinical events by physicians unaware of group affiliation. Anticoagulant treatment and its surveillance (clinical, blood and platelets count, coagulation tests), changes and quality of treatment administered (and whether this was adjusted to clinical context or not) were recorded following adverse outcomes.

The assessment criteria used for PE-related mortality[4], DVT/ PE recurrence[4-6], and bleeding severity[7 8] are provided in Chapter 3 (Figure 3.6). Death was defined as related to PE, cancer, major bleeding, cardiovascular events and other causes. PE was a "definite cause" of death if confirmed by autopsy, a "probable cause" if objectively confirmed recurrent event occurred before death, or a "possible cause" if sudden death was unexplained by another cause or another condition than PE[4]. A new thromboembolic event (DVT, PE or both) was considered as a symptomatic event confirmed by objective testing showing for DVT a thrombus progression, a thrombosis in another site, or a re-occlusion after partial or complete recanalization; and for PE a new thrombus on CTPA or V/Q scan[4] (i.e. a progression of the thrombus as compared to initial state or involvement of other sites), with reference to expert panel. Bleeding was defined as fatal, major (when symptomatic and located in a critical organ (intraocular, intracranial, retroperitoneal, adrenal, spinal, pericardial, ...) or with a loss in hemoglobin ≥ 2 g/dl or requiring red blood cells concentrate or whole blood transfusion ≥ 2 units), non-major but clinically relevant (when severe or overt bleeding was objectively documented requiring hospitalisation or prolongation of hospitalisation but not including the definition criteria of major bleeding, or minor[9 10]. Serious adverse events (SAEs) were recorded and defined as events resulting in death, life threatening, leading to hospitalisation or prolongation of hospitalisation, leading to persistent

or significant disability, or an important medical event[11]. Cardiac death, acute coronary syndrome and myocardial infarction were considered as major adverse cardiac events.

Assessment of ascertainment strategy

Impact of case-ascertainment

Patients missed and patients found by the "Passive" method were compared for recruitment rate, type of patients (patient characteristics, prognostic variables, risk-assessment models at baseline), treatment and outcomes (mortality, recurrence and major bleeding). Management of patients was not changed because of their identification in this audit and was at the discretion of the clinicians responsible for the patient.

Completeness of case-ascertainment

Completeness of case ascertainment was assessed further through "Cold pursuit". This included identifying any PE patients who were re-hospitalised for various reasons that may be related to the occurrence of adverse outcomes or to a need for investigation work-up, but had been missed in their previous hospitalisation. Furthermore, hospital records in the hospital's Health Information Management Department, which are compiled according to the French PMSI system ("Programme de médicalisation des systèmes d'information"), were checked. Hospital discharge abstract data includes dates of hospital admission and discharge, procedures codes, primary and secondary discharge diagnosis codes, bearing in mind that ICD-10 (International Statistical Classification of Diseases and Related Health Problems - 10th Revision) discharge diagnosis codes have been shown to have satisfactory sensitivity[12] for identifying objectively confirmed PE. Diagnostic lists for VTE case identification with coding according to French diagnosis-related group (DRG)-based prospective payment system is displayed in the appendices (A7.3)

Quality of data collection of prognostic information

The ability to obtain prognostic information was evaluated regularly for prognostic variables at baseline and outcome variables on follow-up. Quality assessment of baseline data concerned completeness, feasibility, adequacy and reliability, in time achievement, reasons for success, and barriers and strategies to obtain complete data collection. This may be important when selecting prognostic variables that are most easily available for potential use in prognostic models. Quality assessment of follow-up data concerned completeness of follow up, completeness/ feasibility/ adequacy and reliability of data collection, in time achievement, reasons for complete ascertainment of outcome, and barriers and strategies to obtain complete ascertainment of outcomes. These checks and information on the event rates for different time periods (in-hospital, at 1-month and 3-month) might be helpful for selecting the optimal duration of follow-up in future prognostic studies.

Barriers and strategies

Barriers encountered and strategies to overcome them were assessed. These included effects of potential changes such as ascertainment that did or did not include week-ends, ascertainment during holiday periods, personnel changes, and changes in computerized case-identification searching methods (softwares). I assessed the “Hot Pursuit" method versus the number of admissions from hospital records according to the time of such changes but this could have been done by comparing ascertainment over months or years, on the basis of severity (unstable PE, high-risk groups) or of the sources of patients.

Cost of ascertainment strategy

Cost was estimated in relation to the time spent to find for a single patient for the following tasks: case-identification, inclusion in the study and data collection of prognostic and outcome variables (details in Appendices A7.3: Role of research team).

Data analysis

My data analysis plan was to provide firstly a ***descriptive analysis*** of the whole sample at baseline (results of the recruitment process, sample size, care pathways) and on follow-up (lost to follow-up, withdrawals, type of events and event rates at different time-points, missing data for individual variables and overall). This was to be followed by a ***comparative analysis*** between patients detected versus missed by the "Passive" method, two independent and mutually exclusive groups. Under-ascertainment of the "Passive" method was assessed by the additional number and proportion of patients found by the "Hot Pursuit" method but missed by the "Passive" method. Under-ascertainment by both "Passive" and "Hot Pursuit" methods was assessed by the additional number and proportion of patients identified through only the "Cold Pursuit" method from hospital records or new hospitalisations. Both methods were compared in terms of patient characteristics, prognostic profile according to existing prognostic models, and mortality rate at different time-points (8-day, 30-day, and 3-month). The issues and the additional time costs when using the "Hot Pursuit" method were considered in order to check the value of this method.

Results for ***categorical variables*** were provided as percentages with 95% confidence intervals. For ***continuous variables***, I used median, interquartile range, mean and standard deviation. When needed (for skewed variables and small numbers), analysis used log-transformed data. A two-sample t-test was used for continuous variables or a two-sample Wilcoxon rank-sum (Mann-Whitney) test most suitable for the assessment of scores, and a chi-squared (chi^2) or Fischer exact test for categorical variables. Results were considered statistically significant at p-value below 0.05. A regression analysis was used to assess the effect of variables on type of patient detection method.

Data analysis included a ***standard survival analysis*** using time to event data for all-cause mortality with the Kaplan-Meier method to estimate the cumulative incidence function, log-rank test to compare cumulative incidence curves, and standard Cox regression model (Cox

proportional hazard) to assess covariates. I performed a ***survival competing risk regression analysis*** because PE-related death is of most importance in assessing outcomes in patients with acute PE and patients may have died from causes unrelated to PE. These competing risk events may prevent PE-related death events from ever happening, and the effect on the probability of dying from PE means that standard survival analysis may lead to biased results[13] [14]. The cumulative incidence function for PE-related death was calculated by accounting for the presence of competing risk events treated as censored in an informative manner[14] and using sub-distribution hazards to test the effect of covariates[15]. Analysis was performed on the whole study cohort and in the stable PE patient sample. The effect of variables significantly related to death and PE-death was investigated using a backward step regression analysis. Stata/SE 13.1 software was used for data analysis.

Sample size

Data from the hospital showed a potential for inclusion of 400 to 500 patients with PE within a 2-year observation period. Given the objective of the study to assess under-ascertainment by the "Passive" method [combined ("Hot Pursuit" + "Passive") – "Passive"], the primary outcome was the proportion (expressed in percentage) of patients found by the "Passive" method from all study population ascertained (n detected by "Passive") / (n detected by "Hot Pursuit" + "Passive"). This was expected to be around 97 - 98%.

Using power and sample size in Stata, with a two-sided binomial test for one-sample comparison of proportion to hypothesized value, a sample of 400 gives an estimated 90% power to show that the proportion detected is above 95% conditional on the true proportion being 98%. Thus, if the true value is 98% (H0: null hypothesis), there is 90% power to detect a difference from 95% (Ha: alternative hypothesis) with a sample of 400 patients. In sensitivity analysis, if the true value is 97% (not 98%) there is 53% power to show the proportion is above 95%, but 83% power to show that the proportion is above 94%. The power is 86% with a sample of 450 and 89% with a sample

of 500 (H0: 97%, Ha: 94%). Therefore, I planned for a sample of at least 400 patients collected over two years.

Ethical and administrative considerations

My study primarily aimed to monitor and improve the performance of the hospital, with conclusions being applicable primarily to the hospital sponsoring and funding the study. The study was classified as an audit and the Oxford University Ethics Committee determined that it did not raise any issues of research ethics with human participants (Appendices A7.1). Local Institutional Review Board approval was obtained on January 27, 2011 (Appendices A7.2) and patients were given an information notice about the study. In accordance with local policy on data protection, a declaration was made on February 02, 2011 (N° 1481813v0) to the CNIL (Commission nationale de l'informatique et des libertés), which is "an independent French administrative regulatory body whose mission is to ensure that data privacy law is applied to the collection, storage, and use of personal data"[16]

RESULTS

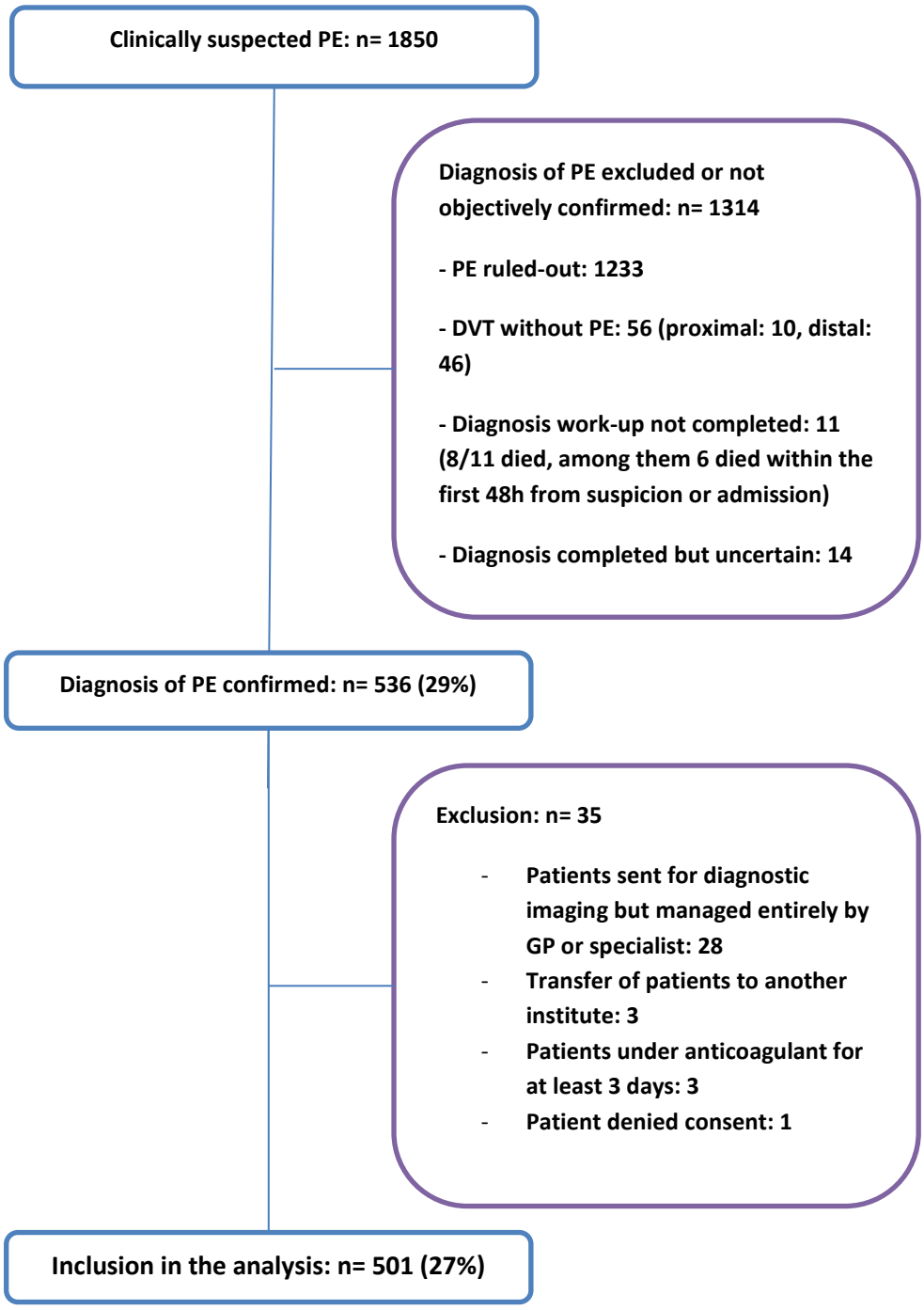
Recruitment and inclusion

Study recruitment lasted for 24 months from 18th September, 2011 to 18th September, 2013. A 3-month supplementary period was needed for follow-up of patients recruited in the last three months.

During the recruitment period, 1850 patients presented with a clinically suspected PE. The diagnosis of PE was excluded or not objectively confirmed in 1314 patients: PE was ruled out in 1289 patients of whom 56 had a diagnosis of DVT being confirmed despite the diagnosis exclusion of PE (10 DVT were proximal and 46 distal), the diagnosis work-up was incomplete in 11 patients

(among whom, 8 died with 6 dying within the first 48 hours from suspicion or admission), and the diagnosis was uncertain in 14. The diagnosis of PE was confirmed in 536 patients (29%). Among these, 35 were not included for the following reasons: 28 were sent to the hospital for diagnostic imaging and were managed directly by their GP or specialist, 3 were transferred to another institute at their request or at the request of their physician, 3 were under anticoagulant for at least 3 days and one denied consent for the use of their data. Therefore, 501 patients (27%) were included in the analysis (Figure 7.1).

Figure 7.1: Patient Flow-chart



Case-identification and diagnosis

Among these 501 symptomatic PE patients, 462 (92.2%) were identified through the “Passive” method and 39 (7.8%) were missed but were found by the “Hot Pursuit" method. Source of patients and in-hospital healthcare pathway are displayed in appendices for the whole population sample, and for the “Passive” and “Hot Pursuit” groups (Table A7.4.1). Most patients were outpatients (91.6%) and their sources of referral were GPs (26.9%), other hospitals (21%) and other medical specialties (43.7%). The other patients were inpatients (8.4%) who developed PE while in the hospital. They came from surgical and medical departments (geriatrics, oncology, cardiology, respiratory medicine, infectious diseases, internal medicine, etc). The table shows the first and second places of hospital stay. The first place is where patients are first referred to and the second place is where they were subsequently admitted to.

Comparison analysis confirmed the expected difference in the delay to case-identification between the group of patients missed and detected by the “Passive” method, with a longer delay in the missed group: 26 (66.7%) identified within 24 hours in the missed group versus 442 (95.7%) in the detected group. There were no statistically significant differences between groups for delay (from admission in out-patients or from suspicion in in-patients) to the diagnosis, the clinical delay from onset of PE or DVT symptoms to diagnosis, the presence of PE-associated DVT symptoms, the diagnostic scoring system according to Wells, Revised Geneva and simplified Geneva clinical prediction rules and the distribution of the results of the diagnostic tests performed (Table 7.1).

Table 7.1: Patient characteristics - Case-identification and diagnosis

Case-identification and diagnosis	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N		N		N		
Delay to case-identification - < 24h - 24 – 48h - > 48h	501	 468 (93.4) 20 (4) 13 (2.6)	462	 442 (95.7) 13 (2.8) 7 (1.5)	39	 26 (66.7) 7 (17.9) 6 (15.4)	0.000
Delay to diagnosis - < 24h - 24 – 48h - > 48h	483	 411 (85.1) 44 (9.2) 28 (5.6)	444	 378 (85) 41 (9) 25 (6)	39	 33 (84.6) 3 (7.7) 3 (7.7)	0.824
Clinical delay from PE symptoms (days)	484	8.53 ± 14.41 3 [1, 10]	450	8.66±14.65 3 [1, 10]	34	6.79 ± 10.79 2 [0, 7]	0.565
Presence of DVT symptoms	501	190 (37.9)	462	178 (38.5)	39	12 (30.8)	0.393
Clinical delay from DVT symptoms (days)	148	10.57± 15.18 5.5 [2, 12.5]	142	10.72± 15.31 6 [2, 13]	6	7 ± 12 1 [1, 7]	0.120
Clinical prediction rule - Wells	501	5.29 ± 5.09 5.5 [4, 7]	462	5.31 ±5.11 5.5 [4, 7]	39	5.04 ± 4.30 4.5 [4, 7]	0.394
- Revised Geneva	501	7.23 ± 3.75 7[5,9]	462	7.24 ± 3.79 7[5,9]	39	7.18 ± 3.26 7[5,9]	0.883
- Simplified Geneva	501	4.13 ± 2.54 4[2, 6]	462	4.14 ± 2.58 4[2, 6]	39	4 ± 2.17 4[2, 6]	0.914

Diagnostic tests							
- US – DVT	485		459		26		0.966
No DVT		135 (27.8)		128 (27.9)		7 (26.9)	
Distal DVT		127 (26.2)		121 (26.4)		6 (23.1)	
Proximal DVT		223 (45.8)		210 (45.7)		13 (50.0)	
- CT – PE	411		382		29		0.244
No PE		16 (3.9)		16 (4.2)		0 (0.0)	
Proximal bilateral		163 (39.7)		153 (40.0)		10 (34.5)	
Proximal unilateral		112 (27.2)		106 (27.7)		6 (20.7)	
Distal bilateral		61 (14.8)		55 (14.4)		6 (20.7)	
Distal unilateral		47 (11.4)		40 (10.5)		7 (24.1)	
Bilateral no details		12 (2.9)		12 (3.1)		0 (0.0)	
- V/Q – PE	122		112		10		1.000
No PE		1 (0.8)		1 (0.9)		0 (0.0)	
PE		118 (96.7)		108 (96.4)		10 (100.0)	
Not conclusive		3 (2.5)		3 (2.7)		0 (0.0)	

Mean ± sd, median [interquartile range], N (%).

Patient characteristics at baseline

Demographic characteristics (Table 7.2) were in brief: median age [interquartile range] of 74 [60, 83] years, 219 (43.7%) were male, and 459 (91.62%) were outpatients.

Clinical characteristics and risk factors are shown in Table 7.3. In brief, 190 patients (37.9%) presented with DVT symptoms/signs, 77 (15.4%) had acute medical conditions, 54 (10.8%) recent trauma, 42 (8.4%) recent surgery, 91 (18.2%) active cancer, 22 (4.4%) non-active cancer, 80 (16%) complete immobility, and 123 (24.6%) history of venous thromboembolism.

Comorbidities (Table 7.3) show that 28 (5.6%) had a coronary artery disease, 79 (15.8%) heart failure, 29 (5.8%) chronic obstructive pulmonary disease, 26 (5.2%) other chronic pulmonary disease, 26 (5.2%) ischemic or hemorrhagic stroke < 3 months, 64 (12.8%) cognitive disorder and 40 (8%) chronic renal failure.

