Management of older patients with suspected venous thromboembolism

Henrike J. Schouten

MANAGEMENT OF OLDER PATIENTS WITH SUSPECTED VENOUS THROMBOEMBOLISM

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MANAGEMENT OF OLDER PATIENTS WITH SUSPECTED VENOUS THROMBOEMBOLISM

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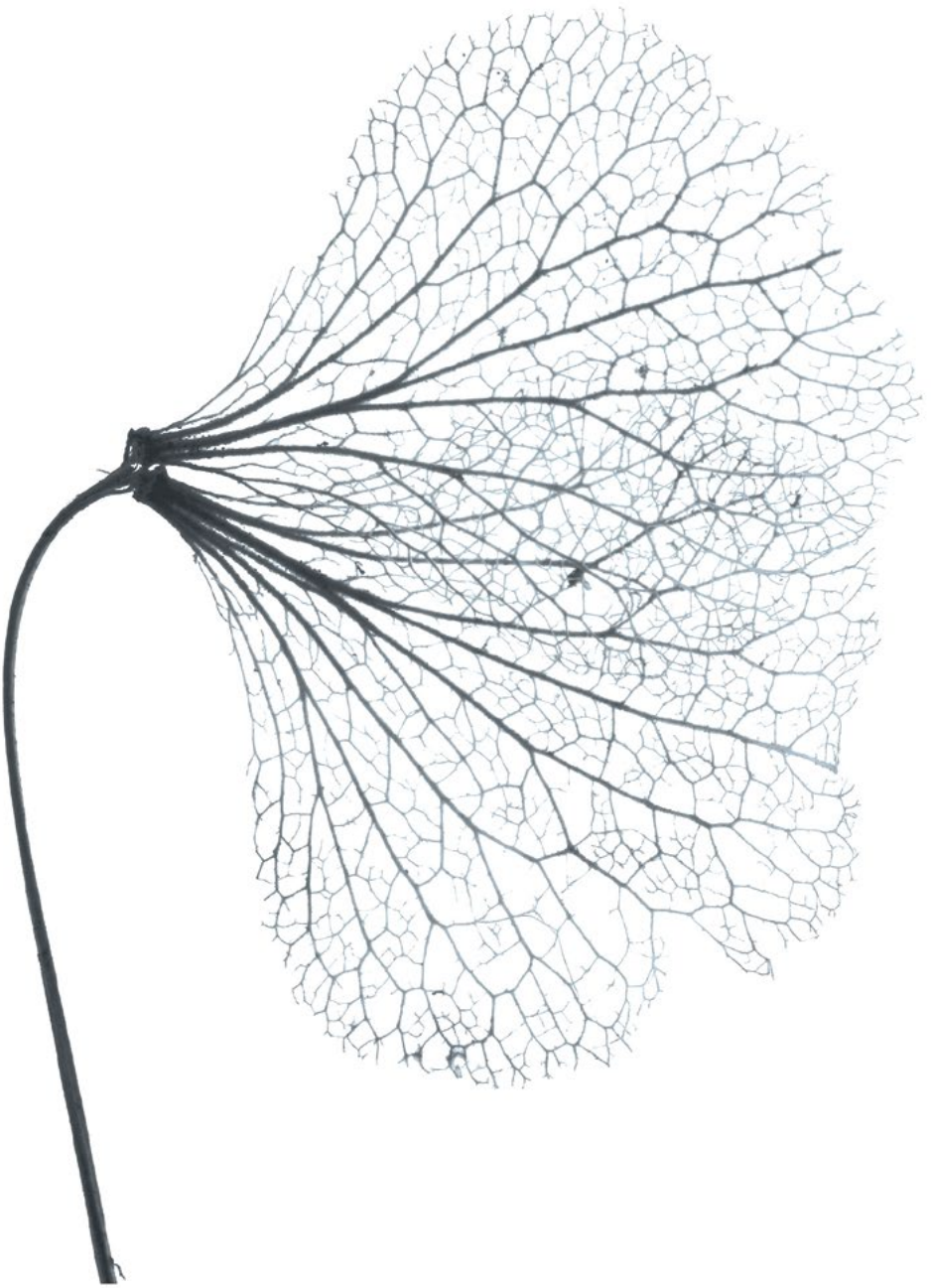


CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Case

An elderly care physician consults a 87-years-old female nursing home resident. She suddenly had a red, swollen and painful leg. Fever is absent. The physician considers the diagnosis deep vein thrombosis. As both the incidence and the short-term mortality of venous thromboembolism (pulmonary embolism or deep vein thrombosis) rises with age, he realizes that accurately and timely diagnosing deep vein thrombosis is important.[1-5]

Diagnostic strategy

The physician decides to apply the primary care diagnostic decision strategy for deep vein thrombosis (figure 1) which yields a total score of three points: there was no leg trauma and measuring the calf circumference of both legs revealed a difference of 4 centimeters. In line with the clinical decision rule, he performs a D-dimer test as low D-dimer concentrations in combination with a low clinical probability would rule out deep vein thrombosis.[6;7] However, the test-result is abnormal, contributing for an extra six points on the diagnostic decision score, totaling in nine points (moderate clinical probability of deep vein thrombosis; figure 1). Consequently, the patient should be referred to a hospital for compression ultrasound examination.[6;7]

Clinical dilemma

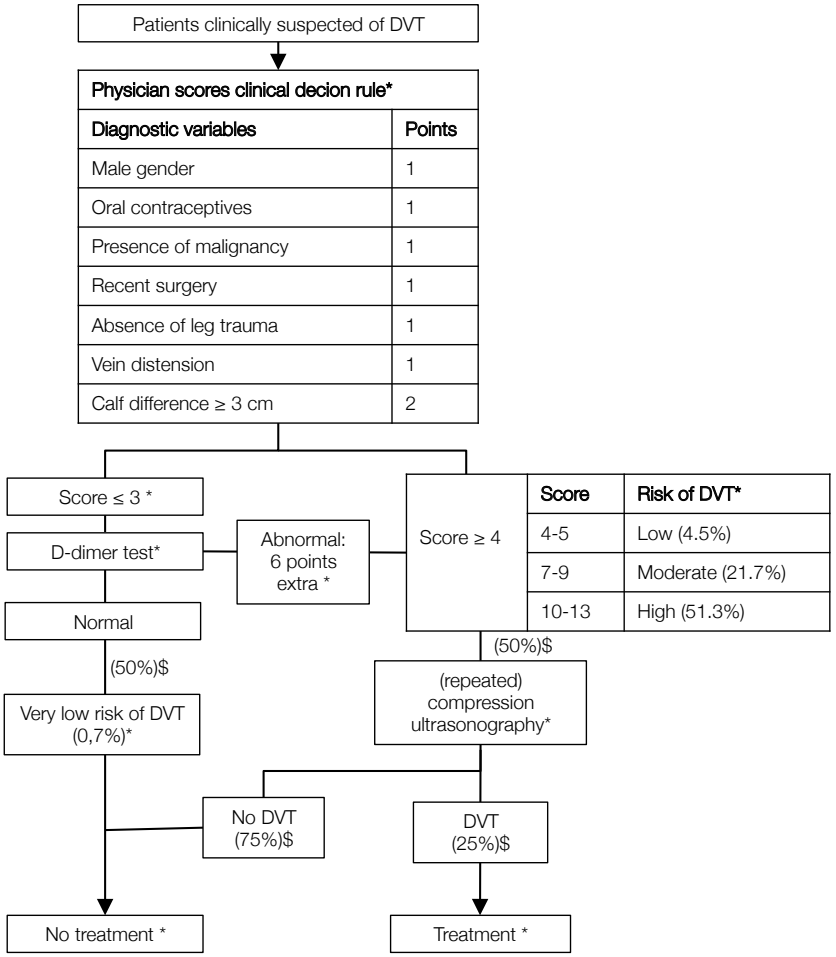
Since the accuracy of the diagnostic strategies for venous thromboembolism has never been investigated in very old nursing home patients, the physician is not sure whether this strategy can be translated to his 87-years-old patient.[8] Furthermore, he feels discouraged to refer this frail, old woman to a hospital for imaging investigation as this may stress her severely. Facing this dilemma and considering the probability of deep vein thrombosis and the subsequent risk of fatal pulmonary embolism as high, he decides to not refer his patient for imaging examinations, but instead to start anticoagulation treatment immediately. During the weekly briefing, he discusses the dilemma concerning this patient with his colleagues. Was this the best possible decision for this patient? And is the clinical decision rule valid when applied to rule in venous thromboembolism in this patient? One colleague argues that the D-dimer test has a high false-positive rate in older patients and therefore dissuades from D-dimer testing in very old patients.

Outline of the thesis

Based on these considerations, the research goals for the studies presented in this thesis were:

1. To assess the accuracy of existing diagnostic decision strategies combined with normal D-dimer testing to exclude venous thromboembolism when applied in older patients,

Figure 1 Diagnostic and treatment strategies for patients with suspected deep vein thrombosis according to primary care guidelines in the Netherlands[6]



Key to symbols: DVT= deep vein thrombosis, *based on Oudega et al[6] and $ probalilities based on Büller et al[7]

and to investigate whether it is possible to apply the clinical decision rules and D-dimer test to distinguish patients with a very high risk of venous thromboembolism.