Clinical findings are shown in Table 7.4. In brief, 29 (5.8%) had unstable haemodynamic status, 42 (8.4%) altered mental status. Median [IQR] was 37 [36.6, 37.4] degrees Celsius for body temperature, 21 [17, 26] (/mn) for respiratory rate, 89 [76, 104] (/mn) for heart rate, 136 [120, 153] (mm HG) for systolic blood pressure, 0.66 (0.52, 0.8] for shock index, 96 [93, 98] (%) for SpO2 at room air, 97 [94, 98] (%) for SpO2 under oxygen, and 3 [2, 6] for oxygen output (l/mn).

Prognostic stratification: Table 7.5 shows prognostic stratification and biomarkers with the median score and risk stratification according to the main prognostic models (PESI, s-PESI, GPS and shock index). Median [and IQR] for PESI score was 94 [75, 117] and for sPESI score 1 [0, 2]. Biomarkers' test result values (median [IQR]) were 3.44 [1.75, 7.84] (µg/ mL) for D-dimer, 659 [133, 2755] (pg/mL) for NT-proBNP and 0.01 [0.01, 0.1] (ng/mL) for cTnI. Tables A7.4.2 to A7.4.5 in the Appendices show the distribution of patients according to the original and simplified versions of PESI, and to the "Passive" detection method; and mortality at different time-points in the

whole study cohort (Tables A7.4.2 and A7.4.3) and in stable PE patients (Tables A7.4.4 and A7.4.5).

The comparison of baseline characteristics between the patients missed versus detected by the "Passive" method showed no statistically significant difference for demographic and clinical characteristics, and most of the risk factors and comorbidities (Tables 7.2 and 7.3) except for the presence of acute medical conditions (11 (28.2%) versus 66 (14.3%) (p=0.034)), active cancer (16 (41%) versus 75 (16.2%) (p= 0.002)), and cognitive disorders (10 (25.6%) versus 54 (11.7%) (p= 0.021)). The comparison of baseline clinical findings (Tables 7.4 and 7.5) showed statistically significant results between groups. Patients in the group missed by the "Passive" method were more unstable (7 (17.9%) versus 22 (4.8%) (p= 0.004)), had more often an altered mental status (8 (21%) versus 34 (7.4%)(p= 0.010)) and deteriorated vital signs (median [IQR]): higher respiratory rate (median 38 [26, 40] versus 20 [17, 26] (p=0.011)), higher heart rate (median 96 [84, 110] versus 88 [75, 103] (p=0.030), lower systolic blood pressure (median 120 [103, 147] versus 138 [120, 154] (p=0.002)) and higher shock index (median 0.76 [0.62, 0.99] versus 0.66 [0.52, 0.79] (p= 0.001)). Significant results for both risk factors/characteristics and clinical findings indicate that patients missed by the "Passive" method but detected by only the active search ("Hot Pursuit") were in worse conditions of health (tables 7.2 – 7.5).

The comparison analysis showed a statistically significant difference between detected and missed patients in the scoring system using PESI, sPESI, GPS or shock index (Table 7.5). There was a statistically significant difference in the distribution of risk categories for PESI but not for sPESI nor for GPS. Patients missed were at higher risk PESI than those identified by the "Passive" method: 32 (82.1%) versus 278 (60.2%) (p= 0.006). D-dimer and NT-pro-BNP results were not statistically significantly different between groups. Cardiac troponin (cTnI) results were higher in the missed group (median 0.1 [0.01, 0.24]) compared with the detected group 0.01 [0.01, 0.09] (p= 0.021).

Table 7.2: Patient characteristics - Baseline demographic characteristics

Baseline demographic characteristics	**All patients**		**Patients found by passive detection**		**Patients missed by passive detection**		**p-value**
	N		**N**		**N**		
Age	501	69.13± 17.70 74 [60, 83]	462	68.90± 17.79 73.5 [60, 83]	39	71.92± 16.51 78 [62, 83]	0.315
Gender (M/F)	501	219/282	462	200/262	39	19/20	0.615
Body mass index (Kg/m^2)	426	26.52 ± 5.42 26 [23, 29]	402	26.63 ± 5.46 26 [23, 29]	24	24.66 ± 4.45 24 [22, 27]	0.084
Source of patients - out-patients - in-patients	501	 459 (91.6) 42 (8.4)	462	 424 (91.8) 38 (8.2)	39	 35 (89.7) 4 (10.3)	0.557

Mean ±sd, median [interquartile range], N (%).

Table 7.3: Patient characteristics - Baseline risk factors and comorbidities

Baseline risk factors and comorbidities	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N		N		N		
Acute medical conditions	501	77 (15.4)	462	66 (14.3)	39	11 (28.2)	0.034
Recent trauma	501	54 (10.8)	462	47 (10.2)	39	7 (17.9)	0.172
Recent surgery	501	42 (8.4)	462	37 (8.0)	39	5 (12.8)	0.359
Obstetrics	501	7 (1.4)	462	7 (1.5)	39	0 (0.0)	1.000
Cancer - No cancer - Non active - Active	501	 388 (77.4) 22 (4.4) 91 (18.2)	462	 366 (79.2) 21 (4.5) 75 (16.2)	39	 22 (56.4) 1 (2.6) 16 (41.0)	0.002
Recent immobility - None - Partial - Complete	501	 336 (67.1) 85 (17) 80 (16)	462	 312 (67.5) 80 (17.3) 70 (15.1)	39	 24 (61.5) 5 (12.8) 10 (25.6)	0.205
Treatment – related VTE	501	97 (19.4)	462	88 (19.0)	39	9 (23.1)	0.529
History of VTE	501	123 (24.5)	462	117 (25.3)	39	6 (15.4)	0.244
Coronary artery disease	501	28 (5.6)	462	23 (5)	39	5 (12.8)	0.057
Heart failure	500	79 (15.8)	461	71 (15.4)	39	8 (20.5)	0.368
COPD	501	29 (5.8)	462	24 (5.2)	39	5 (12.8)	0.065

Other chronic pulmonary disease	501	26 (5.2)	462	25 (5.4)	39	1 (2.6)	0.711
Ischemic or hemorrhagic stroke < 3 months	500	26 (5.2)	461	23 (5)	39	3 (7.7)	0.445
Cognitive disorder	501	64 (12.8)	462	54 (11.7)	39	10 (25.6)	0.021
Chronic renal failure	501	40 (8)	462	38 (8.2)	39	2 (5.1)	0.758

Mean ±sd, median [interquartile range], N (%).

Table 7.4: Patient characteristics - Baseline clinical findings

Baseline clinical findings	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N		N		N		
Haemodynamic status - Unstable - Stable	501	 29 (5.8) 472 (94.2)	462	 22 (4.8) 440 (95.2)	39	 7 (17.9) 32 (82.0)	0.004
Altered mental status	497	42 (8.4)	459	34 (7.4)	38	8 (21.0)	0.010
Body temperature (°C)	409	37 ± 0.89 37 [36.6, 37.4]	376	37 ± 0.89 37 [36.6, 37.4]	33	37.12 ± 0.84 37 [36.6, 37.4]	0.403
Respiratory rate (/mn)	104	22.84 ± 7.57 21.25 [17, 26]	101	22.49± 7.32 20 [17, 26]	3	34.66±7.57 38 [26, 40]	0.011
Heart rate (/mn)	488	91.2 ± 21.25 89 [76, 104]	451	90.53 ± 20.92 88 [75, 103]	37	99.51 ± 23.62 96 [84, 110]	0.030
Systolic blood pressure (mmHG)	493	137.54 ± 27.74 136 [120, 153]	455	138.42 ± 27.77 138 [120, 154]	38	124.39 ± 28.59 120 [103, 147]	0.002
SpO2 room air	387	94.07 ± 5.95 96 [93, 98]	367	94.03 ± 6.02 96 [93, 98]	20	94.85 ± 4.79 96.5 [93.5, 98]	0.468
SpO2 under oxygen	103	95.83 ± 3.44 97 [94, 98]	90	95.97 ± 3.20 97 [94, 98]	13	94.92 ± 4.92 96 [94, 97]	0.288
Oxygen output (l/mn)	104	5.21 ±4.33 3 [2, 6]	91	5.22±4.41 3 [2, 6]	13	5.08 ± 3.88 4 [3, 6]	0.946

Mean ±sd, median [interquartile range], N (%).

Table 7.5: Patient characteristics - Baseline prognostic stratification and biomarkers

Baseline prognostic stratification & biomarkers	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N		N		N		
Prognostic stratification							
- PESI score	501	96.92 ± 35.55 94 [75, 117]	462	95.09 ± 34.72 92.5 [74, 112]	39	118.59 ± 38.53 118 [90, 149]	0.000
- PESI category	501		462		39		0.006
low-risk		191 (38.12)		184 (39.83)		7 (17.95)	
high-risk		310 (61.88)		278 (60.17)		32 (82.05)	
- s-PESI score	501	1.14 ±1.02 1 [0, 2]	462	1.10 ± 0.99 1 [0, 2]	39	1.59 ± 1.23 1 [1, 2]	0.015
- s-PESI category	501		462		39		0.205
low-risk		153 (30.5)		145 (31.4)		8 (20.5)	
high-risk		348 (69.5)		317 (68.6)		31 (79.5)	
- GPS score	501	1.67 ± 1.23 1 [1, 2]	462	1.63± 1.22 1 [1, 2]	39	2.08 ± 1.28 2 [1, 3]	0.022
- GPS category	501		462		39		0.319
low-risk		391 (78.0)		363 (78.6)		28 (71.8)	
high-risk		110 (22)		99 (21.4)		11 (28.2)	
- Shock index	483	0.69 ± 0.26 0.66 [0.52, 0.8]	446	0.68 ± 0.25 0.66 [0.52, 0.79]	37	0.84 ± 0.30 0.76 [0.62, 0.99]	0.001
Biomarkers							
- D-dimer (µg/ mL)	459	5.87± 5.87 3.44 [1.75, 7.84]	436	5.91 ± 5.89 3.45 [1.8, 7.90]	23	5.28± 5.55 2.86 [1.41, 7.49]	0.750

- NTproBNP (pg/mL)	466	2858 ±6098 659 [133, 2755]	440	2668 ±5548 631 [132, 2663]	26	6072 ± 11822 1752 [302, 3802]	0.157
- cTn (ng/mL)	468	0.19± 0.73 0.01 [0.01, 0.1]	438	0.16± 0.53 0.01[0.01, 0.09]	30	0.63± 2.06 0.1 [0.01, 0.24]	0.021

Mean ±sd, median [interquartile range], N (%).

Management

Anticoagulant treatment was initiated within the first days in the hospital by using unfractionated heparin (UFH), low molecular weight heparin (LMWH) or Fondaparinux (indirect anti-Xa) followed by oral vitamin K antagonist, or Rivaroxaban (direct oral anti-Xa). Brief interruption of anticoagulant treatment was observed in 38 patients (7.6%). This was because of bleeding complications in 24 patients or high risk of bleeding (high INR, surgery, trauma or very bad conditions) in 14 patients. In the other situations, anticoagulant treatment was in compliance with standard of care. Thrombolytic treatment was deemed necessary in 11 patients (2.20%) and caval filter in 5 (1.0%). All patients in whom thrombolytics were administered had unstable PE. Thrombolytic therapy was more often used in the missed than the detected group (3 (7.69%) versus 8 (1.73%) (p= 0.047). Median [IQR] for immobilisation in bed within the first days was 2 [1, 3] and for length of hospital stay 7 [5, 9]. There was no statistically significant difference between groups for temporary interruption of anticoagulant treatment, insertion of filter in the inferior vena cava, duration of immobilization in bed, or length of hospital stay (Table 7.6).

Table 7.6: Management and outcome in the whole study sample

Management and outcome	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N		N		N		
Treatment other than usual anticoagulant							
- Thrombolytics	501	11 (2.2)	462	8 (1.7)	39	3 (7.7)	0.047
- Caval filter	501	5 (1.0)	462	5 (1.1)	39	0 (0.0)	1.000
- Temporary interruption of anticoagulant therapy	501	38 (7.6)	462	34 (7.4)	39	4 (10.3)	0.524
Immobilisation in bed	352	2.83 ± 2.48 2 [1, 3]	341	2.84 ± 2.49 2 [1, 3]	11	2.45 ± 2.11 2 [1, 3]	0.386
Length of hospital stay	501	8.87± 8.42 7 [5, 9]	462	8.48 ± 6.87 7 [5, 9]	39	13.54 ±18.33 7 [3, 17]	0.7439
8-day mortality	501		462		39		0.000
- All-cause		18 (3.6)		9 (1.9)		9 (23.1)	
- PE-related		13 (2.6)		7 (1.5)		6 (15.4)	
- Cancer-related		2 (0.4)		0 (0.0)		2 (5.1)	
- Other cause		1 (0.2)		0 (0.0)		1 (2.6)	
- Unknown cause		2 (0.4)		2 (0.4)		0 (0.0)	
1-month mortality	501		462		39		0.000
- All-cause		52 (10.4)		39 (8.4)		13 (33.3)	
- PE-related		18 (3.6)		11 (2.4)		7 (17.9)	
- Cancer-related		15 (3)		11 (2.4)		4 (10.3)	
- Other cause		12 (2.4)		11 (2.4)		1 (2.6)	
- Unknown cause		7 (1.4)		6 (1.3)		1 (2.6)	

3-month mortality	501		462		39		0.000
- All-cause		80 (16)		63 (13.6)		17 (43.6)	
- PE-related		20 (4)		12 (2.6)		8 (20.5)	
- Cancer-related		30 (6)		24 (5.2)		6 (15.4)	
- Other cause		16 (3.2)		14 (3.0)		2 (5.1)	
- Unknown cause		14 (2.8)		13 (2.8)		1 (2.6)	
VTE Recurrence	493		456		37		0.580
- No recurrence		482 (97.8)		446 (97.8)		36 (97.3)	
- DVT		3 (0.6)		3 (0.7)		0 (0.0)	
- PE		3 (0.6)		3 (0.7)		0 (0.0)	
- Fatal PE		5 (1.0)		4 (0.9)		1 (2.7)	
Bleeding	493		456		37		0.105
- No bleeding		439 (89.0)		406 (89.0)		33 (89.2)	
- Minor		25 (5.1)		25 (5.5)		0 (0.0)	
- Non major clinically relevant		6 (1.2)		4 (0.9)		2 (5.4)	
- Major non-fatal		19 (3.8)		17 (3.7)		2 (5.4)	
- Fatal		4 (0.8)		4 (0.9)		0 (0.0)	
Major adverse cardiovascular events	493	1 (0.2)	456	1 (0.2)	37	0 (0.0)	1.000

Mean ± sd, median [interquartile range], N (%).

Follow-up and outcome

Data from 3-month follow-up was complete for all except 10 (2%) patients: 2 were homeless, 3 were living far from the centre, 2 were uncooperative and 3 were lost for unknown reasons. The median for lost to follow-up was 30.5 days (range 4 to 74 days). All but 2 of these 10 patients were in the "Passive" method group, and one of these two patients had unstable PE at presentation. Table 7.6 shows frequency, percentage and cause of death at 8-day, 1-month and 3-month time-points.

During the 3-month follow-up, 80 patients (16%) died in the whole cohort sample which includes both stable and unstable PE patients. Death was PE-related in 20 patients (4%), cancer-related in 30 (6%), due to other causes in 16 (3.2%) and of unknown cause in 14 (2.8%). VTE events occurred in 11 (2.2%) patients: 3 (0.6%) were DVT recurrences and 8 (1.6%) were PE, of which 5 (1%) were fatal. Bleeding occurred in 54 patients (10.9%). It was minor in 25 (5.1%), non-major but clinically relevant in 6 (1.2%), major but non-fatal in 19 (3.8%) and fatal in 4 (0.8%). One patient (0.2%) had a major adverse cardiovascular event.

All-cause and specific cause-related mortality rates in stable PE patients are reported for 8-day, 1-month and 3-month time-points (Table 7.7). Among the 472 stable PE patients, 68 (14.4%) died during a 3-month follow-up. Death was PE-related in 10 patients (2.1%), cancer-related in 28 (5.9%), due to other causes in 16 (3.4%) and of unknown cause in 14 (3%).

The 3-month mortality was higher than expected in the PESI and sPESI low-risk and high-risk groups in both the whole study cohort and the stable PE sample (Table 7.8). Two patients with missing variables died by 1 month and were classified at low-risk: one by s-PESI (missing room air O2, SpO2 93% under O2 2l/mn, respiratory rate 38) and the other by both PESI and s-PESI (missing O2 room air, SpO2 98% under O2 2l/mn). In the worst-case scenario, when considering missing data as normal, 3-month all-cause death in the low-risk group was 2.6 (0.9, 6.0) for PESI and 3.9 (1.4, 8.3) for s-PESI (Tables A7.4.2 – A7.4.5). In the best-case scenario, when considering these

two patients as high-risk, event rates in the low-risk group according to PESI and s-PESI remain slightly higher than expected. Of note, the event rate in the high-risk group is higher than in other studies using PESI models (Tables A7.4.2-A7.4.5).

Comparison analysis for the whole study cohort including both stable and unstable PE show a statistically significant difference between detection groups for 8-day, 1-month and 3-month mortality, but not for VTE, bleeding and major adverse cardiovascular events (Table 7.6). In "stable only PE" patients, similar results were found with a statistically significant difference for 8-day, 1-month and 3-month mortality (Table 7.7). Table 7.8 shows statistically significant differences in 3-month mortality rate between detection groups for a same risk category with PESI and s-PESI in the whole study cohort as well as in the stable-only PE sample (Table 7.8).

In multivariate analysis including variables of age, sex, source of patients, detection method, haemodynamic status, acute medical condition, cancer, and brief interruption of anticoagulant tretament, the only variables that remained statistically significant were "Passive" detection, haemodynamic status and cancer for 8-day, 1-month or 3-month mortality, and age for 1-month and 3-month mortality.

Deaths in patients missed by the "Passive" method*:* Among the 17 patients missed by "Passive" identification who died, 5 were unstable on admission (one with active cancer), and 12 were stable (9 with active cancer, 1 neurologic condition, 1 associated cerebral vein thrombosis and cognitive disorder, and 1 orthopedic intervention for trauma). Among the 17 patients who died, 4 had other acute medical conditions on admission with severe pulmonary infections. Most of these patients (12) were first admitted to the emergency department, with 3 admitted to pneumology, 1 to oncology and 1 to geriatry. Patients were treated with anticoagulants: 8 had UFH, 6 LMWH, 2 Fondaparinux and 1 died on admission before starting anticoagulant treatment. Two patients had thrombolytic therapy and died from PE. The median time to death in these 17 patients was 5.6 days (range 1 to 65 days).

Table 7.7: Outcome in stable PE patients

Outcome	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N		N		N		
8-day mortality	472		440		32		0.001
- All-cause		8 (1.7)		4 (1)		4 (12.5)	
- PE-related		4 (0.8)		2 (0.4)		2 (6.2)	
- Cancer-related		1 (0.2)		0 (0.0)		1 (3.1)	
- Other cause		1 (0.2)		0 (0.0)		1 (3.1)	
- Unknown cause		2 (0.4)		2 (0.4)		0 (0.0)	
1-month mortality	472		440		32		0.003
- All-cause		40 (8.5)		32 (7.3)		8 (25)	
- PE-related		8 (1.7)		5 (1.1)		3 (9.4)	
- Cancer-related		13 (2.7)		10 (2.3)		3 (9.4)	
- Other cause		12 (2.5)		11 (2.5)		1 (3.1)	
- Unknown cause		7 (1.5)		6 (1.4)		1 (3.1)	
3-month mortality	472		440		32		0.001
- All-cause		68 (14.4)		56 (12.7)		12 (37.5)	
- PE-related		10 (2.1)		6 (1.4)		4 (12.5)	
- Cancer-related		28 (5.9)		23 (5.2)		5 (15.6)	
- Other cause		16 (3.4)		14 (3.2)		2 (6.2)	
- Unknown cause		14 (3)		13 (2.9)		1 (3.1)	

N (%)

Table 7.8: 3-month all-cause mortality in relation to the haemodynamic status, to the results of "Passive" detection, and to PESI and sPESI risk-classification

PE patients	All patients		Patients found by passive detection		Patients missed by passive detection		p-value
	N	All-cause death	N	All-cause death	N	All-cause death	
Both stable and unstable							
- PESI low-risk	191	5 (2.6)	184	4 (2.2)	7	1 (14.3)	0.172
- PESI high-risk	310	75 (24.2)	278	59 (21.2)	32	16 (50)	0.000
- s-PESI low-risk	153	6 (3.9)	145	4 (2.8)	8	2 (25)	0.032
- s-PESI high-risk	348	74 (21.3)	317	59 (18.7)	31	15 (48.4)	0.000
Stable							
- PESI low-risk	190	5 (2.6)	183	4 (2.2)	7	1 (14.3)	0.173
- PESI high-risk	282	63 (22.3)	257	52 (20.2)	25	11 (44.0)	0.002
- s-PESI low-risk	153	6 (3.9)	145	4 (2.8)	8	2 (25)	0.032
- s-PESI high-risk	319	62 (19.4)	295	52 (17.6)	24	10 (41.7)	0.004

N (%)

Survival analysis

Mean follow-up for survivors was 88.8 days, range 4 to 90 days, median 90 days [IQR: 90, 90]. The mean follow-up for patients who died was 12.6 days, range 1 to 68 days, and median 3 days [IQR: 1, 19.5]. The 3-month survival rate in the whole cohort sample was 83% (95% CI: 79% to 86%). The Kaplan-Meier curve shows the lower 3-month survival rate for patients missed by the "Passive" method (Figure 7.2): 56 % (95% CI: 39% to 70%) among those missed by the "Passive" method and 86% (95% CI: 82% to 89%) among those identified by the "Passive" method. The log-rank test provided a chi2(1) = 33.99 (p = 0.0000). In sensitivity analysis, other tests for equality of survivor functions (Cox, Wilcoxon–Breslow–Gehan, Tarone–Ware, Peto–Peto–Prentice, Fleming–Harrington) also showed highly significant test results. Similar results were obtained in the stable-only PE sample: 3-month survival rate 62% (95% CI 44% to 77%) in the missed group versus 86%: (83% to 89%) in the detected group: chi2(1) 18.59 for log-rank test, $p < 0.0001$). These results are also statistically significant in the unstable PE group (chi2(1)= 5.10, p= 0.0239).

Cox regression analysis including variables concerning "Passive" detection, age, sex, acute medical condition, cognitive disorders, cancer and haemodynamic status showed statistically significant hazard ratios (95% CI) for "Passive" detection 0.39 (0.23, 0.68), haemodynamic status 4.1 (2.19, 7.65), age 1.02 (1.01, 1.04) and cancer 2.32 (1.83, 2.93) at 3-month for the whole study sample. These results hold true and are similar for 1-month and 8-day follow-up for other variables apart from age, which was not significant at the 8-day time-point and for haemodynamic status which was much more significant 16.29 (6.16, 43.05). I added heart rate and systolic blood pressure to the model for stable PE patients and the statistically significant variables at 3-month were "Passive" detection 0.52 (0.27, 1.00), age 1.03 (1.01, 1.05), cancer 2.41 (1.85, 3.13), heart rate 1.03 (1.02, 1.04) and systolic blood pressure 0.99 (0.98, 0.99). "Passive" detection, cancer and heart rate were also significant at 8-day and 1-month, and age was significant at 1-month.

The competing risks regression analysis for PE-related death at 3 months for the whole sample study showed a statistically significant subhazard ratio for “Passive” detection 0.19 (0.07, 0.53) and for haemodynamic status 14.9 (5.78, 38.41). Results were not significant for age, sex, cognitive disorders, acute medical condition and cancer (p=0.064 for cancer). In stable patients, subhazard ratio was significant for “Passive” detection 0.19 (0.05, 0.68), cognitive disorders 3.89 (1.09, 13.87) and cancer 3.09 (1.58, 6.02). Results were not significant for age, sex, acute medical condition, systolic blood pressure and heart rate. For the whole study sample, figures 7.3 and 7.3bis show that the cumulative incidence competing risk survival curves for patients identified and missed by the “Passive” method are very distant. Figure 7.4 shows that the curves for missed and identified patients are similar in stable PE (lines at the bottom) but distant in unstable PE (at the top). Patients missed versus those identified by the “Passive” method were at higher risk of death from PE.

Figure 7.2: 3-month all-cause mortality

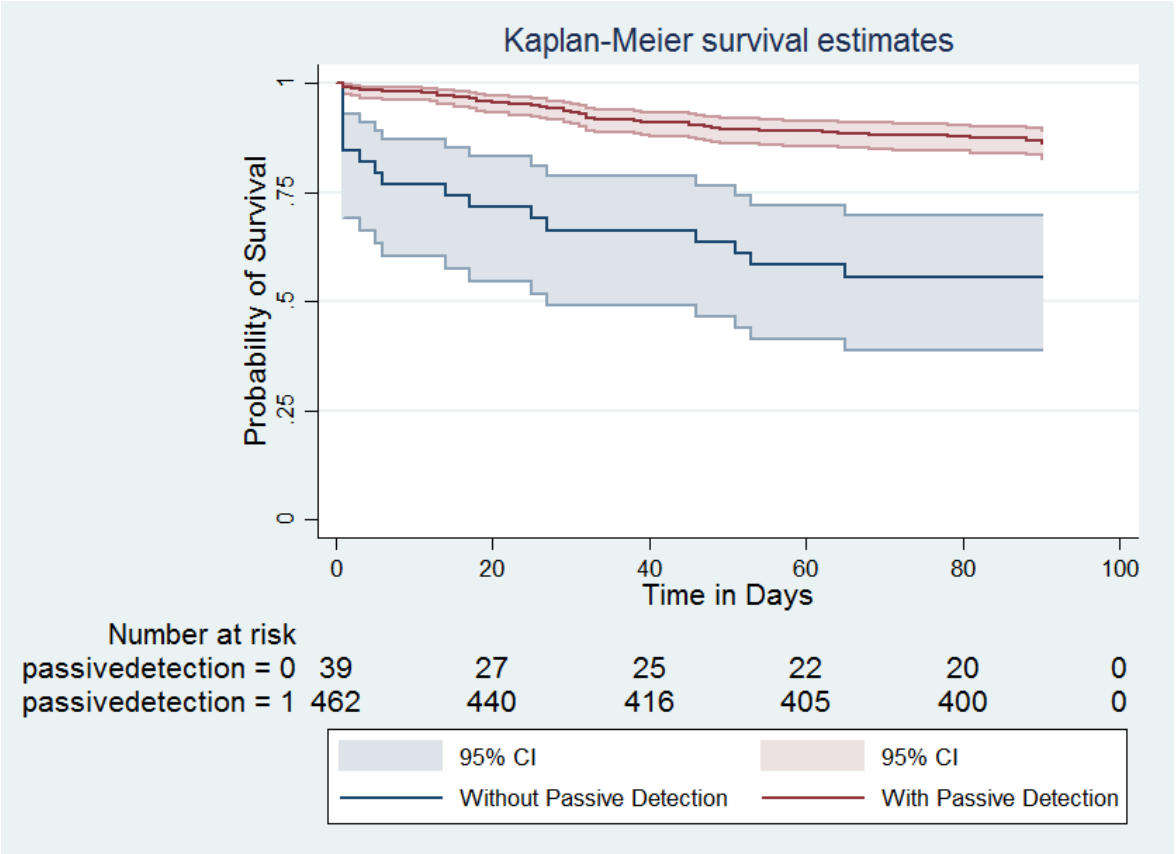


Figure 7.3: 3-month PE-related mortality

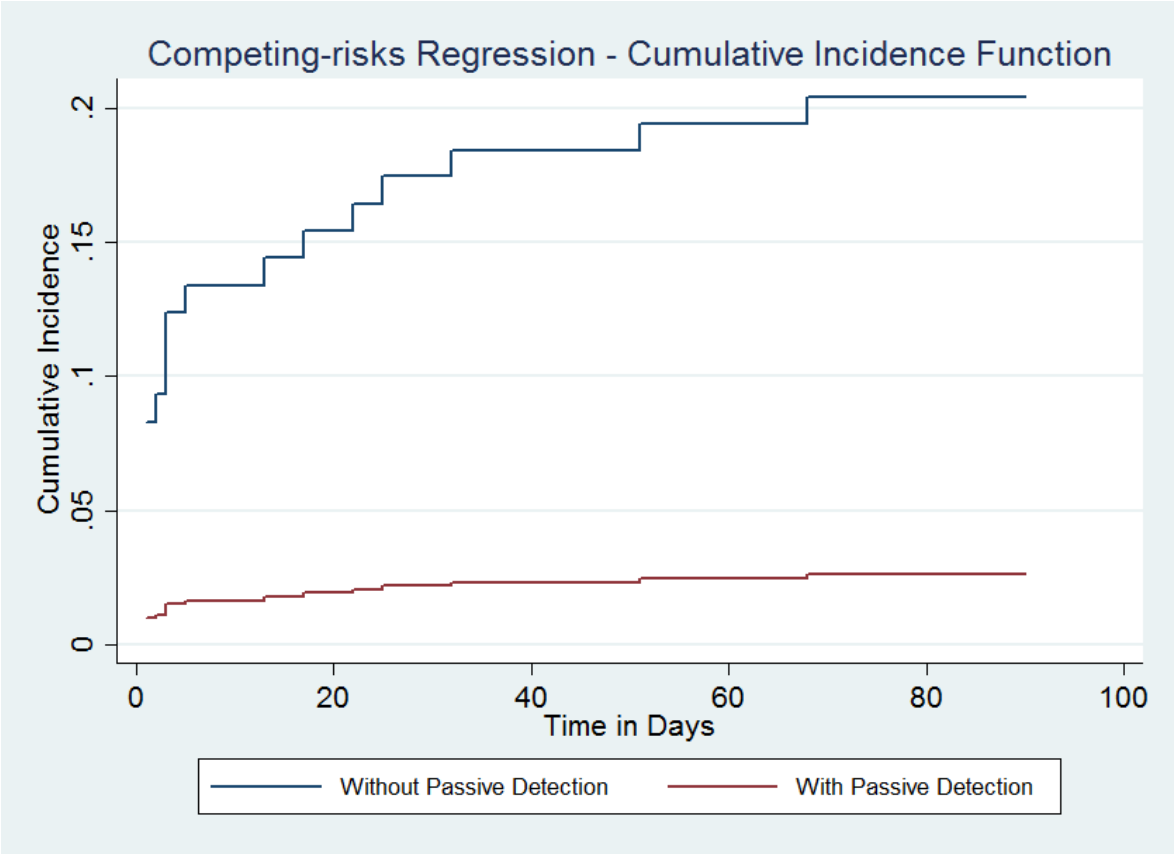


Figure 7.3bis: 3-month PE-related mortality

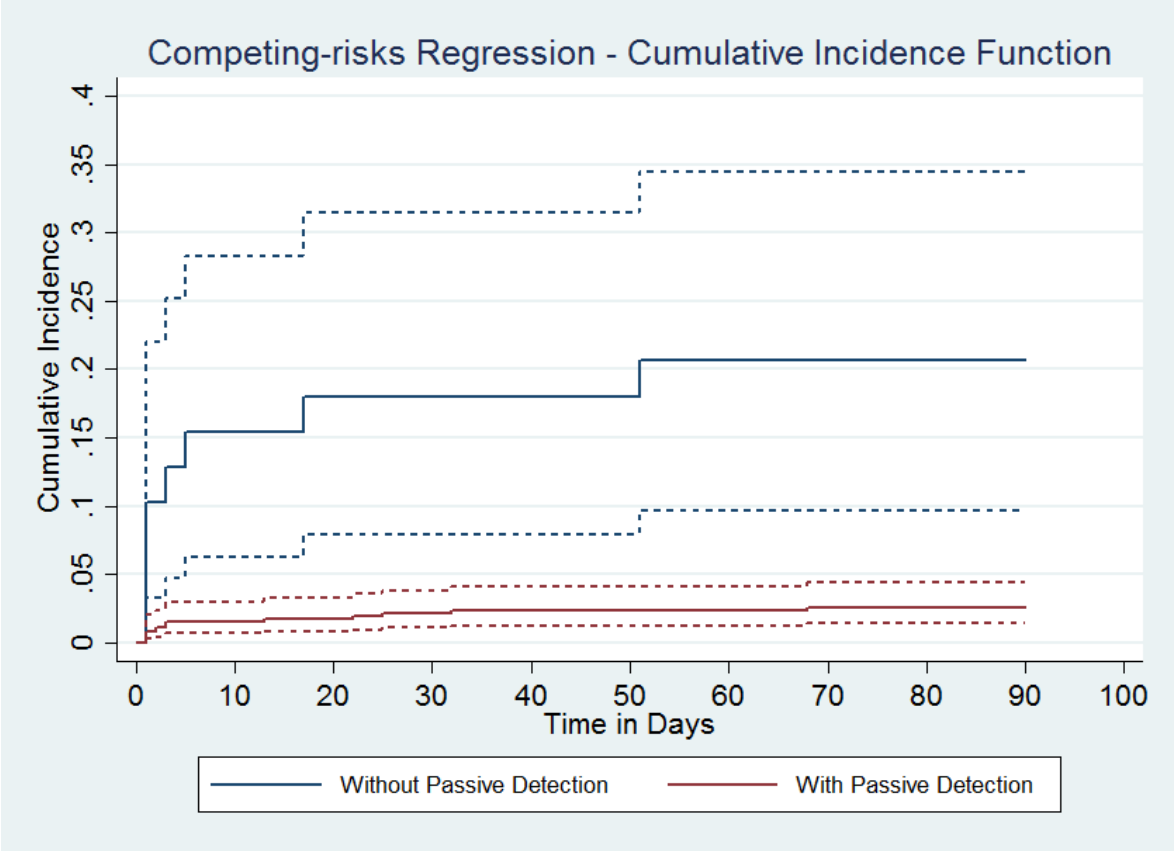
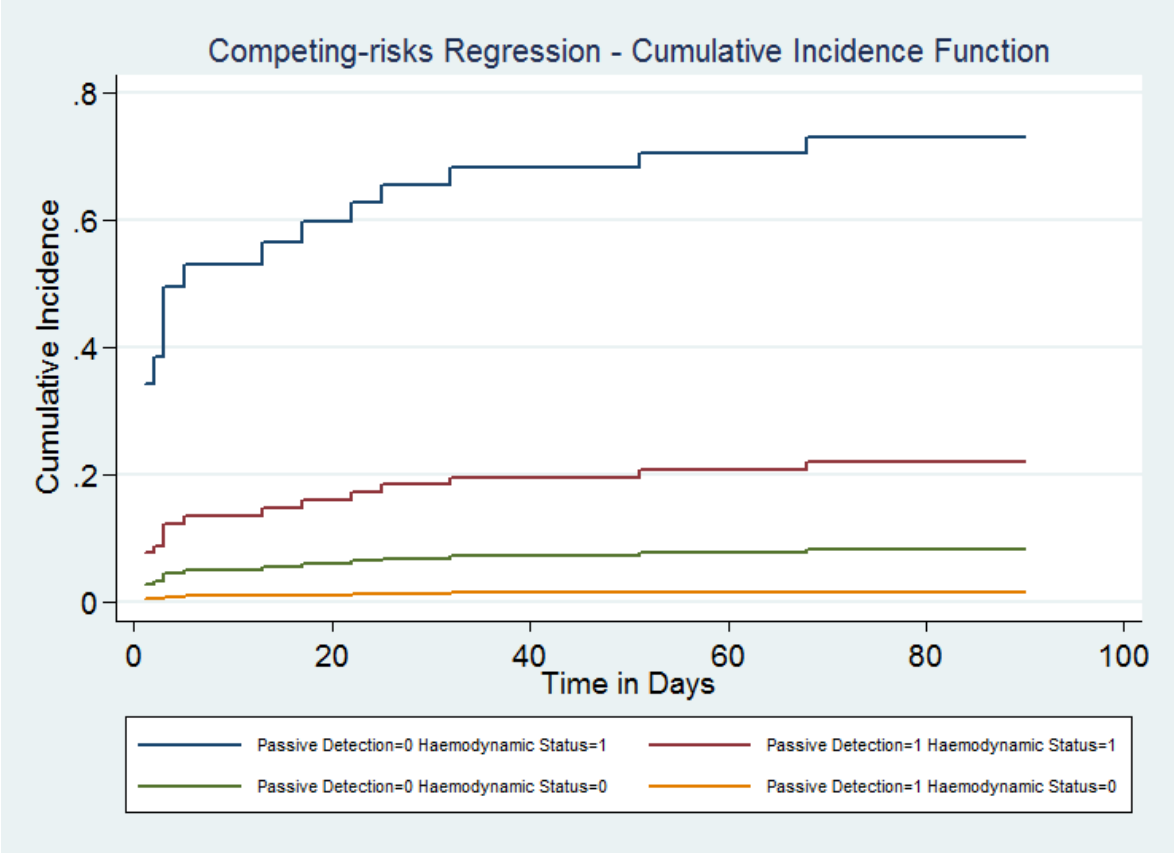


Figure 7.4: 3-month PE-related mortality



Assessment of ascertainment strategy

The test of the ***efficacy*** of the ascertainment strategy by comparing it to a reference method that combines patient detection during re-hospitalisation and hospital medical information record system ("Cold Pursuit") showed a low under-ascertainment rate. This found only three additional symptomatic PE patients that had not been identified by the "Hot Pursuit" method. This corresponds to a high detection performance (99.4%) for the ascertainment method that I developed. All three of these patients had presented a lobar or segmental artery PE, and only one had an associated deep vein thrombosis, and none of them was known to have a poor outcome.