2. To establish the diagnostic value of D-dimer testing for excluding suspected venous thromboembolism in older patients, with a particular interest in whether increasing the threshold for test positivity is a safe and more efficient strategy than using the conventional cut-off.[4]

3. To explore elderly-care physicians' considerations and motivations to withhold additional diagnostic investigations in nursing home patients with a clinical suspicion of venous thromboembolism

The outline of this thesis parallels these three research goals. The thesis is further introduced in **chapter 2**, were we elaborate on the generalizability of diagnostic decision strategies to elderly patients and on the aims of those strategies versus the needs of elderly patients.
The **chapters 3 and 4** describe a prospective external validation study on strategies to safely exclude venous thromboembolism in older patients in primary care or in long term care facilities and investigate the possibility to rule-in the diagnosis with a clinical decision rule; in **chapter 3** we focused on strategies for deep vein thrombosis. In **chapter 4**, we validated and subsequently updated the Wells'-rule for pulmonary embolism.[9]
In the **chapters 5 and 6** we assessed the diagnostic value of D-dimer testing to exclude venous thromboembolism in suspected older patients. In **chapter 5** we externally validated age-adjusted cut-off values for the D-dimer test to exclude venous thromboembolism in a safe and more efficient manner in older primary care patients.[10] We further assessed the role of D-dimer testing to exclude venous thromboembolism in older patients, using either conventional or age-adjusted cut-off values, by means of a meta-analysis in **chapter 6**.
In the **chapters 7 and 8** of this thesis, we studied physicians' decisions to refrain from further diagnostic investigations in older patients. **Chapter 7** describes a systematic review on such 'non-diagnosis' decisions and in **chapter 8,** these 'non-diagnosis' decisions were further explored in a study using both qualitative and quantitative research methods. The main findings of the thesis are summarized and discussed in **chapter 9.**

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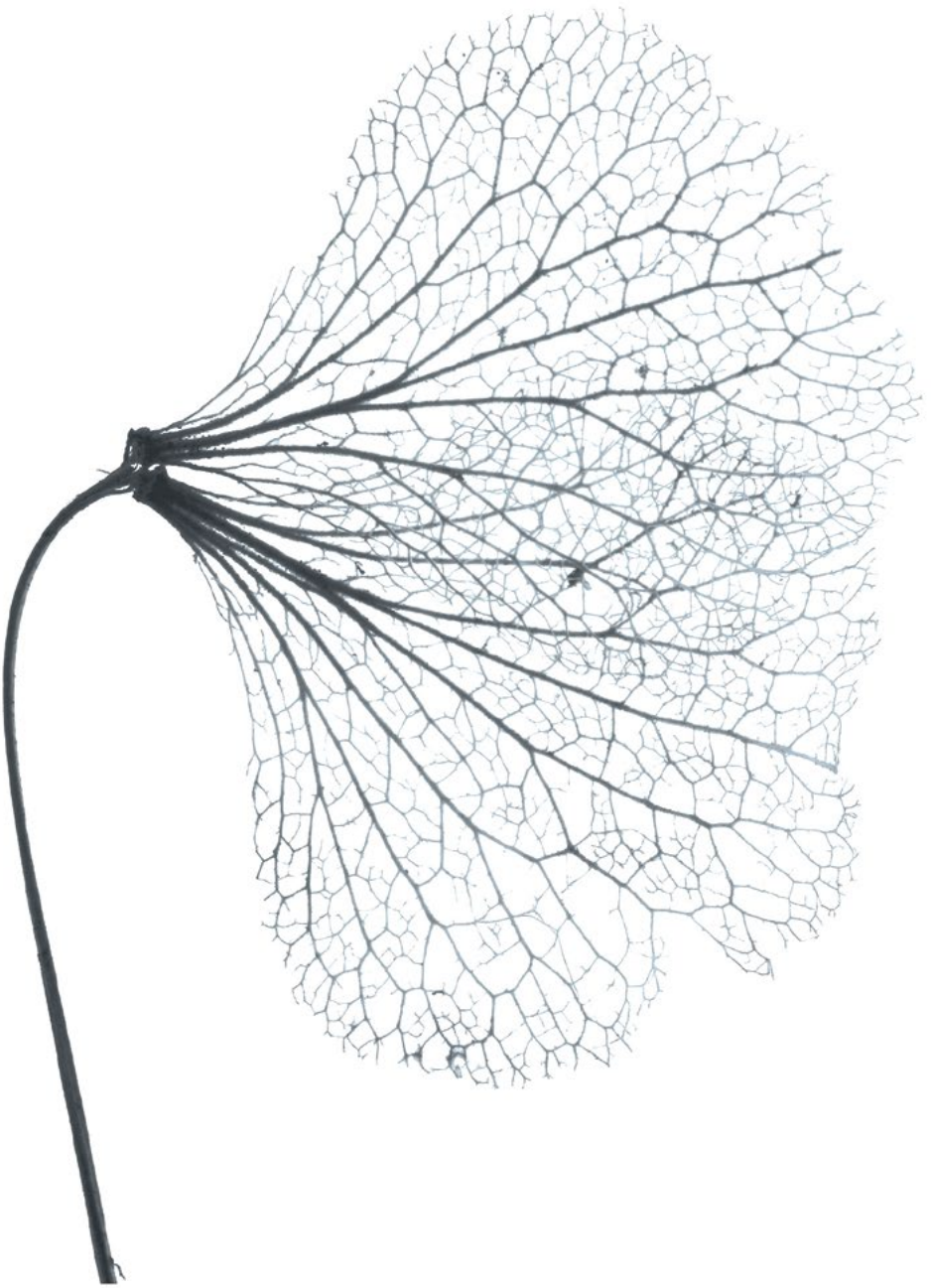

CHAPTER 2

NEED FOR TAILORED DIAGNOSTIC STRATEGIES FOR VENOUS THROMBOEMBOLISM FOR OLDER OUT-OF-HOSPITAL PATIENTS

Schouten HJ, Koek HL, Moons KGM, van Delden JJM, Oudega R, Geersing GJ.

Based on: Eur J Gen Pract. 2013 Jun;19(2):123-7.

ABSTRACT

Venous thromboembolism (pulmonary embolism and deep vein thrombosis) is common in older patients and short-term mortality risk increases with age. Hence, notably in older patients, accurately and timely diagnosing venous thromboembolism can be lifesaving. However, most clinically suspected individuals turn out to have no venous thromboembolism after imaging examination. Therefore, many physicians would feel reluctant to refer older patients as this can be very burdensome for these patients. Consequently, it is possible that older patients are often not referred for diagnostic work-up (risk of underdiagnosis) or that treatment for venous thromboembolism is initiated without confirmation by further testing (risk of overtreatment). An accurate diagnostic strategy which can safely exclude, and timely diagnose venous thromboembolism without the need of burdening referrals in many patients might therefore serve the needs of older patients. Such strategies have been derived and validated in both primary and secondary care patients suspected of venous thromboembolism. However, the generalizability of these strategies to older patients may be hampered, and their accuracy has never been tested in elderly populations; this in spite of the high prevalence of venous thromboembolism and the potential for misdiagnosis and thus mistreatment in these patients. Validation - and if needed adaptation - of current diagnostic strategies for venous thromboembolism for application in older patients is needed.

VENOUS THROMBOEMBOLISM IN OLDER PATIENTS

As the incidence of venous thromboembolism is strongly associated with age, venous thromboembolism is a major health problem in the ageing societies in the Western parts of the world.[1-5] The estimated incidence rate for venous thromboembolism in older people varies from 4 to 9 per 1,000 person years in whom the short-term mortality can be as high as 15%.[2-6] Hence, notably in older patients, accurately and timely diagnosing venous thromboembolism can be lifesaving. However, diagnosing venous thromboembolism is not straightforward as isolated signs and symptoms are not sufficient to in- or exclude venous thromboembolism.[7;8] This is even more so in older patients in whom typical signs and symptoms of venous thromboembolism are often mimicked by co-morbidity.[9;10] On the other hand, the prevalence of venous thromboembolism in suspected patients is relatively low, even in a high risk population such as the elderly; typically, 30% or less of clinically suspected patients have confirmed venous thromboembolism when referred for reference testing.[10-12] Thus, many older patients are being unnecessarily referred to secondary care facilities for further diagnostic (imaging) tests,[13;14] whilst particularly these frail older frail patients are vulnerable for distress and complications resulting from transitions to hospital-care.[15-17]

Generalizability of diagnostic decision strategies in older patients

To correctly exclude the presence of venous thromboembolism without the need for further referral or work-up, so-called diagnostic decision models or -rules, based on a weighed combination of signs and symptoms, can be applied. Such rules have been derived and their safety and cost-effectiveness has been extensively tested in both primary and hospital care patients suspected of venous thromboembolism (e.g. the Wells strategy for pulmonary embolism and Oudega-rule for deep vein thrombosis).[18-21] In order to be helpful in the diagnostic workup of venous thromboembolism the decision strategies need to be generalizable, that is, they should be able to produce accurate predictions among patients from a different but plausibly related population.[22] However, diagnostic models are sensitive to changes in patient populations, and often perform worse when applied in different patients.[22;23] For example, diagnostic models developed in a hospital setting may perform poor in a primary care setting due to differences in patient characteristics, physicians experience and prior-probabilities.[22-24] For older patients in nursing homes and primary care, the higher incidence and the often more obscure presentation of venous thromboembolism may alter the diagnostic accuracy of existing clinical decision rules for venous thromboembolism.[3;4;9;10;25;26] Moreover, the D-dimer concentration increases with age, which may lead to more false positive D-dimer results in older patients.[10;27;28] All these features may result in an over- or underestimation of the probability (an error in calibration), or in a reduced discriminative power between the presence or absence of venous thromboembolism for older patients.[29] Hence, generalizability of diagnostic models for venous thromboembolism - which are derived in adult patient populations - towards elderly patients warrant further investigation.