Effectiveness: My new ascertainment method identified 39 more patients, corresponding to a potential increase of 7.8% in the recruitment for a study of the prognosis of acute PE patients in my hospital. It also provided insights for what the true event rate would be in the whole study sample and identified differences between identification strategies in patient profile and prognostic patterns that may be potentially useful for patient management and for the hospital.

Assessment of the ***efficiency*** of the strategy requires both health and economic evaluations. Estimated costs in average time spent by the research team (excluding time spent by the physicians) for a single patient from identification to completion of a 3-month follow-up and for data collection was 9 hours at the start of my study and nearly 5 hours at its end. This change was mainly due to the use of electronic data information systems. In total, the effective time spent by research assistants for the study was 6,600 hours.

Main barriers were related to the difficulty of extending every day ascertainment to week-ends and holiday periods as this may have increased early detection useful for patient management. This would have needed more personnel and should be balanced against the increase in the cost of the strategy for future development. Other barriers were changes in personnel, delays between staff leaving and new staff joining, and the time needed for adaptation of the new recruits. The under-ascertainment of three patients by the new strategy occurred during that

time. Because so few patients were missed by the Hot pursuit method, I did not compare study periods such as for the last 100 versus the first 100 patients, or compare findings on the basis of severity (unstable PE, high-risk groups), sources of patients or outcomes. Other changes that occurred during the study were helpful, including the implementation of software for case-identification searching in medical units (emergency department and others) and diagnostic units (radiology, nuclear medicine, vascular ultrasound and clinical laboratories), and the use of patient electronic source documents and source data records in combination to paper files. Logistic problems related to diagnosis, case-identification, follow-up, data collection and others were resolved by frequent meetings and discussion.

DISCUSSION

Summary of main results

My case-ascertainment strategy helped to find almost 8% more patients with PE in the hospital. It can be considered as a near-complete ascertainment as a comparison with the reference method combining case-identification upon re-hospitalisation and use of the hospital medical information record system, shows that very few extra-patients were missed, with a very high sensitivity of 99.4% for the "Hot Pursuit" detection of PE patients. The strategy was effective because patients found with the new method have different characteristics and are at higher risk, with a 16% 3-month all-cause death. Patients missed by the usual method but detected by the new strategy are different. They are at higher risk in terms of comorbidities (acute medical conditions, cancer), prognostic profile (haemodynamic status, vital signs, needs for thrombolytic therapy) and outcomes, and may need specialist care. There was a statistically significant difference in 8-day, 1-month and 3-month all-cause mortality rates between patients identified by the "Passive" method and those found by only the "Hot Pursuit" method, which was independent from patient

management. Moreover, to assess how much “Hot Pursuit" surveillance contributed to PE-related death, a competing risk regression multivariate analysis found a statistically significant lower sub-hazard ratio for 3-month PE-death in patients identified as compared to those missed by the “Passive” method: sub-hazard ratio 0.19 (95% CI: 0.07, 0.53) in the whole sample study and 0.19 (0.05, 0.78) in the only stable patients. Also, both haemodynamic status and active cancer contribute significantly for the difference between patients missed versus identified by the “Passive” method by increasing the risk of events.

The first use of direct methods to determine the completeness of different ascertainment strategies seems to have been done in a population-based stroke incidence study (Oxford Vascular Study)[17]. The authors found that their strategy, using supplementary methods including access to carotid and brain imaging referrals and assessment of patients referred as "transient ischemic attack" or "recurrent stroke", can lead to near-complete ascertainment as compared with the “core method” alone which provided significant under-ascertainment.

My study suggests that the between-study heterogeneity in patient characteristics and inconsistency on reported event rates for a same follow-up period in published prognostic studies and published prognostic models may be related not only to study design, management and study quality but also to patient selection. Patients in very poor health who may follow different care pathways are usually not included in randomised trials or cohort studies but their absence means that event rate and bad prognosis may be underestimated and prognostic models may be overoptimistic. Therefore, improved ascertainment strategies may be very important for both the assessment of prognostic studies and models and for identifying patients for possible inclusion in studies of the effects of interventions, such as randomized trials.

Our study has some limitations.

We could not expand the strategy to cover all week-ends and holiday periods. Although this did not mean that we failed to find patients, such an expansion would help with earlier detection and

be useful for appropriate clinical management and future research in prognosis studies or randomized trials. It would reduce selection bias and support the recruitment of all patients presenting with PE. Practical and logistic barriers for the diagnosis, data collection of prognostic information at baseline and follow-up during the study were resolved through meetings and discussion and appropriate and good quality complete data information was collected on prognosis and outcome. The study has also shown what is feasible and manageable in future research, highlighting how to collect prognostic variables for potential use in clinical models. Finally, although implementing such a strategy for case-identification and for obtaining good quality prognostic information is expensive, it is essential for both internal and external validity of study results and may be worth the cost. This needs to be assessed in more depth in cost-effectiveness analysis, with both the hospital and the societal point of views.

To assess under-ascertainment of the new strategy, I relied on hospital records using ICD-10 discharge diagnosis codes for identifying PE cases. The sensitivity of this method (defined as the percentage of patients identified by predefined ICD-10 codes among positive cases of acute objectively confirmed PE) was 88.9% (95% CI: 85.6, 92.2) in a study in 25 hospitals[18]. I used this method in combination with the identification of missed patients from new hospitalizations in order to detect extra cases missed by both the "Passive" and the "Hot Pursuit" methods. It was intended to use ICD discharge diagnosis codes every week or month but as the number of missed cases was too small and this was burdensome with no immediate impact, it was done once at the end of the study.

Accurate and reliable diagnostic classification is important to include only patients with PE. Multiple diagnostic tests (D-dimer, US and CT PA) are often used integrated within diagnostic strategies to rule-out and rule-in PE. Diagnostic studies not systematically based on frontline assessment of clinical probability and D-dimer test, and diversity of management may have resulted in over-diagnosis of PE and over-treatment (and, hence, cost). However, I did not include

patients whose diagnostics were not strictly complying with standard diagnostic criteria[2 19 20]. The prevalence of PE in my study, 27%, is consistent with the prevalence of validated diagnostic strategies in other studies[21-23]. My study raises also the difficulty in the diagnosis of PE in a real world setting, as some patients were not included because their diagnosis was uncertain (14/1850 patients) despite the use of adequate imaging modalities, or because the diagnostic work-up was incomplete (11/1850 patients) which is depending more on patient status (bad conditions) than on physician behaviour. Finally, as my research question was not to assess the validity of diagnostic strategies, out-patients and in-patients in whom the diagnosis was uncertain or not completed and patients in whom the diagnosis of PE was ruled out were not followed-up.

Population event rates are high in my study. This evidence might be not generalizable to other settings because of the patient characteristics in my sample, the care pathway specific to my geographic area, the case ascertainment strategy used and other reasons that are discussed below. I found high event rates for all-cause mortality of 3.6% at 8 days, 10.4% at 1 month, and 16% at 3 months. All-cause mortality was chosen because it is a "hard" outcome, which is most reliable for comparison with results from other studies and systematic reviews. The in-hospital ("early") all-cause mortality rate that I found is not as high as the summary all-cause mortality rate in the systematic review (Chapter 4), which was 6% [95% CI: 4.8 – 7.4] (31 studies); and 30-day all-cause mortality rate is similar to that in the derivation (9.2%) and the internal validation (9.5%) samples of the original PESI model, which included a large cohort of 15,531 patients. Mortality rates reported in cohort studies and registers vary from 2.7% to 6.7% at 1 week[24-27], from 5.4%[25] to 8.6%[26] at 1-month, and from 8.2% to 16.2% at 3 months[24 26 28-30]. The reported mortality rates may be even higher: 33.2% and 37.2% respectively at 1 month and 3 months in a US population-based study[31], and 21% at 3 months (control subjects 1.3%) in the Swedish national cohort[32]. The Tromsø Study[26] results (reported in the supplementary materials of the article) are similar to my results (3.1% the first day, 4.2% at 7days, 8.6% at 1 month and 16.2% at 3 months) and the hospital in that study was the only hospital in the region, which is the local

context for my study, and all hospital care and relevant diagnostic radiology for VTE in the Tromsø community were provided exclusively by the study hospital. It is important to highlight, as reported in the Tromsø study article, that "despite advances in VTE management, the rates of adverse events are still fairly high". The strengths of the Tromsø study are that it "included unselected VTE patients recruited from the general population covering both the community and the hospital setting, thoroughly identified and individually validated first and recurrent events, ..., and data collected from a recent calendar period"[26].

Explaining the high population event rates in my study and other studies

These high event rates may be explained by the patient characteristics. My study has a high proportion of high-risk patients and this is related to the clinical condition (15.4% had acute medical conditions, 10.8% recent trauma, 8.4% recent surgery, 18.2% active cancer, 16% complete immobility, and 24.6% history of venous thromboembolism), to the presence of comorbidities (15.8% heart failure, 5.8% chronic obstructive pulmonary disease, 5.2% other chronic pulmonary disease, 5.2% ischemic or haemorrhagic stroke < 3 months, 12.8% cognitive disorders and 8% chronic renal failure) and to the haemodynamic status (5.8% had unstable haemodynamic status, 8.4% altered mental status). This is also shown in the distribution of PESI and sPESI risk groups and event rates within these groups, as well as the level of biomarker tests.

Population event rates may depend on population selection and this is conditional on the patient care pathway in a specific geographic area. In studying a patient care pathway, one should consider the source of patients (who refers the patient: GP, specialist, medical centres or hospitals), the place where the patients are referred to (ED, ICU, the Thrombosis service and other services involved in diagnosis and management of VTE) and the places where the patients are subsequently admitted, and how these different elements interact. In my case-ascertainment study, patients were referred to either the ED (which then sent them to different services/ departments), or they were referred directly to the vascular medicine department or a specific

department. There were also interconnections between services, so that a patient could be admitted to a second service. Factors that may influence or determine the patient care pathway are the number of hospitals/ centres in a specific geographic area that might refer the patients or take part in their initial management, the hospital policy for patient care, bed availability and management in the hospital and in the services/ departments, type of referral centre (well-known centre and specialty) and patient typology (presentation at the initial phase considering clinical symptoms and signs and clinical context).

Population event rates may also depend on factors other than patient care pathway. These include case-ascertainment (case-identification and follow-up), which may change risk profile, diagnostic strategy used to rule out and rule in acute PE, study design, eligibility criteria in a study, and patient treatment and management. Complete case-ascertainment in a specific setting may help to recruit all patients from the different services where they have been admitted, resulting in a different risk profile and a different event rate in the whole population sample than in its different services components. This applies to a specific setting and may be not relevant in other settings. Thus, the high event rate in my study for the whole PE cohort and the stable-only PE sample is consequent to the case-identification and follow-up of all patients with PE in the hospital, owing to the ascertainment strategy and this is relevant to our specific setting.

In summary, short-term population event rates depend on the type of study (whether the study is a prospective or retrospective cohort, a register or a randomized trial), patient recruitment (care pathway, geographic area, referral, setting, ascertainment strategy), eligibility criteria for the study, diagnostic strategy for PE, patient typology and risk profile, type of treatment and management, duration of follow-up, and type and methods of assessment of outcomes. This complexity means that event rates may vary across studies depending on the setting and on the ascertainment strategy that is used and it is important that these are well described.

Clarity about case ascertainment is important for clinical practice and future research, such as that outlined in Chapter 8. Advantages of good case ascertainment are the potential for a full recruitment of patients with acute PE to avoid selection bias, good quality prognostic information (patient typology, risk profile), and complete follow-up and data on outcomes to provide reliable event rates. It enhances the internal validity of a prognostic study because it provides appropriate and reliable information on patient typology, risk profile and event rate which is important in the construction and the validation or updating of a model. It enhances the external validity and the generalisability of the study, which is highly important for the case of future patients. However, there are disadvantages such as costs and the need for more staff and time.

Prognostic stratification according to PESI models shows a higher proportion of patients at high-risk and higher event rates within low-risk and high-risk groups in our study as compared to the summary results of our systematic review **(Chapter 4)**. This may be explained by the higher event rate in the study population owing to the ascertainment strategy, the retrospective analysis of data used for stratifying patients according to the models, and the classification method used for including missing data in the stratification process. Considering missing data as normal (as was done in the construction and internal validation of the original PESI models [33 34]), s-PESI appears more affected than PESI by this classification and shows higher event rate in low-risk group as compared with the original s-PESI[34] study and with the result of PESI in my study. This may be related to the difference in the weights assigned to variables in each model. Equal weights of 1 are assigned to each variable in the s-PESI and none of the variables in the (final) model is included in the low-risk group. Assigning a null value for a missing variable may erroneously classify a patient as being at low-risk instead of classifying him (her) at high-risk, leading to the overestimation of event rates in the s-PESI low-risk group. The impact is less important for PESI in which weights assigned to variables are different and based on values from 10 to 60. This further underlines the potential importance of clinical judgment and hospital checklists in this situation.

The higher event rate within risk groups, even in the stable PE sample, suggests the need for an external validation study for both PESI models in a high-risk population cohort using complete case-ascertainment. Although this is not statistically significant, the event rate in the s-PESI low-risk group in my study is unusually high and higher than in PESI low-risk groups even in the best case scenario when considering patients with missing data as being at high-risk. This indicates that sPESI needs to be evaluated in an impact study to assess its safety for low-risk patient group, as was done for PESI in the OTPE study[35].

Competing risk was assessed to identify PE-related death useful for tailoring patient care and for management. Identifying PE-related death after discharge from hospital was more difficult than within the hospital, which could partly explain the increasing percentage of unknown causes of death after discharge at 1-month (1.4%) and 3-month (2.4%) of follow-up, as compared to the lower rate for 8-day follow-up (0.4%) in this study. Of interest, are the higher all-cause and non PE-related mortality rates with longer durations of follow-up. To better assess prognosis in acute PE, we need overall mortality at different time-points and early PE-related mortality (8-day with respect to the length of hospital stay and 1-month) to adequately measure how to manage low-risk and high-risk categories in relation to non-PE and PE deaths.

I acknowledge the small sample size in the group of patients missed by the "Passive" method as compared with the larger sample size of the group of patients identified and where poor outcome results may be diluted.

Because of the non-experimental study design, diversity of management across medical services in this study may have influenced the results. However, outcomes were not related to the quality of patient management but rather to patient typology, as shown by the data the need for tailored patient pathways and specialised care.

CONCLUSIONS

The ascertainment strategy that I developed and tested in this study achieved nearly complete ascertainment. It was effective in identifying more patients with PE in the hospital, who have different clinical characteristics and are at higher risk at baseline with increased all-cause and PE-related mortality rates on follow-up.

This strategy could be further improved by earlier detection (through coverage during the week-end and holiday periods) and would be useful not only for appropriate clinical management but also for future research in prognosis studies or randomized trials. The hospital needs to continue to improve the quality of the diagnosis and management of patients with PE by using validated diagnostic strategies and standardized treatment procedures and by sharing patient care with the thrombosis unit.

The ascertainment strategy may be very useful for future prognostic research because patients with poor condition may follow different care pathways and not be included in randomized trials or cohort studies, leading to underestimation of events rates and prognosis and the development of prognostic models that are overoptimistic. Although the implementation of such a strategy for the identification of all PE patients and for obtaining good quality prognostic information might be expensive, it is essential for internal and external validity of any results and may be worth the cost.

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Chapter 8 – Physician's Clinical Judgment in Addition to Simplified PESI for Selecting Patients with Acute Pulmonary Embolism for Out-Of-Hospital Management.

SHORT TITLE: Physician's Clinical Judgment

ACRONYM: Physician-sPESI study

This chapter has been prepared in the form of a research protocol, using the guidance from the University of Oxford Research Support[17] and the Clinical Research Study Protocol Template[18]. It outlines the design of a trial that would build on the programme of research I have presented in this thesis, in order to provide more evidence to improve the management of patients with acute PE.

[17] http://www.admin.ox.ac.uk/researchsupport/about/

[18] http://www.admin.ox.ac.uk/researchsupport/ctrg/sponsorship/protocol/

INTRODUCTION

Prognostic models and hospital checklists are two validated methods for the assessment of patients with acute pulmonary embolism (PE) for out-of-hospital management. My systematic review of prognostic models in acute PE (Chapter 4) showed that these assessment methods may provide similar results in terms of safety when compared in outcome studies. Whether or not they are used in routine practice, any decision on whether an individual patient should receive out-of-hospital management will also depend on clinical judgment by the physician, which intuitively uses clinical and social criteria (some of which are included in the prognostic models and checklists) in combination with other clinical, laboratory, and imaging factors. My survey (chapter 6) showed that some physicians in emergency departments or outpatient clinics do not rely solely on prognostic models and report clinical judgment or hospital checklists as being as good as or better than these models. However, my searches of the medical literature did not find studies assessing the impact of using clinical judgment for selecting patients with acute PE for out-of-hospital management, but I did find some research into how a combination of contraindications to outpatient management might be used, with wide variation of these criteria between studies.

The study described in this protocol would assess what clinician's intuition adds to sPESI (simplified PE severity index) when selecting patients for home management. I chose sPESI as a reference strategy because it is the simplest method recommended for use by the 2014 ESC (European Society of Cardiology) guidelines, the one to which hospital checklists have been compared (Chapter 4 and Chapter 5), and the model that was the most validated and provided the best safety in the low-risk group in my systematic review (Chapter 4).

BACKGROUND

In low-risk patients with acute pulmonary embolism (PE), ***home treatment*** became possible with the use of subcutaneous injections of low molecular weight heparins (LMWH) or anti-Xa anticoagulant agents instead of intravenous administration of standard unfractionated heparin, and with the intervention of the anticoagulation clinics for dose adjustment of oral vitamin K antagonists (VKA). This is now even easier with the use of direct oral anticoagulant agents (DOAC)[1] given at fixed doses with no need for dose adjustment. Compared with conventional treatment and a 10-day hospital stay, an early discharge or a complete outpatient management will result in substantial cost savings[2-4], a reduction in hospitalisation-related complications and an increase in patient satisfaction and quality of life.