Current decision strategies versus the needs of older patients

One may also question whether the diagnostic decision strategies optimally serve the needs of elderly patients. The primary goal of the current diagnostic strategies for venous thromboembolism is to provide the physician the assurance that venous thromboembolism is not falsely excluded.[19;30;31] Therefore, in the current strategies, only very low proportions of false–negative results are deemed acceptable, and only in patients with a very low risk of venous thromboembolism (commonly a threshold of 1% to 4% is used) further imaging examination is withheld.[19;30;31] Although primary care studies demonstrated that this safe 'rule-out strategy' - encompassing a diagnostic decision rule and D-dimer testing - was able to exclude venous thromboembolism in 45 to 50% of patients, this strategy (still) led to a substantial proportion of patients being referred to a hospital.[19;32] Three out of four patients who were referred for additional diagnostic work-up turned out to have no venous thromboembolism (false–positive cases, see chapter 1, figure 1).[19;32] As the main aim of this strategy was to safely exclude venous thromboembolism, this proportion of referred patients in whom no venous thromboembolism was present, was deemed acceptable. However, for older patients the journey to a hospital and the undergoing of diagnostic research is often more burdensome and complicated.[15;16;33;34] Many physicians would therefore feel reluctant to refer frail older patients to a hospital for exclusion of venous thromboembolism and consequently might decide not to refer these patients for work-up despite an underlying 'high' risk of venous thromboembolism (i.e. risk of under diagnosis). Alternatively, it is also possible that treatment for venous thromboembolism is initiated in actually 'low risk' patients, thus without confirmation by further testing (i.e. risk of overtreatment).[35]

Implications

Current available diagnostic strategies recommend referral for further imaging examination for 1 out of 2 patients with suspected venous thromboembolism (see chapter 1, figure 1), whereas diagnostic decision strategies that would spare a higher proportion of older patients the possible hazardous referral for imaging examination might better serve the needs of elderly patients. Therefore, we advocate validation and - if possible and needed - subsequent adaptation of the current diagnostic strategies for elderly patients with suspected venous thromboembolism by a so-called 'updating study'.[22] Diagnostic decision strategies should be tailored to the needs of older patients by recommending imaging examination in only a small proportion of them. This could be achieved by a two-track policy with both rule-out and rule-in strategies:

1. The proportion of elderly patients in whom venous thromboembolism can be safely excluded without imaging examination can be enlarged by application of age-adjusted D-dimer levels in elderly patients.[36-38] Furthermore, a diagnostic decision strategy with the focus on improved efficiency (i.e. increasing the proportion of patients in whom deep vein thrombosis can be ruled out without the need for imaging examination, e.g.

by applying a higher cut-off value) might be more appropriate in the elderly (inherently accepting that the proportion of falsely missed venous thromboembolism cases also rises). Given the risks and burden involved with referral to a hospital in older patients, one could argue that applying the strict recommendation of missing a maximum of 1 to 4% of venous thromboembolism cases, is too stringent for elderly care.

2. If possible, a rule-in approach should be developed for frail older patients outside the hospital for whom referral for additional diagnostic investigations is considered too burdensome. Patients with very high probabilities for venous thromboembolism according to such an approach are treated without further diagnostic imaging examination.

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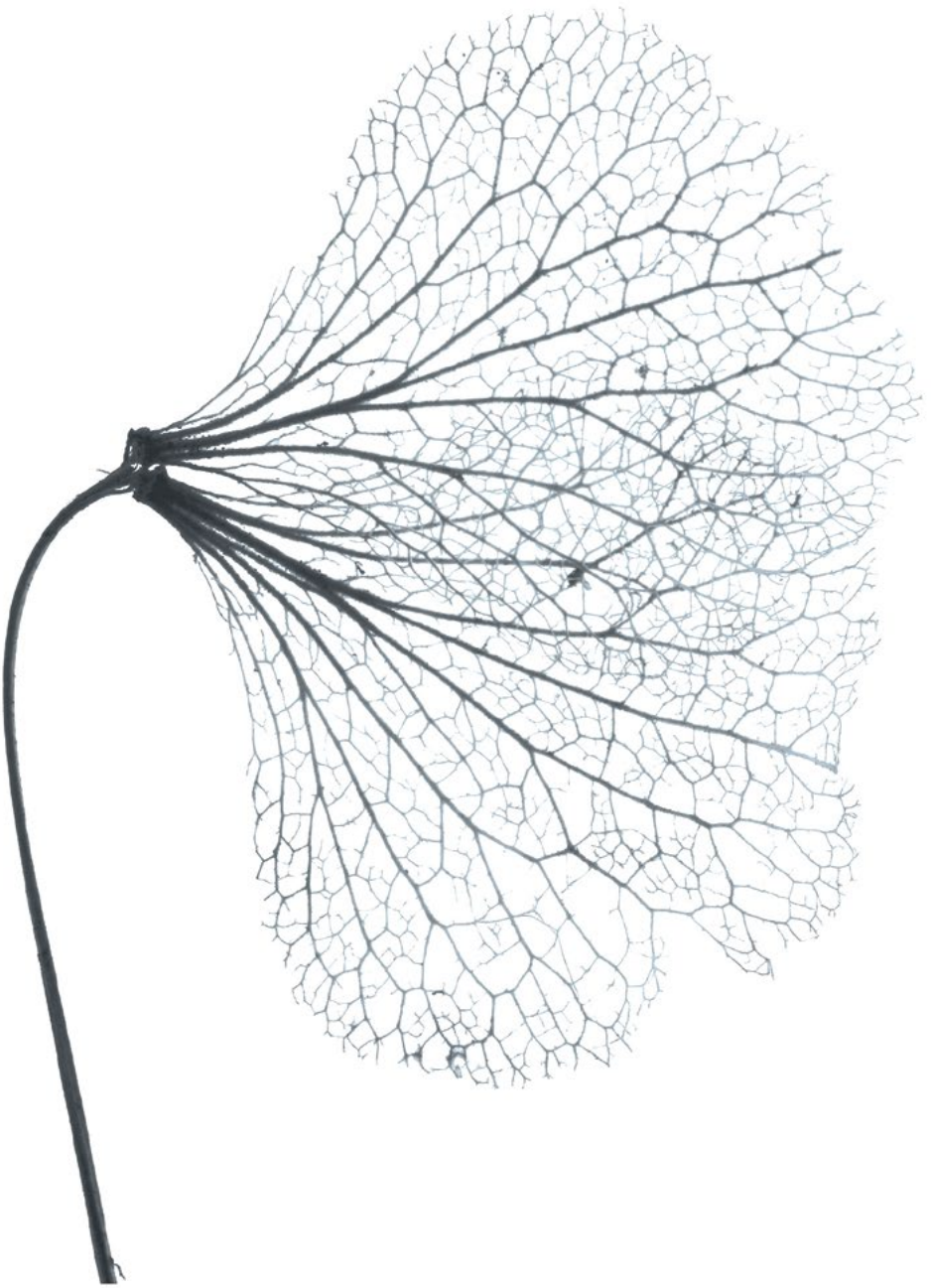


CHAPTER 3

ACCURACY OF DECISION STRATEGIES IN DIAGNOSING DEEP VEIN THROMBOSIS IN FRAIL OLDER OUT-OF-HOSPITAL PATIENTS:

A VALIDATION STUDY

Schouten HJ, Koek HL, Moons KGM, Oudega R, van Delden JJM, Moons KGM, Geersing GJ.

Submitted.

ABSTRACT

Background We aimed to assess the accuracy of the 'Oudega-diagnostic decision rule' to exclude deep vein thrombosis (DVT) in older out-of-hospital patients suspected of DVT. This rule has been developed and validated notably in younger suspected primary care patients.

Methods In older primary care and nursing home patients (≥60 years) with clinically suspected DVT, physicians recorded the score on the Oudega-rule and D-dimer test. DVT was confirmed with a composite reference standard including ultrasonography examination and 3-month follow-up. The proportion of patients with DVT and a very low probability of DVT according to the Oudega-rule (failure rate), and the proportion of patients with a very low probability (efficiency) was calculated.