Such results might be obtainable provided that a high quality of ***healthcare organization*** is implemented, such as that in place in Canada where around 50% of PE patients are treated at home[5 6]. Patients are discharged under anticoagulant treatment from the emergency department with a scheduled visit to the Thrombosis Centre within the first 24 to 48 hours. Outpatient management is done in collaboration with the General Practitioner by the Thrombosis Unit team who check if treatment is adequate, plan follow-up visits and checkup for etiology assessment, and explain treatment to the patient.

The main challenge is the ***selection of patients who are suitable for outpatient management*** and the need for highly accurate prediction methods to help with this (Table A8.1). Prognostic models[7-9] and hospital checklists[5 6 10-15] are two validated strategies that are suggested for use in the assessment of the suitability for out-of-hospital management in patients with acute pulmonary embolism (PE), and my systematic review of prognostic models in acute PE (Chapters 4 and 5) showed that they may provide similar results in terms of safety when compared in outcome studies.

For ***prognostic models***, the 2014 ESC (European Society of Cardiology) guidelines[16] recommend the use of the original or the simplified versions of the PE severity index (PESI and sPESI respectively - Table A8.2) for the identification of patients at low-risk who may be suitable for home treatment or early discharge. sPESI has the advantage of being easier to use than PESI. It is the one to which hospital checklists have been compared[6 13], and the one that was the most validated and that provides the best safety in the low-risk group. However, slightly fewer patients are classified at low-risk with sPESI (37%) than with PESI (41%) (Chapter 4).

Criteria against home management of patients with acute PE include those in the Ottawa[5 6], Davies[10], Hestia[11-15] (Table A8.3, Table A8.4 and Table A8.5) and other checklists. These have helped clinicians to regard home treatment as feasible in a higher proportion of patients with acute symptomatic PE (around half of them in the original studies with Hestia), with a low event rate on follow-up which is similar to that obtained with the PESI[6] and s-PESI[6 13] models. Hestia the most well-known hospital checklist has been assessed and proved effective for selecting patients for out of hospital management in two impact studies[11 15] without an incremental value for CT-RVD[14] or NTproBNP[15] when added to the strategy. It includes hospital criteria related not only to the severity of PE, but also to clinical and social factors, bleeding risk and contra-indication to low-molecular weight heparin and direct oral anticoagulant therapy. As such, it includes many clinical and social variables that are very close to those of the clinician's gestalt except for the laboratory and imaging variables that may be included in the clinician's gestalt. It is also important to note that the feasibility and safety of home treatment in acute PE has been reported in systematic reviews[17 18].

Clinician gestalt, judgement or intuition is another method of selection for deciding which patients can be managed at home. It combines clinical and social criteria (some of which are included in prognostic risk assessment models and checklists) along with other clinical, laboratory, and imaging factors, and is routinely used for deciding when an individual patient could be

discharged. My survey on the use of prognostic models in acute PE (Chapter 6) found that some physicians in emergency departments or outpatient clinics are reluctant to rely on prognostic models to decide whether to treat patients at home or in the hospital, for a variety of reasons. Many of these physicians reported clinical judgment or hospital checklists as being as good as or better than prognostic models. They believe that assessment based on their own clinical judgment might be at least as safe as using prognostic models because it expands the scope of risk assessment to a larger number of variables that might be not included within the prognostic models or the checklists. In a systematic review of studies comparing diagnostic clinical prediction rules with clinical judgment across a range of medical conditions, it was shown that none of the clinical prediction rules evaluated were superior to clinical judgment[19]. According to Hendriksen et al[20], "… probabilities estimated by a prediction model are not considered to replace but rather help the doctor's decision making". My searches of the medical literature did not find any studies reporting on the use of clinical judgment for selecting patients with acute PE for out-of-hospital management but did identify some research into how combination of contraindications to outpatient management are used, but with a wide variation of these criteria between studies. In one study[21], the authors assessed retrospectively the impact of relative contraindications to home management in emergency department (ED) patients with low-risk PE according to PESI and evaluated the association between outpatient treatment suitability criteria and 5-day and 30-day adverse events. Nearly two-thirds of patients presenting to the ED with low-risk PE were potentially suitable for outpatient therapy. Relative contra-indications to outpatient management were associated with an increased frequency of adverse events at 30 days among patients with low-risk PE. The study was not large enough to show an association with adverse events at 5 days and was retrospective. It suffers from several biases and data collection limitations: the use of adequate strategies to rule-in and rule-out the diagnosis of PE might have been inconsistent because of the number of participating centres (21 medical centers and 160 medical offices), abstractors were not blinded to the study hypothesis, there was incomplete data collection for

PESI because of its complexity and for the factors against home management because data were gathered retrospectively, there was potential for errors in relating physician's decision of outpatient unsuitability to a specific relative contraindication (variables highly facility specific), the sample was not a series of consecutive patients and follow-up was incomplete because only those patients with complete 30-day outcome data were included.

These limitations and the general scarcity of studies assessing the utility of physician's judgment in addition to a prognostic model for outpatient management support the need for a new observational prospective cohort study. Although it would be of interest to compare clinician's intuition versus other strategies, such as sPESI, any attempt to make a direct comparison between clinician's intuition and the use of these models is likely to suffer from a contamination of clinician's intuition with knowledge they gain from the models. Therefore, the study described in this protocol would assess the value of adding clinician's intuition to sPESI ("clinical judgment + sPESI" combined strategy) for selecting patients for home management, with the findings of sPESI alone and the combined strategy being assessed separately and blindly. Another limitation of trying to make a direct comparison in a single arm prospective cohort study is that it would not be possible to investigate outcomes for patients who are discharged because they are deemed suitable for out-of-hospital management by sPESI but deemed unsuitable by clinical intuition, because the actual management of the patient will depend on clinical intuition, since this determines patient management. For similar reasons, although a randomised trial would be the most robust design to compare patient outcomes if the "clinical judgment + sPESI" combined strategy is used versus the outcomes if a "sPESI" alone strategy was used, this is not feasible because it is unlikely that patients in the second group would be discharged if sPESI=0 but the clinician did not feel it was safe to discharge the patient. Likewise, a randomised trial of the "clinical judgment + sPESI" combined strategy versus a "clinical judgement" alone strategy would not be in keeping with current clinical guidance that requires the use of a prognostic model. I chose s-PESI as the reference prognostic model because it is the simplest model recommended

for use by the 2014 ESC (European Society of Cardiology) guidelines[16] , the one to which hospital checklists have been compared[6 13], and the one that was the most validated and that provided the best safety in the low-risk group in my systematic review (Chapter 4).

The study described in this chapter would assess the ***additional value of clinician gestalt to sPESI*** (combined strategy) when deciding which patients with acute PE to send home. The combined strategy will lead to four subgroups. Two subgroups correspond to the sPESI low-risk patient group: a subgroup suitable for home management (there is an agreement with sPESI alone and no factor against discharge i.e. no contraindication for outpatient management and no need for hospital care) with such patients being discharged within 24 hours and another subgroup unsuitable for home management (there is a disagreement with sPESI because of factors against home management such as a contraindication for outpatient management or a need for hospital care) with such patients being admitted to the hospital. The other two subgroups correspond to the sPESI high-risk group, and management decisions are usually in agreement with sPESI and patients are admitted to the hospital following the recommendations of the 2014 ESC guidelines[16].

My study concerns the first two subgroups and will focus on the group who are kept in hospital because of ***factors against home management*** even though they are considered as low-risk PE (sPESI=0). According to Vinson et al[21 22] who systematically reviewed publications on home treatment of patients with acute PE, "all of the prospective studies of the management of ED patients with acute PE use some combination of contraindications to outpatient management" and "although ***several criteria are used uniformly in nearly all of these studies, wide variation exists***". Data from publications suggest that among patients at low-risk sPESI or PESI the proportion of patients suitable for out-of-hospital management when combining prognostic model with clinical judgment (sPESI= 0 and Hestia hospital checklist= 0) is 0.69 according to Zondag et al[13] and 0.64 (PESI=0 and no extra factor i.e. no relative contraindications to home

management) according to Vinson et al[21]. In the above studies[13 21], the criteria against outpatient management were assessed retrospectively, in contrast to the study of Kabrhel et al[23] where data were collected a priori within 24 hours of PE diagnosis. There are also other important differences in the criteria used in these studies. With Hestia, only clinical and social predefined variables are used, but the studies of Kabrhel et al[23] and Vinson et al[21] also included radiological variables and biomarkers at the discretion of the treating physician. Furthermore, in the study of Kabrhel et al[23], variables used were compared and not added to prognostic models. In the OTPE[9], a non-inferiority randomized trial, 470 patients (30%) were at low-risk PESI (PESI I and PESI II categories). PESI assessment is based on 11 criteria (Table A8.2) and when combined with a further 14 "study exclusion criteria", 73% of these patients were suitable for outpatient management (i.e. 22% of the initial cohort). Although the recording of all these criteria could make the process cumbersome for routine practice, the lower proportion of patients at low-risk and the zero mortality at 14 days in patients at low-risk PESI as opposed to a highest proportion and a highest mortality rate in the Otero's study[24] (using Uresandi's Spanish criteria)[25] might suggest a better selection of patients with PESI according to Howard and Salooja[26].

The variation between studies in the proportion of patients who are in the low-risk subgroups and in the factors against outpatient management strengthen the need for a prospective cohort study that could assess precisely the proportion of patients who are unsuitable for outpatient management based on physician's clinical judgment in addition to sPESI (ie sPESI=0 and at least one factor against outpatient management) and identify what these factors against home treatment are. It is also useful to know 1/ if adding clinician gestalt to sPESI could further identify patients with PE with an even lower risk suitable for complete outpatient management and even higher risk unsuitable for outpatient management, and identify the factors that predict events; and 2/ the length of hospital stay in each category.

The study would help answer a first question: How often is sPESI overruled by clinical judgment in patients at low-risk PE (i.e. how often do patients with acute PE and a sPESI=0 have at least one factor against home management)? **It would also help answer a second question**: What are the factors that determine that a sPESI=0 patient is not suitable for home management?

METHODS

Study objectives

Primary objective: The primary objective is to assess the proportion of patients unsuitable for outpatient management among those judged to have low-risk PE (i.e. the proportion of patients having sPESI=0 but at least one factor against home treatment) and identify the factors against out-of-hospital management in this patient group**.**

Secondary objectives: The secondary objectives are to assess: 1/ the risk of adjudicated 7-day and 30-day adverse events in patients suitable and in patients who are unsuitable for home management among patients at low-risk PE (sPESI=0) and identify factors associated with adverse events (predictors); 2/ the length of hospital stay in both patient categories; and 3/ the consistency between a strategy based on sPESI and that based on sPESI combined with clinical judgment.

Outcome measures

Suitability for outpatient management: Suitability or unsuitability for outpatient management and the determinant factors are recorded for every patient for "sPESI + Clinical judgment" along with the sPESI score (details in study design).

Factors against outpatient management: Factors that determine management following the combined strategy are of particular interest when patients are kept in the hospital despite a sPESI score of 0. They represent "relative contraindications" to home management in patients considered as sPESI low-risk. They may be related to VTE (PE, thrombosis risk), contraindications to anticoagulant treatment, comorbidities needing hospital care, social and environmental conditions, and patient and physician preferences. They might include clinical variables that are common to sPESI and Hestia, as well as other clinical biological and imaging variables. A list of factors is provided below (Table 8.3).

Event rate: The outcome that is most relevant for measurement in patients in an "outpatient suitable" subgroup is different from that in the "outpatient unsuitable" subgroup. This is related to the differences in the type of observation of patients treated at home and in the hospital. This differential observation may lead to surveillance or detection bias, and it confounds direct comparison of outcomes between these two subgroups. In the outpatient unsuitable subgroup, the main outcome is a composite of all-cause death, VTE recurrence, clinical deterioration events and interventions that typically require hospitalisation[19] as defined by Kabrhel et al[23], major and clinically relevant non-major (CRNMB) bleedings and unscheduled hospitalization/ visits. Whereas in the outpatient suitable subgroup, the same composite outcome would be considered but without clinical deterioration since that cannot be assessed as it would be assessed in the hospital. Because of a wide variation in length of hospital stay (LOS) in a recent review (average, 14.6 days; median, 12.4 days)[27] and a trend to a decrease in mean of length stay from 13.6 to 9.3 days[28] or less (5.6 days)[3] thanks to the use of non-vitamin K direct oral anticoagulants[2-4], the time-point for assessing event rates will be set at 7 (±2) days. As factors associated with early outcomes are different from those associated with later outcomes[23], adverse events (clinical deterioration not included) will be assessed at 30 days as other secondary outcomes.

[19] (i.e. hypotension, hypoxaemia or need for respiratory support, endotracheal intubation or positive pressure ventilation, cardiopulmonary resuscitation, use of intravenous vasopressors or inotropic, advanced cardiac life support measures, new dysrhythmia, new unstable dysrhythmia, thrombolysis/ thrombectomy)

Length of hospital stay includes initial and further unscheduled hospitalisations, and will help to measure resources utilization.

Study design

Type of study

The study will be a multicenter observational prospective cohort single-arm study (one sample).

Flow chart of the study protocol

Study flow is displayed on figure 8.1. First, sPESI is assessed by the research technician using variables from the source document leading to the attribution of a sPESI score. This assessment is blinded to the physician's assessment which would determine whether or not the patient is suitable for outpatient management, by using her/his clinical judgment, which includes sPESI and other formal criteria (contraindications for out-of-hospital management).

Duration of participation in the study

The expected duration of participant participation is one month, with scheduled visits or telephone calls at days 2 (±1), 7 (±2) and 30 (±2).

Study schedule

The study schedule is displayed on Table 8.1, showing case identification, assessment of study eligibility, informed consent, recording and collection of demographic and medical data, risk assessment using sPESI model, physician's clinical judgment and decision, actual management and treatment, length of hospital stay and outcome assessment.

Figure 8.1: Study flow

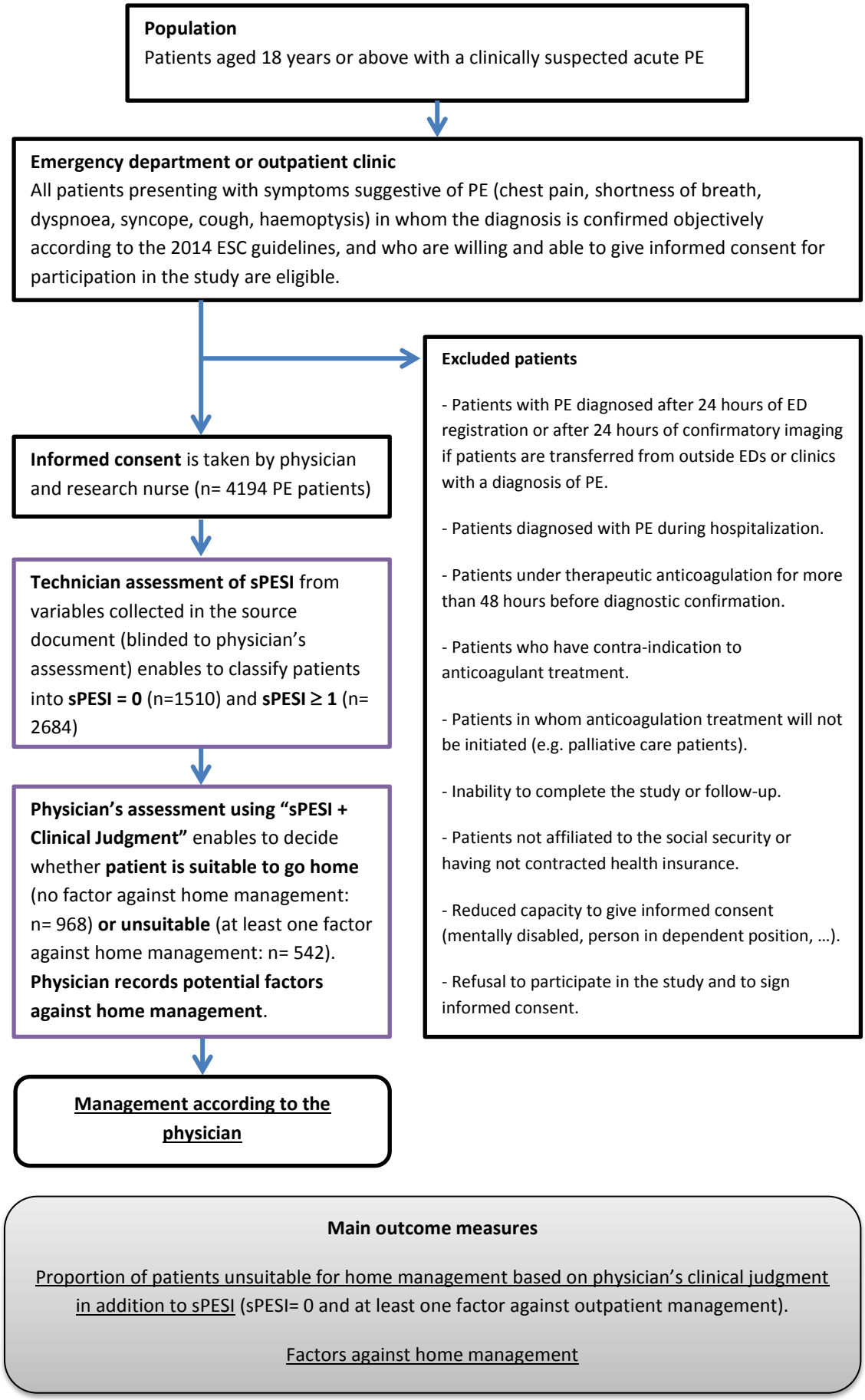


Table 8.1: Study Schedule.

	Visit 1: Enrolment	**Visit 2:** Day 2±1	**Visit 3:** Day 7±2	**Visit 4:** days 30±2
Case identification	x			
Check for study eligibility	x			
Obtain informed consent	x			
Demographic data[1]	x			
Medical history[1] - Comorbidities[1]	x			
Vital signs[1]	x			
Clinical symptoms and signs[1]	x	x	x	x
Variables related to sPESI[1]	x			
Variables related to clinician's gestalt[1]	x			
Laboratory tests and biomarkers[1]	x			
Venous ultrasound[1]	x			
Lung scans (CTPA, V/Q) [1]	x			
Transthoracic echocardiography[1]	x			
Risk assessment using s-PESI model[1]	x			
Physician's clinical judgment and decision[1]	x			
Actual management[1]	x	x	x	x
Actual treatment [1]	x	x	x	x
Death[2]	x	x	x	x
Symptomatic recurrent DVT/ PE[2]	x	x	x	x
Major and clinically relevant bleeding[2]	x	x	x	x
Clinical deterioration[2]	x	x	x	x
Unscheduled hospitalisation/ visits[2]		x	x	x
Adverse Events[2]	x	x	x	x
Length of hospital stay (+ rehospitalisation)[1]	x	x	x	x

[1]Standardised e-CRF, Variables related to clinician's gestalt include sPESI variables too [2]Outcome assessment by scheduled visits or by telephone calls using standardised questionnaire.