Results DVT occurred in 164 (47%) of the 348 study participants (mean age 81 years). The probability of DVT was very low in 69 patients (Oudega score ≤3 points plus a normal D-dimer test; efficiency 20%); of whom four had nonfatal DVT (failure rate 5.8%; 2.3 to 14%). With a simple revised version of the Oudega-rule for older suspected patients, 43 patients had a low risk of DVT (12% of the total population) of whom only one had DVT (failure rate 2.3%; 0.4 to 12%).

Conclusions In older suspected patients, application of the original Oudega-rule to exclude DVT resulted in a higher failure rate as compared to previous studies in younger suspected patients. A revised and simplified Oudega-strategy specifically developed for elderly suspected patients resulted in a much lower failure rate though at the expense of a lower efficiency.

INTRODUCTION

Leg complaints are relatively frequent in older patients.[1] Deep vein thrombosis (DVT), which predominantly occurs at an advanced age, is one of the more serious conditions in the differential diagnosis for these patients as missing a diagnosis poses patients at risk of possibly fatal pulmonary embolism.[2] Yet - given the often non-specific complaints in these patients - the diagnosis DVT can be confirmed in only one in five older patients with clinically suspected DVT.[3-6] Referring all patients for reference testing (venous imaging) is often no option as frail older patients are vulnerable for distress and complications resulting from the journey to a hospital and the undergoing of diagnostic tests.[7-11] Hence, the difficulty in the diagnostic workup of DVT in such patients is to adequately and timely distinguish the patients in whom referral and treatment can be safely withheld from those who need to be referred to secondary care facilities for confirmation of the diagnosis and subsequent anticoagulant treatment.

The widespread implementation of diagnostic decision rules in primary and secondary care has resulted in an increased efficiency in the diagnostic work up for DVT in the past decade.[12;13] In a management study on a diagnostic decision rule in primary care, we found that referral to secondary care could be safely withheld in almost half of the suspected patients.[14] The benefits of such a strategy might particularly apply for frail older patients, provided that it can safely rule-out DVT in a substantial proportion of them without needing to be referred for imaging examination. However, diagnostic decision strategies tend to perform worse when applied outside the setting as where they are derived from and validated in.[15;16] Strikingly though, the accuracy of diagnostic decision strategies in suspected DVT has never been investigated in frail older patients outside the hospital. We therefore conducted this prospective external validation study to evaluate the accuracy of an existing clinical decision rule which was developed and validated in primary care, to safely exclude DVT in older out-of-hospital patients.[14;17-19]

METHODS

Setting and participants

The Venous Thromboembolism in the Elderly (VT-elderly) study was a prospective observational study with 3 months follow up. Patients residing in nursing homes and older primary care patients (aged 60 years or over) with clinically suspected venous thromboembolism (VTE; either DVT or pulmonary embolism, or both) were eligible for inclusion. Patients were enrolled by elderly-care physicians and general practitioners across the Netherlands between October 2008 and April 2013. Only the patients primarily suspected of DVT (based on pain, swelling or redness of the lower extremity) were included. Patients were excluded if they denied providing informed consent or if they received treatment with anticoagulants at presentation (coumarins or oral direct thrombin- or

factor Xa-inhibitors). The local ethics review board of the University Medical Center Utrecht, the Netherlands, judged the study as exempt from review according to the national law (08-124/E).

Diagnostic strategy under study

The primary aim was to validate the accuracy of the Oudega-rule in frail older out-of hospital patients. This rule was originally developed to exclude DVT in primary care patients without the need for referral to secondary care for ultrasonography examination. Physicians systematically recorded medical history, signs, symptoms and the result on the Oudega-rule for each patient (see table 1).[17] The D-dimer test is incorporated in this clinical decision rule and contributes for 6 points if abnormal. Physicians were provided with qualitative point-of-care D-dimer tests (Clearview Simplify D-dimer assay®) and with written instructions for the acquisition and interpretation of this test. To calculate the patient's total score on the Oudega-rule, physicians either applied this point-of-care test (for 70% of the study participants) or used the results of quantitative D-dimer assays in local laboratories for which values of 500 µg/L and higher were considered abnormal. Though referral for compression ultrasonography examination of the lower extremity was recommended for all patients who had a total score >3 on the Oudega-rule (table 1), it was left to the physicians' discretion whether patients were indeed referred. If the patient was considered to have a very low probability of DVT (based on a total score on the Oudega-rule ≤3 points), imaging was not recommended.

Outcome assessment

The primary endpoint of this study was the presence of VTE during 3-month follow up. At 3 months, follow up was performed for all patients to assess the occurrence of any VTE event and - if applicable - cause of death. All patients who were not referred to a hospital for objective testing despite a score > 3 on the Oudega-rule were evaluated by an adjudication committee of 3 experts. If - based on signs, symptoms, D-dimer testing and all available clinical information - VTE was deemed present by the committee, patients were classified accordingly. Deaths were similarly adjudicated by this committee as likely or unlikely related to VTE.

Hence, in this study, VTE was considered present if 1) there was a finding of DVT on lower limb ultrasonography; or 2) confirmed pulmonary embolism on computed tomography pulmonary angiography of the chest; or 3) death within 3 months probably related to VTE or 4) if patients were adjudicated as VTE present.

Statistical analyses

Missing values for clinical items of the Oudega-rule, the D-dimer test, or in follow up data (4.6%; 6.1% and 0.9% respectively) were multiple imputed.[20] The primary analysis included the proportion of patients with symptomatic VTE during 3 months follow-up within those with a very low risk on the Oudega decision rule (total ≤3 points; this is the failure rate), as well as the proportion of

Table 1 Clinical decision rules under study

Oudega strategy[17]	
Variables	Points
Male gender	1
Use of estrogens (oral contraceptives or hormonal replacement therapy)	1
Presence of malignancy	1
Recent surgery	1
Absence of leg trauma	1
Vein distension	1
Calf difference ≥ 3 cm	2
D-dimer abnormal	6
Posttest probability based on the Oudega rule	
Very low	0 to 3
Low	4 or 5
Moderate	6 to 9
High	10 to 13
Wells strategy[12]	
Variables	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
Posttest probability based on the Wells rule	
Unlikely	≤1
Likely	≥2
Low	<1
Moderate	1 or 2
High	>2

Table 2 Characteristics of the study participants

Patient characteristics **n= 348**	**Frequency** **n (%)**
Patients with confirmed VTE	164 (47.1)
Demographic characteristics	
Male	89 (25.6)
Age, years, mean (standard deviation)	80.9 (10.2)
Residency -Home for the elderly/other institute/ community dwelling -Nursing home	 54 (15.6) 294 (84.5)
Symptoms	
Painful leg	222 (63.8)
Swollen leg	327 (93.9)
Redness of leg	179 (51.4)
Acute onset of symptoms	219 (62.9)
Duration of complaints, days, median (interquartile range)	2 (5)
Signs	
Edema of the distal leg	308 (88.5)
Edema of the proximal leg	120 (34.5)
Tenderness of deep veins	138 (39.7)
Distension of collateral veins	60 (17.2)
Difference in calf circumference ≥3cm	216 (62.4)
D-dimer abnormal	270 (77.6)
Medical history	
Bedridden or chairbound	170 (48.9)
Previous episode of DVT	36 (10.3)
Previous episode of pulmonary embolism	20 (5.7)
Varicose veins/venous insufficiency	117 (33.6)
Active malignancy	42 (12.1)
Immobilization or surgery in previous month	36 (10.3)
Co medication	
Use of estrogens (hormonal replacement therapy)	4 (1.1)
Antiplatelet therapy	110 (31.6)
Prophylactic dose of low molecular weight heparin	32 (9.2)

very low-risk patients among the total suspected population (efficiency). For calculation of 95% confidence intervals, the exact binomial Wilson-Score method was used.
In addition, we performed post-hoc analyses. We refitted the original model within our population, thereby re-estimating all coefficients and the intercept and retained those predictors, that were statistically significantly associated with VTE based on the log likelihood ratio test at p-value <0.10. This model was adjusted for optimism and overfitting using bootstrapping techniques.[21]
Second, we estimated the efficiency and failure rate for patients with an 'unlikely' (≤1) or a 'low' (<1) score according to the Wells-rule for DVT, combined with a normal D-dimer test.[12] Finally, we examined to what extent both original rules in combination with D-dimer testing, were able to include VTE. All analyses were performed using R-2.15.3 for Windows.

RESULTS

Study participants

A total of 394 older patients with suspected DVT were initially evaluated of whom 46 were excluded based on predefined exclusion criterions (figure 1, flowchart). A total of 348 participants (26% males, mean age 80.9 years) were included in the study of whom the majority (n=294, 84.5%) resided in nursing homes. Almost half of the participants (49%) were bedridden or chairbound and 42 participants (12%) had an active malignancy (table 2).
Based on our composite reference standard, VTE was present in 164 patients (47%). A total of 45 study participants died during the 3-month follow up (all-cause 3-month mortality-rate 13%) and in four of these patients (8.9%) VTE was presumed as probable cause of death (and thus counted as VTE present). Major bleeding or a clinically relevant non-major bleeding occurred in 14 patients during the 3 months follow up (4.0%; figure 1).

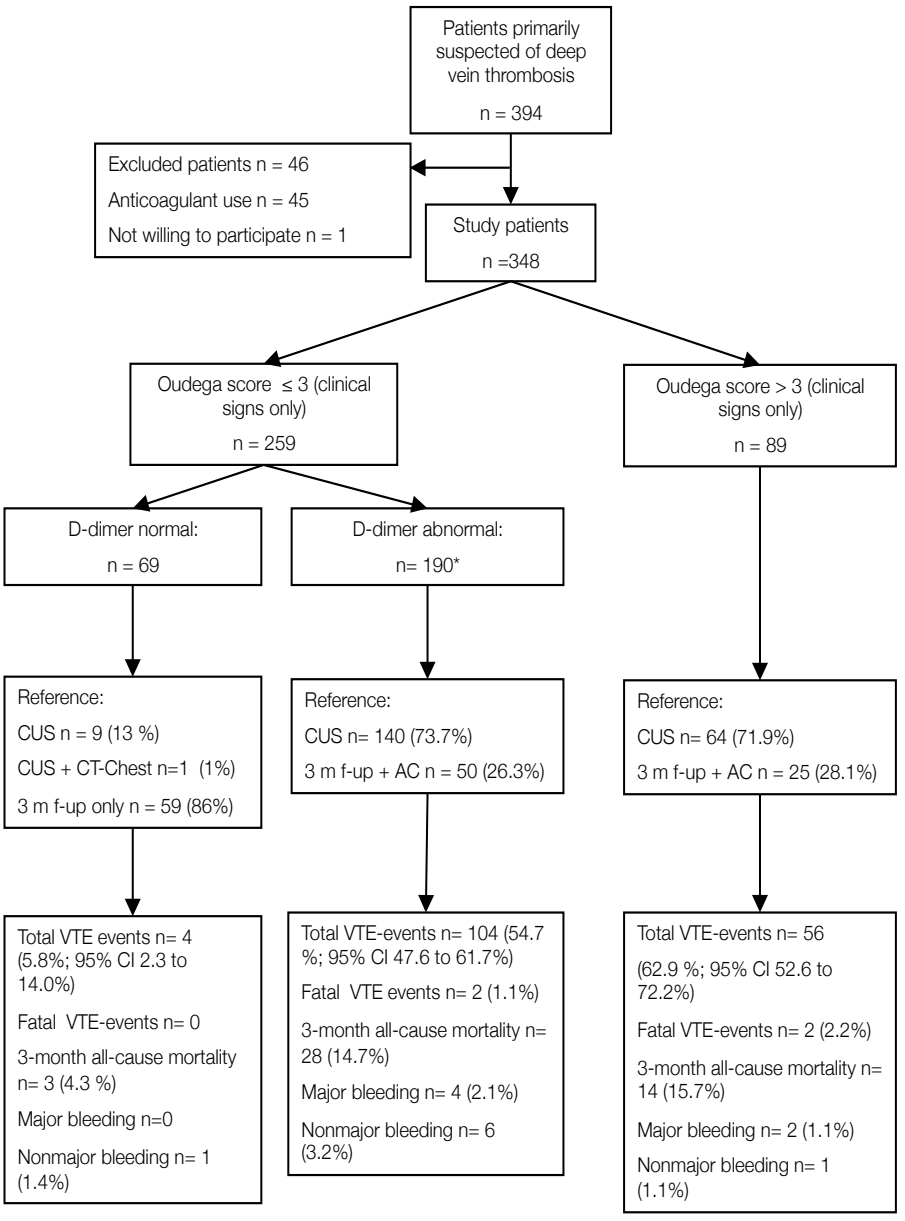
Diagnostic accuracy of the original Oudega-rule

Among the 348 study participants, 69 had a score of 3 or lower on the Oudega-rule (20% of the total population; 95% confidence interval 16 to 24%, table 3). In the 3-month follow up VTE was confirmed in four of these patients (failure rate 5.8%; 2.3% to 14%). Details of these patients are listed in table 4. Lowering the threshold on the Oudega-rule did not reduce the failure-rate (appendix 1).
VTE was diagnosed in 55 of the 80 patients with a high risk (score > 10) according to the Oudega-rule (23% of the total population, positive predictive value of 69%; 58% to 78%).

The diagnostic accuracy of the Wells-rule

If physicians would have used the Wells-score for DVT, a total of 61 study participants would have had a combination of the Wells-rule indicating an unlikely probability of DVT and a normal

Figure 1 Flow of participants through the study, using the Oudega-strategy[17]



* 6 point-of care tests returned a non-interpretable or unvalid result which were classified as abnormal result. VTE=venous thromboembolism; CI= confidence interval; CUS= compressionultrasonography of the lower extremity; 3 m f-up = 3 months follow-up; AC= adjudication committee; D-Dimer abnormal= Clearview Simplify test abnormal or quantitive D-dimer ≥500 µg/L

Table 3 Distribution of patients according to scores of the Oudega strategy.

Total number of patients= 348 Probability of VTE based on Oudega rule[17]	Number of patients (%; 95% confidence interval)	Number of patients with VTE (%; 95% confidence interval)
Very low risk (0 to 3)	69 (19.8; 16.0 to 24.3)	4 (5.8; 2.3 to 14.0)
Low risk (4 or 5)	9 (2.6; 1.4 to 4.8)	1 (11.1; 2.0 to 43.5)
Moderate risk (6 to 9)	190 (54.6; 49.3 to 59.8)	104 (54.7; 47.6 to 61.7)
High risk (10 to 13)	80 (23.0; 18.9 to 27.7)	55 (68.8; 57.9 to 77.9)

Table 4 Detailed description of the four patients designated to have a 'very low' risk of VTE according to the Oudega-rule* but diagnosed with VTE.

	Description	Reference test; number of days after initial evaluation
1	90-years old community dwelling woman, chair bound. Since four days painful left leg. Oudega-score=1 (absence of leg trauma). Point-of-care D-dimer test normal. Initial compression ultrasonography shows thrombophlebitis of the vena saphena magna. After two weeks; cough, chestpain and dyspnea d'effort; quantitative D-dimer 5760 µg/L and confirmed pulmonary embolism.	CUS, 0 days; CT-chest, 14 days
2	76-years old woman, chair bound, nursing home resident. Acute onset of painful, red and swollen leg with proximal edema. Recently immobilized due to fall. Receives prophylactic dose of low molecular weight heparin. Oudega score= 2 points (calf circumference difference of 3 cm). Point-of-care D-dimer test normal. Due to persistent complaints, compression echography examination after 2 weeks.	CUS, 14 days
3	85-years old woman, chairbound nursing home resident. Since 5 days red, painful and swollen right leg. Venous insufficiency in medical history. Oudega score=3 points (calf circumference difference of 8 cm, collateral vein distention). Point-of-care D-dimer test normal.	CUS, 0 days
4	86-years old woman, chair bound, nursing home resident. Acute onset of swelling of leg, no pain, no redness. Collum fracture one year ago. Oudega score= 2 points (calf circumference difference of 4 cm). Point-of-care D-dimer test normal.	CUS, 0 days

* as scored by their physician; CUS= compression ultrasonography of the lower limb.

D-dimer test (efficiency 18%; 14 to 22%; table 5). Three of these patients were diagnosed with VTE (failure rate 4.9%; 1.7 to 14%). Among the 47 patients with a score below one and a normal D-dimer test ('low risk'), VTE was confirmed in one patient (efficiency 14%; 10 to 18%; failure rate 2.1%; 0.4 to 11%).

A total of 175 patients (50% of the total population) had a combination of an abnormal D-dimer test and a 'likely' (≥2) probability according to the Wells-rule of whom 123 were diagnosed with VTE (positive predictive value of 70%; 63 to 77%).

Table 5 Performance of the Wells rule for DVT.[12] Probability of VTE in different categories of the Wells score in combination with D-dimer testing

Total number of patients= 348 Probability of VTE based on Wells- rule	Number of patients (%; 95% confidence interval)	Number of patients with VTE (%; 95% confidence interval)
Low scores		
'Unlikely' Wells score (≤1) for DVT combined with normal D-dimer test	61 (17.5; 13.9 to 21.9)	3 (4.9; 1.7 to 13.5)
'Low' Wells score (≤0) for DVT combined with normal D-dimer test	47 (13.5; 10.3 to 17.5)	1 (2.1; 0.4 to 11.1)
Moderate scores		
'Likely' Wells score (≥2) OR abnormal D-dimer test	112 (32.2; 27.5 to 37.3)	38 (33.9; 25.8 to 43.1)
Moderate Wells score (1 or 2) *	181 (52.0; 46.8 to 57.2)	68 (37.6; 30.8 to 44.8)
High scores		
'Likely' Wells score (≥2) for DVT combined with an abnormal D-dimer test	175 (50.3; 45.1 to 55.5)	123 (70.3; 63.1 to 76.6)
'High' Wells score (≥3) for DVT combined with an abnormal D-dimer test*	118 (33.9; 29.1 to 39.0)	88 (74.6; 66.0 to 81.6)

*patients who had a combination of a 'low' Wells score and abnormal D-dimer', or a combinations of 'high' Wells score and normal D-dimer are not depicted in this table

Refitting the Oudega-rule

When refitting the Oudega model in our population of older patients (table 6), only three variables (calf-circumference difference, D-dimer test and gender) remained in the model. Applying this simple refitted and shrunken model to our data, VTE was present in 1 of the 43 patients with both a calf-circumference difference < 3 cm and a normal D-dimer test result (failure rate 2.3%; 0.4 to 12%; efficiency 12%, figure 2). A total of 203 patients had an abnormal D-dimer result combined with a calf circumference ≥ 3 cm or with male gender (58% of the total population); 138 of them had VTE (positive predictive value of 68%; 61 to 74%).