Participant identification

Population, patient and setting

Consecutive patients presenting to the emergency department or to the outpatient clinic with a clinically suspected acute PE. Patients will be identified by the case ascertainment strategy developed in my pilot study, using daily ascertainment in emergency departments, medical units and diagnostic units (Chapter 7). Patients will be assessed for study eligibility if they have a symptomatic acute PE confirmed by objective imaging testing, whether the PE is provoked or unprovoked. Patients are eligible if PE is diagnosed within 24 hours of ED registration or within 24 hours of confirmatory imaging if patients are transferred from outside EDs or clinics with a diagnosis of PE. The diagnosis criteria for the confirmation of PE will be in compliance with the 2014 ESC guidelines[16], which require a chest computed tomography angiogram showing at least segmental PE, a high probability ventilation perfusion scan or a venous ultrasonography or CT venography showing proximal deep vein thrombosis. Patients with unstable PE defined as a shock or hypotension (i.e. a systolic blood pressure < 90 mmHg or a systolic pressure drop by ≥40 mmHg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis) [16] will also be included.

Patient eligibility

Inclusion criteria

- Patients with a clinically suspected acute PE who are admitted to the emergency department or to the out-patient clinic and have the diagnosis of PE confirmed by objective testing as defined above, whether the PE is provoked or unprovoked.
- Male or Female, aged 18 years or above.
- Participant willing and able to give informed consent for participation in the study.

Exclusion criteria

- Patients with PE diagnosed after 24 hours of ED registration or after 24 hours of confirmatory imaging if patients are transferred from outside EDs or clinics with a diagnosis of PE.
- Patients diagnosed with PE during hospitalization.
- Patients under therapeutic anticoagulation for more than 48 hours before diagnostic confirmation.
- Patients who have contra-indication to anticoagulant treatment.
- Patients in whom anticoagulation treatment will not be initiated (e.g. palliative care patients).
- Inability to complete the study or follow-up.
- Patients not affiliated to the social security or having not contracted health insurance.
- Reduced capacity to give informed consent (mentally disabled, person in dependent position, …).
- Refusal to participate in the study and to sign informed consent.

Patient recruitment

Physicians in ED or medical units will give patients a study information sheet that outlines the nature of the study, including possible benefits and harms, details of ethics approval, and advice that they can decline to participate or withdraw at any time without this affecting their medical care. Physicians will then obtain verbal consent. Full informed written consent will be taken subsequently by a research nurse/ technician. The flow of patients through the study is shown in Figure 8.1.

Recruitment rate

A total of 4194 PE patients will be recruited over 36 months (115/ month) to allow final recruitment of 1510 low-risk PE patients. This will need 23 participating centres for a recruitment rate of 5 PE patients by month for each centre.

Strategies and management

Simplified PESI: In order to avoid contamination bias, variables for sPESI are recorded automatically on admission in the source document by the nurse or the junior doctor, then sPESI is scored by the research technician or assistant according to the data in this source document. The s-PESI model includes 6 items equally weighted (1 point for each item). If sPESI $\geq$1, the patient is considered at high-risk. If the total score is null (sPESI=0), the patient is considered at low-risk and suitable for out-of-hospital management according to sPESI. The type and number of sPESI variables will be recorded (Table A8.2).

Simplified PESI + Physician's clinical judgment: The suitability for out-of-hospital management is assessed by the physician using sPESI and her/his own clinical judgment, which might include the use of formal checklists. Their decision will take account of the estimated risk and the presence of factors against out-of-hospital management from the patient's social and medical information based on clinical, laboratory and imaging data. Physicians participating in the study should not use any another prognostic model for deciding whether the patient is suitable or not for home management.

Assessment: Strategies to be used within the first 24 hours are shown in the study flow (Figure 8.1). For each strategy, suitability for home discharge is determined as well as any factors that are against discharge. Finally, patients are classified as "outpatient suitable" or "outpatient unsuitable" by the physician.

Management: Management is done according to the decision of the responsible clinicians. Patients who are suitable for complete outpatient management would be discharged within 24 hours from diagnosis. Those who have at least one factor against home management would stay in the hospital for at least 24 hours. All patients will have a standardised anticoagulation treatment either by "Low Molecular Weight Heparin" (LMWH), oral vitamin K antagonist (VKA) or direct (anti-Xa or anti-IIa) oral anticoagulant (DOAC), taking account of contraindications and

precautions of use[16] [29]. The anticoagulants to be used are those that have Marketing Authorisation for the treatment of PE. It is important to note that all approved anticoagulants have similar effects on the risk of VTE. The choice of the type of anticoagulants (Table A8.6) and the decision to treat at home or in the hospital will be at the discretion of the physician in charge of the patient. If the decision has been taken to manage the patient as an outpatient, they will be discharged home within 24 hours either from the emergency department or from the Thrombosis Unit. All patients in either group of PE severity will be followed by the Thrombosis Unit at days 2 (±1), 7 (±2) and 30 (±2). Patients considered unsuitable for home treatment will have the same schedule for follow-up visits, except for the supplementary visits during their stay in the hospital.

Data collection at baseline

Patient characteristics are collected at baseline including demographics, comorbidities, risk factors, clinical findings and other factors that explain the decision against home management (Table 8. 2).

Reasons against out-of-hospital management may be related to VTE factors (like PE severity, high thrombotic risk, and need for hospital care or interventions for PE), contra-indications to anticoagulant treatment (high-risk of bleeding in general, contra-indications to LMWH or DOAC administered at home), comorbidities or medical conditions other than PE requiring specific hospital care, psycho-social or environmental barriers to treatment adherence or follow up and lack of healthcare organization that may make management at home difficult, and patient's preferences. Factors against out-of-hospital management come from different pre-cited references[9] [12] [21] [23] [30] [31] and from the British Thoracic Society 2017 Guidelines for the outpatient management of PE (in preparation)[20].

[20] Summary of recommendations (in preparation) *(https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-the-outpatient-management-of-pulmonary-embolism/)*

Reasons for home management of patients who meet hospitalization criteria may be related to physician's or patient's willingness to go home (young patient, professional activity, cancer patient).

Analysis will be performed for factors grouped within categories (Table 8.2) and for each individual factor (Table 8.3). The analysis will aim to capture the impact of Hestia criteria, which are indicated by a * in Table 8.2 and Table 8.3, since they are used against home management.

Table 8.2: Categories of factors against out-of-hospital management (from various references cited in the text[9 12 21 23 30 31] and from the British Thoracic Society 2017 Guidelines[21]).

VTE-related factors	***PE severity, thrombosis risk and need for hospital care or interventions for PE*** - Estimated high-risk PE based on sPESI (age > 80, cancer, chronic cardiopulmonary disease, heart rate ≥ 110/min, systolic blood pressure < 100 mm Hg, arterial oxygen saturation < 90%) - Estimated high-risk PE based on other criteria: hemodynamically unstable*, altered mental status, temperature <36° C, coronary artery disease, congestive heart failure, chronic lung disease, chronic renal insufficiency, cerebrovascular disease, malignancy, active malignancy (i.e. treated or palliated, or metastasis), history of VTE, DVT aspects ("massive DVT", DVT location, free-floating thrombus), PE aspects (saddle embolism, central PE, multiple PE), biomarker-related RVD/ischemia (BNP, NT-proBNP, cTnI, cTnT, hs-cTn), CT-RVD or TTE-RVD, right heart cavity thrombi, hypercoagulability (D-dimer level) - PE DVT symptoms (syncope, dyspnoea, chest pain, leg pain, high temperature, haemoptysis, pulmonary infarction, …) - Need for thrombolysis or embolectomy* - Need for vena cava filter insertion, - On anticoagulation at the time of the PE* - History of heparin induced thrombocytopenia*
Contra-indications to anticoagulants	***High-risk bleeding factors in general and contra-indications to LMWH or DOAC administered at home*** - History of bleeding (gastrointestinal, intracranial, …) - Active bleeding or high risk of bleeding*: uncontrolled hypertension, severe renal failure (creatinine clearance < 30 ml/ mn*), severe anemia (hemoglobin), thrombocytopenia (platelet count), cirrhosis or severe liver impairment* (liver enzymes), known bleeding disorder, associated therapy (steroids, non-steroidal anti-inflammatory drugs, antiplatelet therapy), ischemic stroke, recent major surgery. - Other contra-indications: anticoagulation allergy/intolerance
Comorbidities and medical conditions	***Comorbidities or medical conditions other than PE requiring specific hospital care > 24 h*** - Need for hospital care: Oxygen supply to maintain oxygen saturation > 90% > 24 h*,Intravenous pain medication > 24 h*, IV drug administration, transfusion - Treatment for other conditions than PE*[1] - Need for monitoring - Pregnancy*
Psycho-social or environmental conditions	***Barriers to treatment adherence or follow up and lack of healthcare organization that may make management at home difficult*** - Psycho-social*[2] barriers: patient age, homeless, cognitive disorders, psychological (anxiety) or psychiatric problems like psychosis, high alcohol consumption, use of illicite drugs. - Environmental conditions: geographic area too far from the centre, no telephone contact, no transport, no support, problem of compliance to treatment.
Patient's preferences **Physician's preferences**	***Patient/ family resistant to outpatient management*** ***Physician's preferences (explained or unexplained)***

A patient may have more than one factor. Hestia criteria indicated by*.*[1] and *[2] correspond to "medical or social reason for treatment in the hospital > 24 h" in Hestia.

[21] Summary of recommendations (in preparation) *(https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-the-outpatient-management-of-pulmonary-embolism/)*

Table 8.3: Individual factors against out-of-hospital management from various references cited in the text[9] [12 21 23 30 31] and from the British Thoracic Society 2017 Guidelines for the outpatient management of PE[22].

Haemodynamically unstable*, Heart rate ≥ 110/min, Systolic blood pressure < 100 mm Hg, Oxygen saturation < 90% or Oxygen supply to maintain oxygen saturation > 90% > 24 h* Temperature <36° C – Altered mental status PE/ DVT symptoms (syncope, dyspnoea, chest pain, leg pain, fever, haemoptysis, pulmonary infarction, …) Age > 80 Coronary artery disease, Chronic heart failure, Chronic lung disease, Chronic renal insufficiency (CrCl 30 to 60 ml/mn, CrCl < 30 ml/ mn) Cerebrovascular disease, Malignancy - Active malignancy (i.e. treated or palliated, or metastasis), History of VTE DVT aspects ("massive DVT", DVT location, free-floating thrombus), PE aspects (saddle embolism, central PE, multiple PE), Biomarker-related RVD/ischemia (BNP, NT-proBNP, cTnI, cTnT, hs-cTn, …) CT-RVD or TTE-RVD, Right heart cavity thrombi, Hypercoagulability (D-dimer level) On anticoagulation at the time of the PE* History of heparin induced thrombocytopenia* Need for thrombolysis or embolectomy* Need for vena cava filter insertion,
History of bleeding (gastrointestinal, intracranial, …) Active bleeding or high risk of bleeding*: uncontrolled hypertension, severe renal failure (creatinine clearance < 30 ml/ mn*), severe anemia (hemoglobin), thrombocytopenia (platelet count), cirrhosis or severe liver impairment* (liver enzymes), known bleeding disorder, associated therapy (steroids, non-steroidal anti-inflammatory drugs, antiplatelet therapy), ischemic stroke, recent major surgery. Other contra-indications: anticoagulation allergy/intolerance
Intravenous pain medication > 24 h* (or IV drug administration, transfusion) Treatment for other conditions than PE*[1] (hospital care, need for monitoring) Pregnancy*
Psycho-social*[2] barriers: patient age, homeless, cognitive disorders, psychological (anxiety) or psychiatric problems like psychosis, high alcohol consumption, use of illicite drugs. Environmental conditions: geographic area too far from the centre, no telephone contact, no transport, no support, problem of compliance to treatment.
Patient/ family resistant to outpatient management Physician's preferences (explained or unexplained)

A patient may have more than one factor. Hestia criteria indicated by*.*[1] and *[2] correspond to "medical or social reason for treatment in the hospital > 24 h" in Hestia.

[22] Summary of recommendations (in preparation) *(https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-the-outpatient-management-of-pulmonary-embolism/)*

Follow-up and outcomes

Follow-up: A 1-month follow-up period is scheduled with an assessment on admission and at days 2 (±1), 7 (±2) and 30 (±2). These will be by visit to the Thrombosis Unit of the participating center or by telephone call if the patient is not able to attend the visit.

Outcomes: Death, cause of death[32], venous thromboembolic events (VTE)[32 33], clinical deterioration, major and non-major clinically relevant bleeding[34-36], will be assessed by an independent central adjudication committee blinded to the classification done by the physician (combined strategy) and sPESI.

Death is classified as related to PE, cancer, major bleeding, cardiovascular events or other causes. PE will be regarded as the definite cause of death if confirmed by autopsy, a probable cause if an objectively confirmed recurrent event occurred before death, and a possible cause in case of sudden death unexplained by another cause or a condition other than PE[32].

VTE recurrence is considered as a new thromboembolic event (DVT, PE or both) that occurs in a symptomatic patient and is confirmed by objective testing (venous ultrasound, venography) showing for DVT a thrombus progression, a thrombosis in another site, or a re-occlusion after partial or complete recanalization; and for PE a new thrombus on CTPA or V/Q scan[32 33] i.e. a progression of the thrombus as compared to the initial state or involvement of other sites, with reference to an expert panel.

Clinical deterioration is a clinical worsening from a stable to an unstable haemodynamic condition that requires intravenous catecholamine infusion to maintain adequate tissue perfusion and prevent or treat cardiogenic shock, endotracheal intubation, or cardiopulmonary resuscitation[37]. The list of clinical deterioration events and interventions that typically require hospitalisation as defined by Kabrhel et al[23] will be used. This includes the following (in addition to the other outcomes): hypotension, hypoxaemia or need for respiratory support, endotracheal intubation or positive

pressure ventilation, cardiopulmonary resuscitation, use of intravenous vasopressors or inotropic, advanced cardiac life support measures, new dysrhythmia, new unstable dysrhythmia, thrombolysis/ thrombectomy.

Bleeding is defined as "major" when symptomatic and located in a critical organ (intraocular, intracranial, retroperitoneal, adrenal, spinal, pericardial, ...) or with a loss in haemoglobin ≥ 2 g/dl or requiring red blood cells concentrate or whole blood transfusion ≥ 2 units; or "clinically relevant non-major" when severe bleeding or overt bleeding is objectively documented requiring hospitalisation or prolongation of hospitalisation but not including the criteria for major bleeding. Otherwise, bleeding is considered as "minor" [34-36].

Unscheduled hospitalisations/ visits and the reasons for rehospitalisation (such as clinical deterioration) are to be recorded.

Length of hospital stay: This corresponds to the number of days spent in the hospital including rehospitalisation. They are classified as follows: < 24 hours, 1 to 5 days, 6 to 9 days and ≥ 10 days.

Major adverse cardiovascular events: Cardiac death or acute coronary syndrome/myocardial infarction, stroke and transient ischemic attack are considered as major adverse cardiovascular events.

Outcomes measurements

Primary endpoint:

- Proportion of patients who have sPESI=0 and at least one factor against out-of-hospital management, and factors against outpatient management among these patients (to be shown as % with 95% CI).

Secondary endpoints:

- Proportion of patients who have sPESI=0 and no other factor against home management (%, 95% CI).
- Adjudicated 7-day and 30-day adverse events (as defined above) in patients suitable (sPESI=0, no extra factor) and those unsuitable (sPESI=0, at least an extra factor) for home management among patients at low-risk PE and factors associated with adverse events (predictors) (%, 95% CI).
- Length of hospital stay in both patient categories of low-risk sPESI group (including unscheduled hospitalisations within the period of observation) by 7 days and 30 days after admission (median, IQR).
- All-cause death, PE-related death, VTE events and bleeding as single outcomes at different time-points within the two subgroups (%, 95% CI).
- Consistency on the judgment between sPESI alone strategy (as assessed by the research technician) and "sPESI + Clinical judgment" (as assessed by the physician) for classifying patients suitable and unsuitable for home treatment in the whole cohort of patients with PE. If clinician's intuition is to be shown to be a useful addition to sPESI, it needs to be consistent enough with sPESI (alone) to inform decisions about patient management. This will be assessed by the Kappa coefficient of agreement (0.95 CI).

Sample size

Hypotheses to be tested

The null hypothesis to be tested is that a strategy combining sPESI and clinician's intuition (the "combined strategy"), which is based on the assessment of the risk of events in combination with other factors against home management, will yield the same decisions as a strategy based on sPESI alone, which relies solely on the sPESI variables to assess the risk of events. A further null hypothesis is that supplementing sPESI with consideration of a formal list of "relative contraindications"[21] would not identify patients with an even lower risk who might be suitable for complete outpatient

management. If these null hypotheses are disproved, identifying the supplemental factors against home management in low-risk PE should help to identify potential improvements to the sPESI prediction model or at least highlight its limitations.

Sample size for assessing the proportion of patients unsuitable for outpatient management among those at low-risk PE (i.e. sPESI=0 and at least one factor against home management)

The sample size needed is calculated based on a test for 1 proportion: 1-sample, 1-sided (Power 1-ß: 0.8; Type 1 error rate α: 5%)[23].

With Hestia criteria added to sPESI[13], 69% of low-risk sPESI patients would be suitable for complete outpatient management (ie sPESI=0 and Hestia=0). When factors against home management are added to PESI[21], 64.1% of patients are suitable for outpatient management (ie sPESI=0 and no "relative contraindications") as opposed to 35.9% who are not suitable (ie sPESI=0 and at least one "relative contraindication") (Table 8.4, Figure 8.2). Considering that 36.8 % of patients are judged to be at low-risk using sPESI alone (Summary estimate – Chapter 4) and assuming the same distribution of proportion of patients suitable for home management with sPESI as with PESI, leads to an estimate that 23% of patients in a full cohort of patients presenting to hospital with sPESI=0 would be suitable and 13% would be unsuitable for outpatient management.