DISCUSSION

We performed a validation study on the Oudega-rule - which was developed and validated among younger aged primary care patients - to rule-out DVT in frail older outpatients. The proportion of patients in whom VTE could be ruled-out was lower than expected, based on previous validation studies in younger patients. These previous studies demonstrated that imaging examinations (and thus treatment) could be safely withheld in up to 50% of patients, whereas in our study this exclu-

Figure 2 Accuracy of the newly derived clinical decision rule based on calf circumference difference and D-dimer test only.

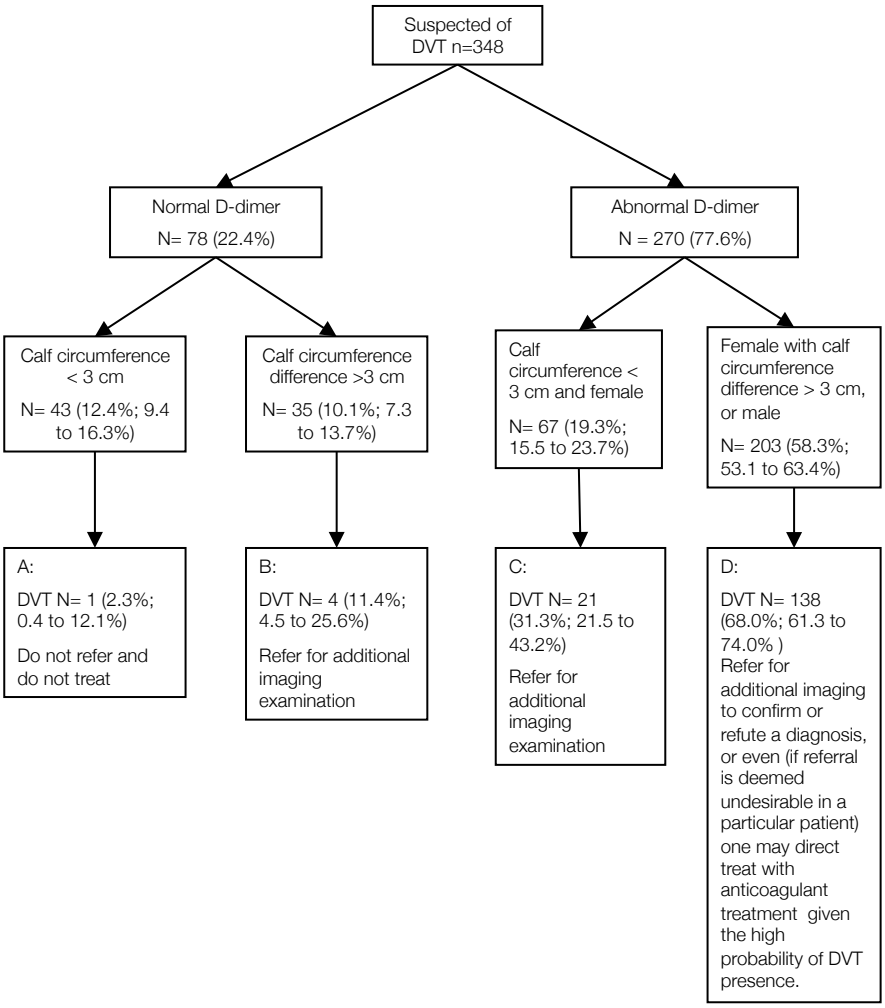


Table 6
Oudega model fitted on VT-elderly data: c-statistic 0.76 (0.71 to 0.80)
Adapted model (internally validated with bootstrapping techniques, correction factor slope 0.93, correction factor intercept 0.02) in VT-elderly data: c- statistic 0.75(0.70 to 0.80)

Variables in Oudega-rule	Regression coefficient in derivation cohort	Points in the rule	Regression coefficient in VT-elderly study	Multivariable model based on original models, odds ratio and 95% confidence interval in VT-elderly	Regression coefficient in newly fitted model in VT-elderly
Male gender	0.59	1	0.59	1.80 (1.00 to 3.22)	0.53
Use of oestrogens	0.75	1	n.a.*	n.a.*	-
Presence of malignancy	0.42	1	0.43	1.53 (0.72 to 3.24)	-
Recent surgery	0.38	1	-0.89	0.41 (0.18 to 0.92)	†
Absence of leg trauma	0.60	1	0.21	1.24 (0.74 to 2.08)	-
Vein distension	0.48	1	0.19	1.21 (0.64 to 2.30)	-
Calf difference ≥ 3 cm	1.13	2	1.11	3.04 (1.81 to 5.13)	0.99
D-dimer abnormal	3.01	6	2.99	19.9 (7.56 to 52.20)	2.78
Intercept	–5.47	-	-3.64	-	-3.50

* n.a.= not applicable, all four patients using estrogens had VTE; †Not provided in original publication; † this variable was manually left out the model as its predictive value was reversed compared to the original model[17]

sion proportion was 20%.[14;18] In addition, the prevalence of VTE was more than twice as high in our elderly study population: 47% as compared to a prevalence between 7% and 20% in previous studies.[14;18;22;23] As a result, patients had a much higher prior-probability for VTE which expectedly also led to a more than twofold higher proportion of 'missed' DVT cases in those patients classified as 'very low-risk' (failure rate of 5.8%, as compared to 1% to 2% in previous studies).[14;17;18;22;23] However the strategy was able to make a substantial reduction from the 47% pre-test probability to the 5.8% post-test probability in the patients in the very low risk category.

Strengths and limitations of the study

This is the first study to validate existing diagnostic decision rules to exclude VTE in a population of frail older suspected patients outside the hospital. Yet, for full appreciation of our results, some aspects warrant comment. First, we found a high prevalence of VTE in our study. This might reflect a lower awareness of VTE among elderly care physicians, with the subsequent risk of selective inclusion of only high-risk patients. However, we emphasize that our study population represents a very old (mean age 81 years) and frail nursing home population with a short life expectancy (3-month all-cause mortality rate 13%) and with many co-morbidities (table 2). Age, nursing home confinement and co-morbidity are all strong risk factors for VTE and might thus have contributed to the high prevalence of VTE in our study population.[4-6;24]

Second, the presence or absence of VTE was defined with a so-called combined reference test; ultrasound and 3-month follow-up.[25;26] For the patients with a low score on the Oudega-rule, we

had to rely on clinical follow-up only to detect any missed thromboembolic disease. Thus, the false negative cases were patients with a score of 3 or lower with worsening or recurrence of their symptoms within 3 months, leading to further examinations and the detection of VTE. Although this is common in VTE research, small (clinically less relevant) thrombi may have been missed in these patients, and thus the false negative rate might be somewhat underestimated.

Third, as part of our research protocol, we recommended referring patients with a score >3 points on the Oudega-rule for reference testing (i.e. leg ultrasound). Nevertheless 75 of those patients (22% of all included patients) did not undergo reference testing. As it is likely that imaging examinations were notably withheld in the frailest patients, we chose to avoid selectively ignoring of these patients as doing so would have resulted in biased estimates.[20] Instead, the presence or absence of VTE in these patients was defined by an adjudication committee who decided on each of these 75 patients whether it was likely or unlikely that VTE was present. This differential verification might have introduced some misclassification of the outcome, but it reflects clinical practice. For this reason we focused - according to methodological standards - on predictive values (i.e. failure rate) rather than on estimates of the sensitivity as the former are not affected by differential verification.[25;26] Fourth, during the study it became evident that D-dimer testing in very old patients yields an extremely low proportion of negative results. Even in absence of VTE, D-dimer tests are often abnormal in older patients.[3] As a result, the number of patients in the 'very low risk' category was lower than we had expected, which led to wide confidence intervals among the calculated VTE prevalence in the patients in the low risk-categories. However, though addition of more patients would lead to narrower confidence intervals, it is unlikely that this would have changed our point estimates for the failure rate and efficiency of the clinical decision rule in frail older patients.

Finally, we used a qualitative point-of-care assay, which has a somewhat lower sensitivity than the high-sensitive ELISA assays commonly used nowadays. This might have increased the failure rate in our study.[27]

Clinical implications

Though based on consensus rather than on evidence, current guidelines state that a diagnostic strategy for DVT is considered safe if its failure rate would be at or below 2%.[28] If one adheres to this strict safety standard of 2%, one has to consider the original Oudega-rule as an unsafe strategy for frail elderly out-of-hospital patients suspected of having DVT. Accordingly, this would actually imply that all frail older patients with any clinical suspicion of DVT should then undergo imaging examinations of the leg, and thus be referred to secondary care.

As this seems unappealing and unrealistic for this frail population, we like to place these findings in perspective. In the current study we found that physicians withheld referral for additional diagnostic workup anyhow in 31% of the nursing home patients despite a score >3 on the Oudega-rule. Clearly, the potential risks and burden of hospital transfers for frail older patients (e.g.

functional decline, risk of falling) implicitly played a role already in this decision-making.[7-10;29-31] These considerations may raise a discussion among elderly care professionals whether the original Oudega rule strategy might still be useful for this distinct population of frail elderly outpatients with suspected DVT, as it can contribute to avoidance of unnecessary and burdensome imaging examinations.

Nevertheless, the medical profession may consider the failure rate of 5.8% or the referral-rate of 80% of the diagnostic strategy as found in our study still as unacceptably high. This prompted us to perform post-hoc investigations on the performance of other strategies in a frail older population suspected of DVT. These analyses - including the use of a lower threshold on the Wells-rule and even the fitting of a new model (table 6) - demonstrated that a lower failure rate of 2.1% could indeed be achieved, yet at the expense of a much lower efficiency of 12 or 14% (see table 5 and appendix 2).

Another option to reduce the referral-rate is considering a so-called rule-in strategy, given the high prior-probability of VTE in this distinct patient population. We found that, irrespectively of the applied strategy, a subgroup of patients with a post-test probability of 68 to 75% could be identified (see table 3, table 5 and figure 2). Possibly in patients with such a 'very high risk' of VTE, anticoagulant treatment may indeed be directly initiated, if referral of the patient is deemed undesirable. The drawback of such a 'rule-in strategy' is that one in three of these frail patients would be exposed to the risks and burden of anticoagulant therapy while no VTE is present. Nonetheless, if the rule-out and rule-in strategies would be combined, clinicians would be able to make a decision for up to 70% of patients for whom burdensome and more costly imaging can be avoided.

Conclusions and implications for further research

The prevalence and thus prior probability of VTE was much higher in our frail older study population with suspected DVT as compared to previous studies in populations of younger adult patients. This resulted in a lower safety and efficiency of the original Oudega and Wells-rules to rule out the diagnosis in frail older patients, although the prior probability of 47% could be reduced to 5.8% with these rules. These findings highlight that frail older patients with suspected DVT represent a clear distinct population in whom the use of clinical decision rules - derived from populations of all ages - does not guarantee safe exclusion of VTE. Furthermore, we found that diagnostic rules can help clinicians to discriminate frail older patients with a high probability of VTE from those with a lower probability; the high prior-probability of 47% for DVT in this particular patient population could be further increased to 68% to 70%. This approach has the potency to rule-in VTE and start anticoagulant treatment if referral is deemed too burdensome. This 'rule-in' approach needs to be validated in other samples of older suspected patients and its acceptability should be discussed among health-care professionals before we can recommend its use in practice.[16]

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APPENDIX 1

Varying thresholds on the Oudega clinical decision rule

1a- Total number of subjects with and without venous thromboembolism (VTE) per score category of the Oudega -rule

Score Oudega-rule *	Normal D-dimer		Abnormal D-dimer	
	VTE absent n	VTE present n	VTE absent n	VTE present n
0 or 6 if abnormal D-dimer*	12	0	11	5
1 or 7 if abnormal D-dimer*	18	1	24	10
2 or 8 if abnormal D-dimer*	15	2	22	38
3 or 9 if abnormal D-dimer*	20	1	29	51
4 or 10 if abnormal D-dimer*	8	1	21	43
5 or 11 if abnormal D-dimer*	0	0	4	10
6 or 12 if abnormal D-dimer*	0	0	0	2

* The D-dimer tests is incorporated in the Oudega rule and contributes for 6 points if abnormal.

1b- Prevalence of DVT across low score (risk) categories of the Oudega-rule

Varying the threshold on the Oudega rule to rule out venous thromboembolism N=348	Number of patients (efficiency) (% of total)	Prevalence of VTE (safety) (% of subgroup)
≤3 (= very low according to original rule)	69 (19.9)	4 (5.8)
≤2	48 (13.9)	3 (6.3)
≤1	31 (9.0)	1 (3.2)

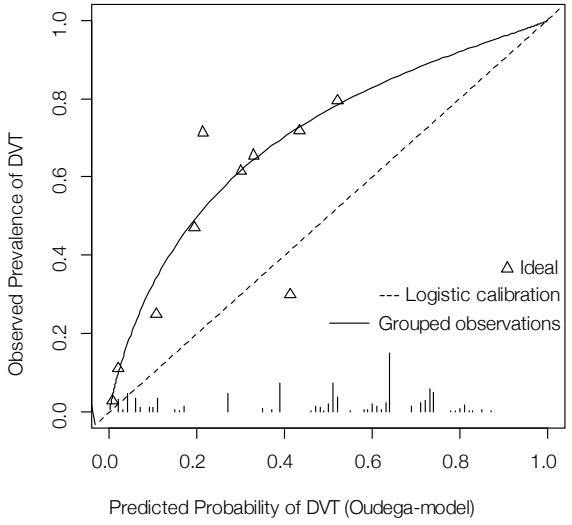
1c- Prevalence of DVT across high score (risk) categories of the Oudega-rule

Varying the threshold on the Oudega rule to rule in venous thromboembolism N=348	Number of patients (% of total)	Prevalence of VTE (true positive rate) (% of sub-group)
≥7 (= moderate to high according to original rule)	254 (73.0)	154 (60.6)
≥8	220 (63.2)	144 (65.5)
≥9	160 (46.0)	106 (66.3)
≥10 (=high according to original rule)	80 (23.0)	55 (68.8)
≥11	16 (4.6)	12 (75.0)
12	2 (0.6)	2 (100)

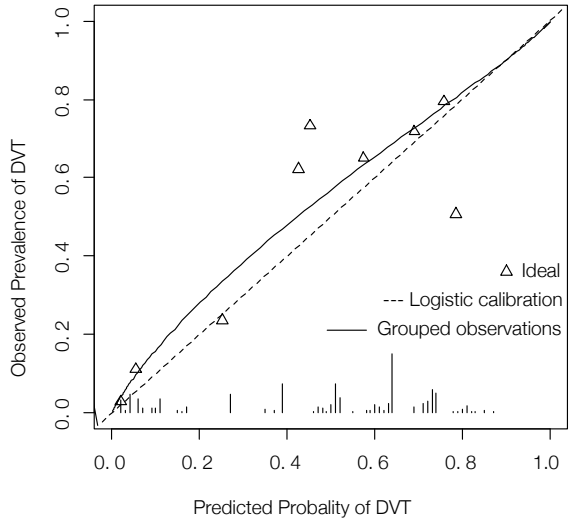
APPENDIX 2

Calibration of Oudega model in VT-elderly data

Calibration of the Oudega model on the VT-elderly data.



Calibration of the Oudega model with updated intercept in the VT-elderly data (according to Janssen et al).[1] Correction factor intercept 1.06.



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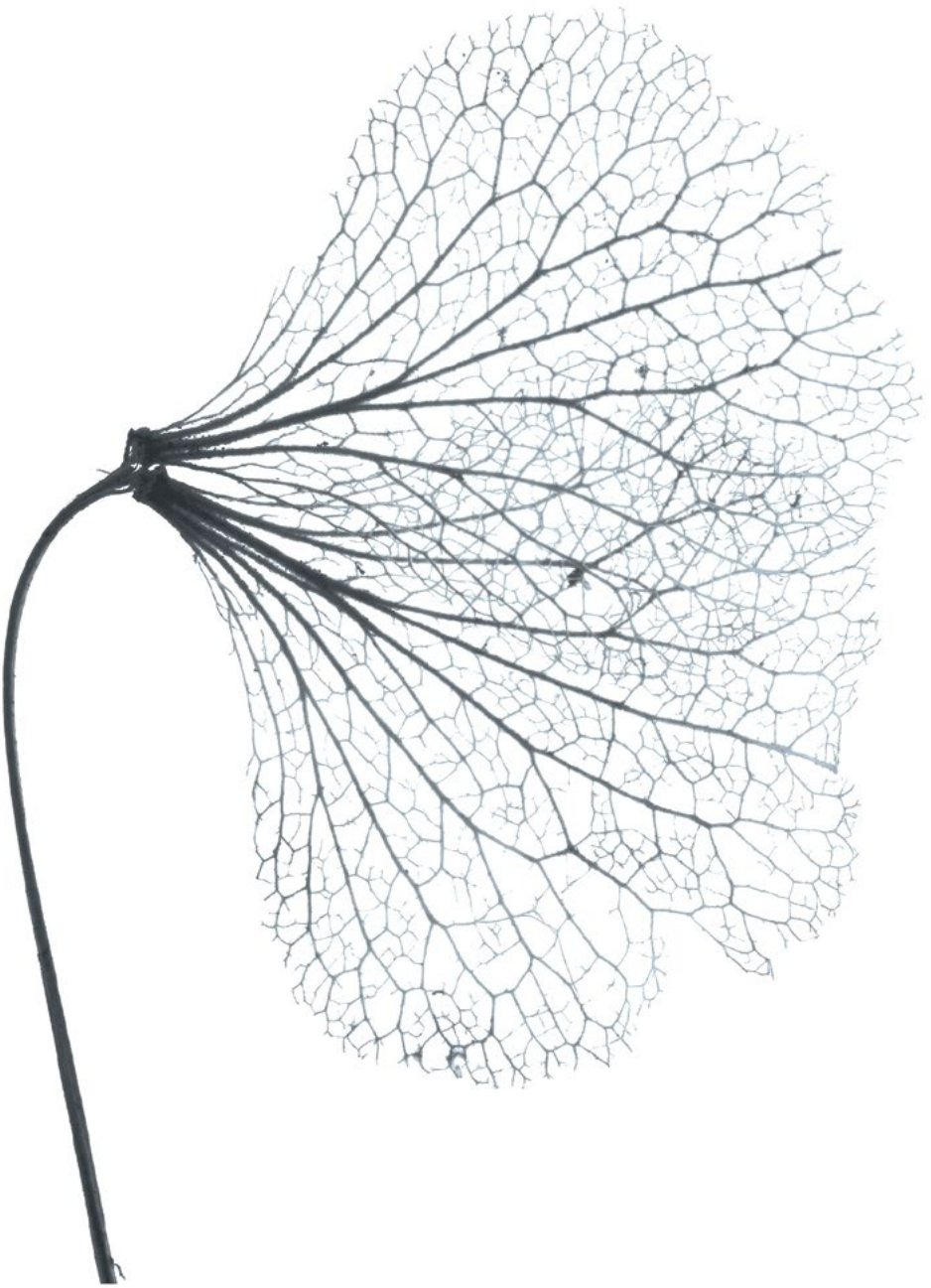