Table 8.4: Suitability for outpatient management according to "sPESI + Clinical Judgment" in patients at low-risk and high-risk PE (sPESI groups)

Subgroups	1	2	3	4
sPESI	=0	=0	≥1	≥1
sPESI + Clinical Judgment	outpatient suitable	outpatient unsuitable	outpatient suitable	outpatient unsuitable
Proportion	0.23	0.13	~0	0.64

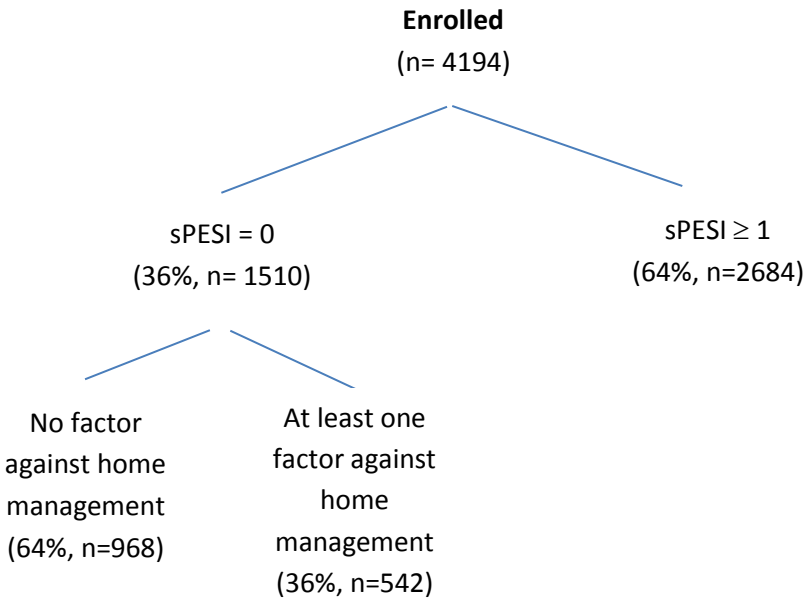
Eligibility for outpatient treatment depends on physician's judgment (including sPESI). Around 36 to 37% of patients are at low-risk sPESI (Chapter 4) and 36% of patients at low-risk (i.e. 13% of the whole cohort) are unsuitable for outpatient management[21].

[23] http://powerandsamplesize.com/Calculators/Test-1-Proportion/1-Sample-1-Sided

Assuming 0.69 as the proportion of patients who are suitable for outpatient management based on the combined strategy among those with low-risk PE (sPESI= 0) and defining a minimum proportion of 0.64 as lower limit of this proportion (i.e. null hypothesis proportion 0.64-0.69, true proportion <0.64), a study population of 542 patients unsuitable for out-of-hospital management among low-risk PE with sPESI (i.e. with sPESI= 0 and at least one factor against home management) will provide 80% power to reject the null hypothesis that the proportion is > 0.64 at an overall one-sided significance level of 5% using a binominal test. This would require a total sample size of 1510 low-risk PE patients, and an overall sample of 4194 PE patients, who would be recruited over 36 months (Figure 8.2). In order to enrol 4194 patients, I expect to assess for eligibility 5242 patients assuming that 20% (n= 1048) will be excluded

This sample size will allow an assessment of factors against home management, adverse event rates and predictors, and agreement between the "sPESI + Physician's clinical judgment" and the "sPESI alone" strategy. For comparison purposes, the sample size for assessing event rates in patients suitable and those unsuitable for outpatient management among low-risk sPESI patients is displayed in Appendices (Table A8.7) as well as the sample size for assessing consistency (Table A8.8) (Appendices: Sample size - supplementary material).

Figure 8.2: Flowchart for sample size estimation



Statistical analysis plan

Baseline characteristics

Baseline characteristics will be collected in the whole population sample and in subgroups and will include demographic data, medical data (variables for context, comorbidities, haemodynamic status, vital signs, right ventricular dysfunction/ myocardial injury, biological and imaging-based markers of thrombus burden), and social data (Table 8.2). Categorical variables will be reported as frequency and percentage with 95% confidence interval (95% CI). Continuous variables will be reported as median, interquartile range, mean and standard deviation.

Outcome variables and outcome parameters

The proportion of patients in subgroups will be presented as percentage with 95% CI.

Factors against home management will be presented with the percentage (and 95% CI) of patients for whom they were reported. Hestia criteria will be accounted for in the analysis as single outcomes and outcomes associated with other factors.

The kappa coefficient[38] will be used to measure ***inter-rater agreement***[24] between "sPESI alone" as assessed by the research technician and "sPESI + Clinical judgment" as assessed by the physician. The Kappa value with (95% CI) will be calculated and will be interpreted as follows[39]: < 0.20 (Poor), 0.21 – 0.40 (Fair), 0.41 – 0.60 (Moderate), 0.61 – 0.80 (Good) and 0.81 – 1.00 (Very good).

Event rates (mainly adverse events, all-cause death) in the whole population and in subgroups according to the combined strategy will be expressed in % (95% CI). In each subgroup (mainly in the low-risk sPESI "outpatient unsuitable" subgroup), the event rates (N with % and 95% CI) for

[24] Kappa= (% observed - % expected) / (1 - % expected)

patients with and without specific factors will be assessed. Univariate and multivariate logistic analyses will be performed to assess whether there are independent factors associated with adverse events in the whole cohort, but this will not be possible in the low-risk outpatient unsuitable subgroup because the event rate is likely to be very small for them. These analyses will be done for the 7-day and 30-day adverse event rates, and all-cause mortality rates, because factors associated with short-term adverse events differ from those associated with 30-day all-cause death according to Kabrhel et al[23]. Univariate analysis will be performed on all variables that may be clinically related to adverse outcomes and variables with p values <0.2 will be included as potential predictors. The final model will include variables that are significant at the 0.05 level. Cut-off values for continuous variables will be provided from those found in the systematic review (Chapter 4 and Chapter 5) and if not available from exploratory data analysis.

Lengths of hospital stay (median and IQR, mean and SD) will be measured for the whole population and within each subgroup.

If needed for comparison, a two-sample t-test will be used for continuous variables and a chi-squared (chi2) or Fischer exact test for categorical variables. When needed (for skewed variables and small numbers), analysis will be done on log-transformed data or a two-sample rank-sum Wilcoxon Mann-Whitney U test. Results will be considered statistically significant at two-sided p-value <0.05.

Statistical software

Statistical analyses will be performed using Stata/SE (StataCorp LP).

ETHICS AND REGULATORY APPROVAL

The study would be conducted in accordance with the principles of the Declaration of Helsinki and in accordance with relevant local laws and regulations and with the recommendations of ICH Good Clinical Practice. The protocol, informed consent form, participant information sheet and any proposed advertising material would be submitted to an appropriate Research Ethics Committee and the local Institutional Review Board for approval prior to the start of the study. Study staff will ensure that participants' anonymity is maintained and participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the Case Report Form, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel.

DISSEMINATION

The study would be registered at https://www.clinicaltrials.gov/ and its findings would be disseminated through peer-reviewed journals, and national and international conference presentations. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, media releases and any other publications arising from the study and authorship will be determined in accordance with the ICMJE guidelines with other contributors being listed in the acknowledgements.

SUPPLEMENTARY MATERIAL

Should this study go ahead, additional material would be prepared to describe the study procedures (including safety reporting, data management, quality assurance procedures, selection of centres, finance and insurance).

DISCUSSION

This study would offer a potential solution to a limitation of prognostic models (namely sPESI) in the management of acute PE patients, by determining the proportion of patients at low-risk sPESI who are not suitable for home management and by identifying the extra factors against home management that are not included in the model. Formally adding clinical judgment to sPESI may help identify patients with PE with an even lower risk of short-term and long-term adverse outcomes than is achieved with sPESI alone.

The results of this study would be compared with those obtained in studies that combined sPESI and Hestia checklist[13], PESI and "relative contraindications"[21] to home management, "study exclusion criteria" in adjunction to PESI[9] and other factors (as in the study of kabrhel et al[23]). The results would provide an evidence-base from which to develop PE care pathway recommendations and may be useful in standardizing care.

Although one potential limitation of the proposed study is that the total number of patients needed would make it as large as the largest studies in the area to date (which might make it particularly difficult to implement unless there is a concerted effort by the international community), its strengths are that it would be prospective and would include consecutive patients with acute PE. Furthermore, it will avoid selection bias and maximise the number of potentially

eligible patients who are screened by using the case ascertainment strategy developed in the study described in Chapter 7.

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Chapter 9: Discussion and Conclusions

INTRODUCTION

The overall aim of the thesis was to present a series of research studies, including systematic reviews and new prospective research, to help with the selection of the most appropriate prognostic models and strategies for risk-stratifying patients with acute PE for outpatient or hospital management, or intensive monitoring and more aggressive therapy (Chapter 1).

This final chapter provides a summary and general discussion about the importance and the limitations of my findings in the context of the existing literature, and the implications that arise for clinical practice and for clinical research. It is presented in three parts: 1/ Summary of research findings: evidence about prognostic models and comparison of their predictive performance, prognostic models in clinical practice, and development methods relative to prognosis assessment in acute PE; 2/ Implications for clinical practice for risk stratification and management; and 3/ Implications for future clinical research, covering methodology issues and ways to improve the assessment of prognosis.

SUMMARY OF RESEARCH FINDINGS

The findings of my research can be summarized following the outline in chapter 1.

1/ What is the evidence about prognostic models in acute PE and how do they compare in terms of performance?

As shown in the early chapters, several prognostic tools are used to assess the risk profile of a patient with acute PE. These include individual prognostic markers (Chapter 2), prognostic models and hospital checklists (Chapter 4), and clinical gestalt. Not all existing prognostic strategies have undergone a model construction study phase and, although some have been validated, it is rare for them to have been tested in impact studies (Chapter 4).

The value of individual prognostic markers as independent prognostic factors remains uncertain and their ability to predict outcome and guide management on their own is controversial. Individual prognostic markers that have been most assessed are age, comorbidities, vital signs, biomarkers (cTn, hs-cTn, BNP, NT-proBNP, H-FABP, D-dimer) and markers for imaging-based RVD (TTE, CT) and thrombus burden (CT, US-DVT) (Chapter 2). My systematic review of systematic reviews of individual prognostic markers showed promising but inconsistent results for biomarkers of right ventricular dysfunction or myocardial injury for identifying risk groups. Imaging tests seem less powerful. As numerous prognostic markers may change a patient's risk profile, individual biomarkers may only be helpful when used in addition to prognostic models and strategies (Chapter 2).

Based on my systematic review of prognostic models, the most validated prognostic models and strategies are the original[1] and the simplified[2] versions of the PESI model. They provide a low event rate in the low-risk group and allow for early discharge or complete outpatient management (Chapter 4). ***This is in agreement with the ESC guidelines[3].*** Using meta-analyses, I showed that the overall 30-day mortality rate was 1.3% [0.8 – 2] in the low-risk group and 10.4% [8.8 – 12.1] in the high-risk group for PESI (12 studies). It was 0.8% [0.4 – 1.5] in the low-risk group and 8.8% [7.1 – 10.8] in the high-risk group for s-PESI (15 studies). A low overall 30-day mortality rate in the low-risk group was obtained with the PE Prognostic Algorithm 0.8% [0.2 – 1.7] but at the expense of a lower overall proportion of patients 21.8% [19.1 – 24.6] (4 studies) in this risk group; compared to 41.1% [38.9 – 43.2] for PESI and 36.8% [34.1 – 39.6] for sPESI. Models

originally not specific to the prognosis (clinical prediction rules used for the diagnosis of PE[4]) or to the domain of PE (Charlson's index[5 6], GRACE[7]) and hospital criteria checklists (Davies[8] and Hestia[9 10]) lack external validation. Hestia is a promising strategy for outpatient management given the low event rate i.e. 0.4% [0 – 1.4] among patients who do not meet any of the hospitalisation criteria and the high proportion of patients who may be managed as outpatients estimated at 37.6% [34.6 – 40.5] (2 studies) (Chapter 4).

Novel and updated models specifically developed for normotensive PE patients improve the ability for identifying patients at lower risk for early death or adverse outcome and those at higher risk. Lower and higher risk groups can be obtained by shifting the cut-off along the risk scale for GPS[11 12], PESI[1], PREP[13], ESC 2008[14] and Bova[15] models; by adding individual prognostic markers to PESI[12 16-22], sPESI[23-25] and PREP[13] clinical model; or by integrating individual prognostic markers of right ventricular dysfunction or myocardial injury and thrombus burden into existing models or with other clinical variables (systolic blood pressure, heart rate) as in the PREP[13], eStiMaTe high[18], FAST 3[26 27], Bova[15] and ESC 2014[3] models. **Improving the performance provides more appropriate event rates for the different risk groups but at the expense of a decrease in the proportion of patients within this risk group**. Therefore, improvement in efficacy is associated with a decline in efficiency. Large validation and impact studies are needed to assess these novel strategies (Chapter 4).

Few studies have examined the impact of prognostic models or strategies on outcomes and current evidence, as included in my systematic reviews, highlights the remaining uncertainty about their actual impact on patient outcomes (Chapter 4). For instance, in the OTPE randomized trial[28], PESI proved clinically useful for selecting patients at low-risk who can be managed as outpatients; but the quality of evidence was ranked as moderate[29] or even very low[30] due to the lack of blinding of outcome assessors, the small number of events with imprecision in the confidence interval and the small sample size. Therefore, the OTPE study does not provide

sufficient evidence to assess the efficacy and safety of outpatient versus inpatient treatment for acute PE on overall mortality, bleeding and recurrence of PE adequately[30]. The small number of events may be related to the highly selected population due to the eligibility criteria for the trial. Outpatient treatment of PE patients selected by the Hestia criteria[31] (alone or combined with NT-proBNP) was associated with a low risk of adverse events but similar comments about sample size, study power and eligibility criteria for the trial apply. PEITHO[32], another impact study, used the ESC 2008 model to select patients at intermediate-high-risk from a group of normotensive PE patients. Management strategies based on this selection were not successful in a randomised trial comparing a thrombolytic versus heparin[32]. This may be related to the lack of predictive ability for the model (inappropriate selection of patients at risk of death from PE), or the lack of effectiveness of the treatment even if patients who are likely to respond to therapy are identified.

In a sensitivity analysis using net benefit[33] [34] (which is a decision-analytic measure), across a range of threshold values for low-risk categories, reference models PESI and particularly s-PESI performed better than other competing models in direct comparisons (Chapter 5). There was an incremental value for prognostic markers most often when added to PESI than to sPESI. This analysis sets the limits for whether it is worth using one model instead of another one given a range of threshold probability values and the population event rate.

2/ How do prognostic models work in clinical practice?

My opinion and practice survey among emergency and expert physicians showed that the most used prognostic tools were prognostic models (30%) and clinical judgment (36%) with PESI, s-PESI and the ESC guidelines as the most used prognostic models. More than half of respondents (57%) used prognostic models in more than half of all cases, but ***62% used prognostic indicators in addition to prognostic models*** (Chapter 6). Independent predictors for the frequency of use of prognostic models were group affiliation to European versus French societies for emergency medicine (adjusted odds ratio: 0.43 (0.23 - 0.81)) and type of hospital (adjusted odds ratio for

university versus non-university hospital: 2.48 (1.37 - 4.47)). Although most physicians were aware of the characteristics for a good prognostic model, 52% reported ***lack of familiarity with the models***. Many physicians reported ***clinical judgment (60%) or hospital checklists (73%) as being as good as or better*** than prognostic models, but that ***few patients were discharged early or treated fully at home***. ***The survey reflects the uncertainty among physicians about a reliance on the use of prognostic models on their own in clinical practice.*** It provides a new evidence base for implementing and evaluating strategies to improve prognostic risk assessment for the management of acute PE patients, and highlights the ***need to consider the impact of using clinical judgment and hospital checklists in future clinical research***.

3/ Where to go further in the development and validation of prognostic models in acute PE?

In prognosis and prognostic models studies, between-study heterogeneity in patient characteristics and inconsistency in reported event rates for the same outcome and follow-up period may be related to patient selection (selection bias). In the absence of reliable case-ascertainment, population and within-risk group event rates may be underestimated, and prognosis and prognostic models may be overoptimistic. ***It is important, therefore, to have an appropriate and well-reported ascertainment strategy in any future research, recognising, though, that this might apply to the specific setting of that research and may be not relevant in other settings with different care pathways.***

The ascertainment strategy I developed to capture all incidental and recurrent VTE events related to symptomatic PE in my hospital and to obtain prognostic information at baseline and on follow-up on the identified patients was effective in identifying additional 8% patients with PE (Chapter 7). These patients had different clinical characteristics (acute medical conditions, cancer, cognitive disorder) and were at higher risk at baseline (unstable haemodynamic status, altered mental status, vital signs, PESI and sPESI scores). They had increased mortality rates, in both the whole population sample as mentioned below and in the subgroup with stable PE. The patients found by

the more intensive approach were suffering from serious conditions and may follow different care pathways, and are usually not included in randomized trials or cohort studies of PE, raising uncertainty about the applicability of the current evidence base to decisions about managing their PE.

Population event rates in the whole study sample were higher than might be expected owing to the extensive ascertainment strategy and the inclusion of the full series of consecutive patients in my analysis. I found that the all-cause mortality rate was 3.6% at 8 days, 10.4% at 1 month, and 16% at 3 months. This was lower than the in-hospital all-cause mortality in my systematic review of prognostic models (6%, 95% CI: 4.8 – 7.4) (31 studies) (Chapter 4), and similar to the 30-day all-cause mortality rates in the derivation (9.2%) and the internal validation (9.5%) samples of the original PESI model which included a large cohort of 15,531 patients. The reported mortality rates in cohort studies and registers vary from 2.7% to 6.7% at 1 week[35-38], from 5.4%[36] to 8.6%[37] at 1-month, and from 8.2% to 16.2% at 3 months[35 37 39-41] (Chapter 2). Some studies have suggested that the mortality rate may be even higher: 33.2% and 37.2% respectively at 1 month and 3 months in a US population-based study[42], 21% at 3 months (control subjects 1.3%) in the Swedish national cohort[43], and 4.2% at 7days, 8.6% at 1 month and 16.2% at 3 months in the Tromsø study[37].

As mentioned above, the high event rates in my study can be explained by the patient characteristics related to the poor clinical conditions, comorbidities and haemodynamic status. In general, population event rates are likely to depend on population selection, which is conditional on the patient care pathway in the specific setting. Complete case-ascertainment in a specific setting may help to recruit all patients from the different services where they have been admitted and this may result in different risk profiles and event rates in the whole population sample and in the different services where patients were detected. Although the specific event rates may not be applicable to other settings, my findings show the importance of clarity in the ascertainment

strategy and in describing the population in any study. The high event rate in my study in the whole PE cohort (501 patients) and in the stable-only PE sample (472 patients) is consequent to the case-identification and follow-up of all patients with PE in the hospital using my specially developed ascertainment strategy. The relevance of my research to other settings, and to the general issue of using research and data from elsewhere when making decisions about the management of patients with acute PE in a specific hospital, is shown in particular by the need it highlights to consider various factors that may impact on the short-term population event rate and explain its variability across studies. These include the type of study (e.g. whether the study is a prospective or retrospective cohort, a register or a randomized trial), patient recruitment (including care pathway, geographic area, referral, setting, ascertainment strategy), eligibility criteria (e.g. whether patients were enrolled under very strict inclusion and exclusion criteria), diagnostic strategy for PE, patient typology and risk profile, type of treatment and management, duration of follow-up, and types of outcome and how these were assessed.

In my study, all-cause mortality rate was also higher in the PESI and sPESI low-risk and high-risk groups, in both the whole cohort and the subgroup of patients with stable PE. This suggests that implementation of such a strategy for the identification of PE and for obtaining good quality prognostic information at baseline and on follow-up is essential for both internal and external validity of a study's results (Chapter 7).

Finally, there is a lack of research into the use of clinical gestalt and how it performs compared to prognostic models or hospital checklists. Therefore, my programme of research culminates in a proposal for a new study (Chapter 8) to assess the added value of a strategy that compares clinician's intuition and sPESI (combined strategy) to s-PESI alone for selecting patients with acute PE for out-of-hospital management. I chose s-PESI as the reference strategy because it is the simplest recommended method for use by the ESC guidelines[3], the model to which hospital checklists have been compared[9 44], and the model that was the most validated and provides the

best safety in the low-risk group in my systematic review (Chapter 4). The need to evaluate formally a strategy that combines clinician's intuition with sPESI is because direct comparison between clinician's intuition and sPESI may lead to contamination of clinician's intuition. The primary objective of the proposed study is to assess the proportion of patients unsuitable for outpatient management among those at low-risk PE (i.e. the proportion of patients having sPESI= 0 and at least one factor against home treatment), and to identify factors that oppose out-of-hospital management in this patient group. Identifying the supplemental factors against home management in low-risk PE should help to identify potential improvements to the sPESI prediction model or at least highlights its limitations. The secondary objectives are to assess: 1/ the risk of adjudicated 7-day and 30-day adverse events in patients suitable and those unsuitable for home management among patients considered as low-risk PE (sPESI=0) and identify factors associated with adverse events (predictors); 2/ the length of hospital stay in both patient categories; and 3/ the consistency between a strategy based on sPESI and that based on sPESI and clinical judgment. The study would be a prospective cohort observational study (one sample) and patients would be identified through the case ascertainment strategy developed in the pilot study (Chapter 7), with daily ascertainment in the emergency department, and in medical and diagnostic units. Reasons against home management will be recorded and a list of explanatory variables will be provided with regard to PE severity and thrombotic risk, contra-indications to anticoagulant treatment, needs for hospital care for comorbidities, psycho-social and environmental barriers for home management, and physician's and patient's preferences. The main assessment would be on enrolment, then on seven days (±2 days) to provide the early phase outcome, and follow-up would continue for one month. As shown in Chapter 8, the study would require the inclusion and follow-up of 542 "low-risk" patients who are unsuitable for out-of-hospital management (i.e. sPESI= 0 but at least one factor against home management) based on the binomial test for 1 proportion: 1-sample, 1-sided (Power 1-ß: 0.8; Type 1 error rate, α: 5%). This would require a

total sample size of 1510 low-risk PE patients, and an overall sample of approximately 4100 PE patients.

IMPLICATIONS FOR CLINICAL PRACTICE

This thesis raises important points relevant to the use of prognostic models in acute PE patients and their importance for prediction and for clinical decision-making. The objective of clinicians is to decide whether a patient with a diagnosis of acute PE should be treated as an outpatient (if at low-risk or suitable for out-of-hospital management) or in the hospital (if at high-risk) and in which department (conventional treatment ward, monitoring unit or ICU); and how he will be treated (by LMWH, OAC, DOAC, thrombolytics, etc …), which is also dependent on the level of risk. The fundamental objective of the models and strategies is to identify patient suitability for different types of management.

However, my research shows that, to date, the ideal and perfect model or strategy for PE prognosis has not been clearly identified and might not yet exist. Such a model should be valid and useful, and, for practical reasons, it should be easy to use, feasible, reproducible, readily available, and affordable.

Identifying patients for early discharge or outpatient management

Studies showed a potential for discharge in low-risk PE patients through the use of validated models and mainly models tested in impact studies. PESI and sPESI are the most widely validated models for identifying low-risk PE patients, but there is uncertainty about how to choose between them in clinical practice.

PESI is the model that was constructed on the largest patient population and settings. Although the original study was a retrospective analysis where diagnostic validity of PE and patient

management could not be adequately assessed, the model has been widely externally validated and updated. PESI provides good discriminatory power and risk gradient. At the suggested cut-off level, 41% of patients are categorized as low-risk, with a low incidence of events and a high sensitivity. PESI is reproducible with a good inter-rater agreement[45 46]. It is the only model that has been assessed and shown to be useful for informing clinical decisions in a randomized trial, but the context of that study was far from that of routine practice in terms of patient selection and management, and, possibly, effectiveness. Furthermore, the PESI model is complex because of the number of variables (which might not be all available to physicians), the various points assigned to the variables and the use of various cut-offs.

sPESI is simpler, memorable and readily available, and, therefore, more practical than PESI. It was derived from PESI using a large cohort, and has also been widely validated and updated in several studies. Agreement between the original PESI and the simplified PESI is fair[47]. About 35% of patients are classified at low-risk by sPESI and there is a slightly lower incidence of outcomes in this risk group as compared with PESI. The sensitivity is high. However, the clinical utility of sPESI has not been assessed in an impact study.

As the event rates in some settings may still be high for outpatient management with either PESI or sPESI, these models may need to be used by shifting the cut-off to a lower level for PESI or by combining a biomarker such as BNP[13 16 48] NT-proBNP[24 49], hscTnT[23 25] or H-FABP [26 27] to either model to accurately identify lower risk patients for safe outpatient management, at the expense of reducing the proportion of patients who benefit from. Most of these biomarkers are readily available in current practice.

There are controversies around the use of prognostic models in clinical practice and a potential role remains for hospital checklists and clinical judgment when considering the appropriateness of outpatient management for a specific patient [29 50]. Clinician's intuition and hospital checklists are based on the assessment of both the risk of events and factors against out-of-hospital

management, while prognostic models like sPESI only assess the risk of the events based on death-related prognostic variables. The proportion of patients suitable for out-of-hospital management among those at low-risk sPESI is 0.69 when the prognostic model is combined with a hospital checklist (sPESI= 0 and Hestia = 0) and 0.64 when it is combined with relative contraindications (sPESI=0 and no extra factor). In a single study[9], the Hestia checklist identified 53% of patients as low-risk with 0.8% [0.2 to 3.2] 30-day all-cause mortality. It safely selected patients with PE for outpatient treatment irrespective of right ventricular dysfunction[31 51]. These findings were replicated in another study[52] (NPV 100%) but only 25.8% of patients were identified as low-risk.

Identifying patients for hospital management and for more aggressive therapy

Prognostic models seem to do less well at identifying high-risk PE patients and at indicating adjusted and aggressive treatment or management. As mentioned above, the PEITHO study[32] was a randomized trial using the ESC 2008-guidelines which failed to demonstrate an impact on patient management in terms of mortality in normotensive PE patients. This might be explained by the low mortality rate in the enrolled group and highlights the need to find a model that helps to select patients at highest risk of adverse events. Other things to consider are the response to treatment in terms of effectiveness and of harm, the need to select patients with a higher response rate and to use the thrombolytic regimen with the lowest dose.

In order to identify patients at increased risk of all-cause or PE-related mortality or complicated course for a given prevalence from among those with normotensive PE, we need to set the risk at higher cut-offs or to combine additional variables like clinical[15], biological[13 15 16 18 26 27 48] or imaging-based prognostic markers of RVD/ischemia[13 15 16] to the existing models. As a consequence, 25-30% of patents have a PE-complicated course (PROTECT study[48], Bova's study[15]) but the proportion of patients at high risk decreases to 3-5%. This patient profiling also needs to consider

response to treatment and bleeding risk level, because these patients might be at very high risk of bleeding.

What about the models recommended by the ESC?

The ESC 2008 recommendations[14] for risk stratification of stable PE into low-risk, intermediate-low-risk and intermediate-high-risk were not based on a model construction study. Furthermore, failure rate in the low-risk category is high in validation studies and is not reassuring, while classification into intermediate-low-risk or intermediate-high-risk inappropriately assigns the same value for RVD imaging tests and biomarkers, and for natriuretic peptides and troponins without previous validation to provide a robust evidence base for this. The ESC 2014 model[3] combines either PESI or sPESI with the ESC 2008 model, with an optional, additional assessment of biomarkers for the PESI or sPESI low-risk group. This patient risk-category may be classified at higher risk with positive RVD-related tests, thereby avoiding a decision to discharge the patient. This situation is not likely to be infrequent because PESI or s-PESI variables may remain unchanged despite the presence of RVD. Finally, the ESC 2014 model assigns the same predictive value for PESI and s-PESI, allowing for a 1-month mortality rate of 1.3% with PESI and 0.8% with s-PESI, and the value and limitations of the ESC classification into intermediate and intermediate-high-risk have been mentioned above.

How to manage patients with acute PE?

When managing patients with acute PE (figure), we need to answer the following questions:

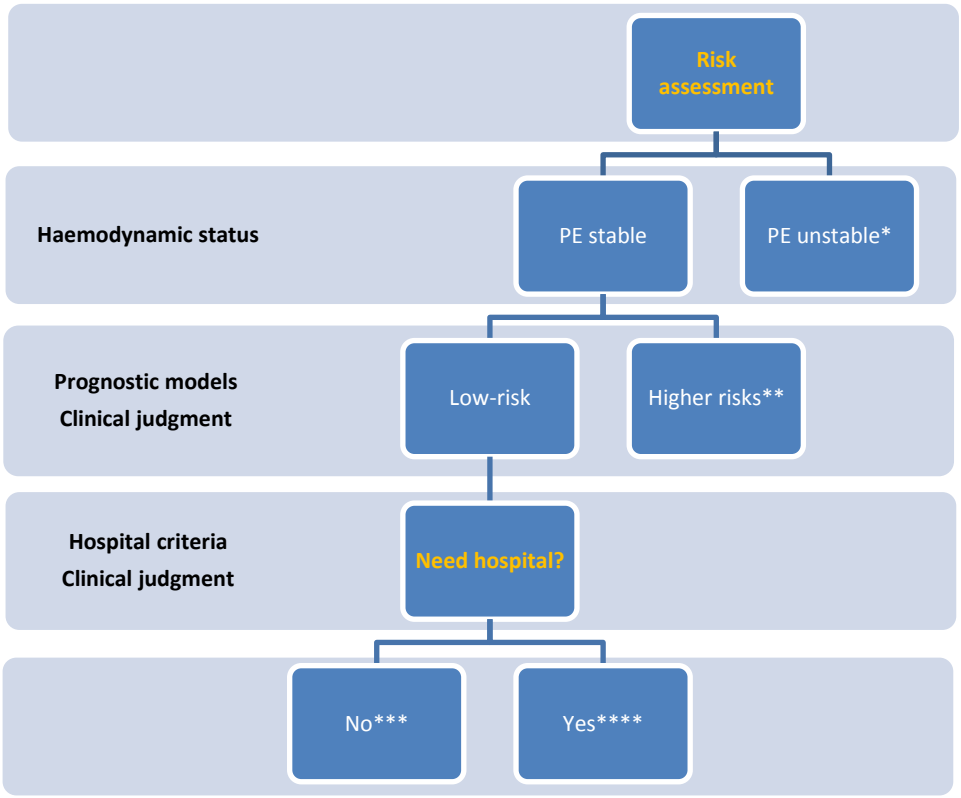
1) Does the patient have an unstable haemodynamic status? This type of patient needs rapid diagnostic and therapeutic management and is suitable for aggressive treatment under monitoring in an intensive care unit because of the high-risk of death in the short term according to the ESC guidelines[3 14].

2) If the patient is stable, is he at low-risk of death within the first month (or at low-risk of death, recurrence, or major/ clinical relevant bleeding within the first 5-10 days)? Prognostic models and clinical judgment would help to answer this question.

3) If the patient is at low-risk, does he need to stay in the hospital? Both hospital criteria and clinical judgment will help to answer this question conditional on the type of care that would be delivered out of the hospital, such as availability of a thrombosis centre, clinical surveillance, and potential for anticoagulation and other medications management; which is dependent on the local health system. Although only patients at low-risk could be discharged early or managed entirely as outpatients, the substantial role for treatment by direct oral anticoagulants at a fixed dose without anticoagulation monitoring means that this should increase the proportion of patients who could benefit from out-of-hospital management.

Normotensive patients who are managed in hospital and thought to be at risk of a complicated outcome may be admitted to a monitoring unit where they could be given aggressive treatment if they deteriorate clinically. Thrombolytic therapy should not be given to normotensive PE patients at risk who have no clinical deterioration, because the risk of major bleeding outweighs the hemodynamic benefit[32 53].

Figure: Ideal management strategy for patients with acute PE



*ICU, aggressive therapy (thrombolytic therapy if there is no contraindication, otherwise endovascular treatment if available), **Discuss optimal management for the patient i.e. either monitoring then escalating therapy if there is a clinical deterioration (harm to benefit for a patient) or usual care, *** outpatient management, **** usual care in the hospital.

IMPLICATIONS FOR FUTURE RESEARCH

Future research needs to answer the question of how to overcome ongoing challenges and uncertainties in prognosis prediction and in the management of patients with acute PE.

Methodological issues: What should be done?

The development of a strategy for assessing prognosis should follow an acceptable standard[54-64] at each phase of development, including the design, conduct, analysis, reporting and assessment of prognostic studies (Chapter 3). This will lead to more consistency among studies in acute PE, where methodology flaws have been common to date (Chapter 4).

When applied to PE, standardization issues should consider the population of interest, the outcome and time-point, the prognostic tools, and the study design; and it is relevant to assess all outpatients admitted to the hospital who have a diagnosis of acute PE and a stable haemodynamic status. Complete case-identification using the case-ascertainment strategy described in chapter 7 will help with the inclusion of a complete series of consecutive patients and reduce selection bias. As the management of stable PE in outpatients is different from that of patients who develop PE in the hospital, it is preferable and more relevant not to mix outpatients and inpatients in these studies. The same holds true for stable and unstable PE; which should not be mixed. To avoid misclassification and over-diagnosis of PE, the diagnostic management strategy should follow existing guidelines[3 14] and predefined standard criteria should be applied. Definitions of outcomes also need be standardized so that they become consistent across studies (e.g. PE-related adverse outcomes, adverse outcomes, adverse clinical outcomes, complicated clinical course, and complicated clinical events). A consensus statement would help to define the relevant outcomes (types of outcomes, single or composite outcome) and time-points to be considered for a specific clinical question more precisely. Consensus is also needed on the acceptable risks for these outcomes when choosing the most appropriate management in stable

PE (for example, highest acceptable risk for outpatient management, lowest acceptable risk for monitoring and lowest acceptable risk for thrombolytic therapy). On follow-up, the assessment criteria used for DVT/ PE recurrence [65-67] and for bleeding severity[68] should also follow guidelines. Prognostic tools need be defined for their normal values (and cut-offs) and for how information (i.e. timing) should be collected at baseline. Studies should be designed for each phase of model development and be appropriate to the research question for model assessment in PE.

How to improve prognosis assessment in acute PE?

The main issue is identifying the major outcome measure that is suitable for answering the research question and to choose a study design relevant to that specific question. In this context, the following paragraphs outline some of the ongoing needs for research to improve prognosis assessment in acute PE.

To identify patients for outpatient management or early discharge, research is needed to compare findings from prognostic models with those from clinical judgment alone, which is the usual method for decision making that includes all potential medical and social prognostic indicators (Chapter 8). We also need to compare sPESI, as a simple and widely validated prognostic model, with Hestia as a complete hospital checklist. The main outcome measure of 30-day all-cause mortality should be used, because this is a common target for all the competing strategies. Choosing a composite outcome that includes major bleeding (in addition to mortality and VTE recurrence) would favour Hestia over sPESI, but different outcomes should also be assessed. As a time-point, 30 days is optimal because it includes the first 7 to 10 days, which is what is measured now and the usual time period spent in the hospital after an acute PE when the patient receives conventional management. Considering PE-related mortality (in competing risk analyses) instead of all-cause mortality, one would ask whether a prognostic model to guide decision for outpatient management in patients at low-risk will still be useful. Given the low PE-related mortality rate, for the same prognostic model a higher proportion of patients would safely

benefit from early discharge or complete outpatient management without the need for a scoring system. Finally, prognostic strategies have been mostly assessed under conventional anticoagulant treatments and it is now of high importance to check how they perform under the new direct oral anticoagulants.

For hospital management and for more aggressive therapy in patients who are in a stable haemodynamic status, a strategy is needed that helps physicians to select patients who will be managed in a monitoring unit and those who will need thrombolytics in ICU. For that purpose, novel models need to be validated and assessed in impact studies. Other types of research may be useful for selecting patients who might better respond to treatment and for selecting those at low-risk of bleeding when using thrombolytic therapy. In patients identified at high-risk of bleeding and thrombotic events, endovascular treatment and reduced dose of thrombolytic treatment need be compared.

Decision analytic modelling assessing clinical utility in a sensitivity analysis in terms of impact on quality of life and cost would help for choosing the optimal model (or combination of model and markers) and the optimal cut-offs for better selecting patients at low-risk and at higher risks.

CONCLUSIONS

Individual prognostic indicators are not sufficient on their own to predict outcomes or inform decisions but need to be integrated within prognostic strategies, or added to them. To date, PESI and simplified-PESI are the most validated and updated prognostic models, and perform better than other models at low-risk thresholds in head-to-head, between-model comparisons. They may be helpful for selecting patients for early discharge and outpatient management, mainly when combined with information on biological or imaging markers of RVD that are generally available in clinical practice. Because of physicians' preferences, other strategies such as the

Hestia hospital checklist and simplified-PESI need to be compared against each other and with physician's clinical judgment. Prognostic models are less helpful for the accurate identification of high-risk patients with normotensive PE, and more appropriate strategies need to be validated and then assessed in impact studies. Methodology issues tailored to PE prognosis should be resolved and standardized to minimise bias. This will require adequate case-identification strategies to obtain more appropriate prognostic information and thus improve study quality. This is important against the background that VTE incidence is similar to that of stroke and that PE is the third most common cause of death from cardiovascular disease after heart attack and stroke. In this respect, it is important to have good information on prognosis when patients with this common and life-threatening condition arrive in hospital. My research, as presented in this thesis, should help on the journey to achieving this.

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