CHAPTER 4

ACCURACY OF THE WELLS-RULE FOR PULMONARY EMBOLISM IN OLDER AMBULATORY PATIENTS

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Submitted.

ABSTRACT

Importance The Wells-rule combined with normal D-dimer testing can be used to exclude pulmonary embolism (PE).

Objective To assess the accuracy of this rule-out strategy in older suspected out-of-hospital patients.

Design Prospective cohort study.

Setting Primary care and nursing homes.

Participants Older patients (≥60 years) clinically suspected of PE.

Main outcomes and Measures The presence of PE was confirmed with a composite reference standard including computed tomography and 3-month follow-up. We calculated the proportion of patients with an unlikely risk according to the Wells-rule (≤4 points) plus a normal qualitative point-of-care D-dimer test (efficiency) and the presence of symptomatic PE during 3-month follow-up within these patients (failure rate). In a post hoc analysis we estimated the efficiency and failure rate of a revised and internally validated diagnostic strategy for older patients.

Results From July 2007 to April 2013, a total of 294 patients were included (mean 76 years, 44% resided in nursing homes). PE occurred in 83 patients (28%). A total of 85 patients had an unlikely Wells-score and a normal D-dimer test (efficiency 29%). In five of these 85 patients, non-fatal PE occurred during 3-month follow-up (failure rate 5.9%; 95% confidence interval 2.5% to 13%). According to a refitted diagnostic strategy for older patients, 69 patients had a low risk of PE (24%) of whom two had PE (failure rate 2.9%; 0.8 to 10%).

Conclusions and relevance The failure rate of the Wells-rule in combination with a qualitative D-dimer test was higher in older patients as compared to previous studies in younger aged patients. A revised diagnostic strategy specifically for older suspected patients resulted in a lower failure rate. External validation of this revised diagnostic approach for older patients with suspected PE is needed.

INTRODUCTION

Given the exponential rise of the incidence of venous thromboembolism with increasing age, the majority of pulmonary emboli occur in older patients.[1-4] The short-term mortality of pulmonary embolism (PE) also rises with age and can be as high as 16% in the elderly.[5] Yet, though accurately and timely diagnosing PE can be lifesaving, this is notoriously difficult in the elderly in whom clinical signs and symptoms of PE are of low diagnostic value and may be mimicked by cardiac or pulmonary comorbidities.[6,7] As a result, physicians need to refer many suspected older patients to 'catch' one confirmed case of PE: typically only 20% of older suspected patients have confirmed PE when actually referred for computed tomography of the pulmonary arteries.[8] This can be frustrating in clinical practice, as particularly the frail elderly are vulnerable for distress resulting from transitions to hospital-care and for nephropathy induced by the contrast needed for computed tomography.[9-12]

Diagnostic decision rules like the Wells-score (see table 1) combined with D-dimer testing have been developed to distinguish a subgroup of patients in whom the presence of PE can be correctly excluded without the need for further diagnostic work-up.[13] This rule-out strategy has been extensively validated in both primary and hospital care, mainly in younger aged patients.[14,15] Notably frail older patients might benefit from such a strategy provided that it can correctly rule-out PE in a substantial proportion of them without needing to be referred for imaging examination.

Surprisingly though, the accuracy of the existing clinical decision rules to rule-out PE has never been tested in frail elderly populations. This is important, as a change in setting results in a different case mix, which can affect the diagnostic accuracy and thus generalizability of decision rules to new patients.[16-18] Therefore, we set out a prospective study to assess the accuracy of the Wells-strategy to safely exclude PE in suspected frail older out-of-hospital patients.[19]

METHODS

This validation-study was based on combined data of two prospective observational studies with 3 months follow up in the Netherlands. The first study, the Venous Thromboembolism in the Elderly study (VT-elderly-study), enrolled community dwelling patients aged 60 years or over and patients residing in nursing homes with a clinical suspicion of venous thromboembolism (either deep vein thrombosis or PE or both) between October 2008 and April 2013.[20] For its' observational character, our study was judged as exempt from review by the local ethics review board of the University Medical Center Utrecht, the Netherlands, according to the national law. To enhance accrual and to reduce patient burden, we also recruited participants of the AMUSE2-study which was performed by the same investigators in primary care setting between July 2007 and December 2010. The main results of this study have been published previously.[14]

Older patients (60 years and over) with a clinical suspicion of PE were eligible for inclusion. This suspicion was based on unexplained (deterioration of) dyspnea, pain on inspiration or unexplained cough. Patients were not eligible for inclusion if they received anticoagulant treatment (vitamin K antagonists or oral direct thrombin- or factor Xa-inhibitors) at presentation or if they declined providing informed consent. All physicians were provided with written instructions about the logistics of the study and with qualitative point-of-care tests (Clearview Simplify D-dimer assay®, Inverness Medical Princeton, NJ USA) plus instructions for the performance and interpretation of this test.

Diagnostic strategy under study

The primary aim of this study was to validate the accuracy of the Wells-rule combined with qualitative D-dimer testing to rule out PE in elderly out-of-hospital patients. Physicians systematically recorded each patient's medical history and signs and symptoms and the patient's score on the Wells-rule (see table 1).[21] Subsequently, the qualitative point-of-care D-dimer test was performed. Physicians were recommended to refer all patients with either a 'likely' score on the Wells-rule (>4 points) or an abnormal D-dimer test and to withhold referral in patients with an 'unlikely' score (≤4 points) on the Wells-rule plus a normal D-dimer test. However, the pragmatic design of the study left it to the physicians' discretion whether a patient was indeed referred for further diagnostic investigations. Though not obligatory for the research protocol, for 208 study participants (60.1% of the total population) a quantitative D-dimer test was performed and analyzed in local laboratories.

Outcomes

The presence of PE was confirmed with a composite reference standard including computed tomography of the chest, VQ-scanning, compression ultrasonography of the leg and 3-month follow-up. At 3 months, follow up was performed for all patients to assess the occurrence of any venous thromboembolic event, major and clinically relevant non-major bleeding complication (according to the definition of the International Society on Thrombosis and Hemostasis)[22] and - if applicable - cause of death. PE was considered present if 1) there was confirmed PE on computed tomography pulmonary angiography or VQ-scanning of the chest or 2) in case of confirmed deep vein thrombosis with ultrasonography of the leg or in case of 3) death within 3 months which was probably related to PE.

All patients who were not referred to a hospital for objective testing despite a score > 4 on the Wells-rule or an abnormal D-dimer test and all patients in whom anticoagulant treatment was initiated without objective confirmation of the diagnosis were evaluated by an adjudication committee of 3 experts. If - based on all available clinical information - PE was deemed present by the committee, patients were further classified and analyzed accordingly. Deaths were similarly evaluated by this committee and were adjudicated as probably or unlikely related to PE.

Analyses

Some participants had missing values for one or more items of the Wells-rule or the D-dimer test or had incomplete follow up data (1.4%; 3.0% and 4.7% respectively). To minimize the effect of bias associated with selectively ignoring these patients, missing values were multiple imputed by the chained equations procedure, given the at random pattern of 'missingness' (MAR).

The primary analysis focused on the proportion of patients with an unlikely risk (a Wells-score ≤4) plus a normal D-dimer result among the total suspected population (i.e. efficiency), and the proportion of patients with symptomatic PE during 3 months of follow-up within the patients with an unlikely risk plus a normal D-dimer result (failure rate; i.e. 1 minus the negative predictive value). Binominal exact 95% confidence intervals were calculated according to the Wilson Score method.

Next we performed post-hoc analyses. We calculated the 3-month incidence of PE within different score-categories of the Wells-rule and in the unlikely risk categories according to the modified and the simplified Wells-score as proposed by Gibson and colleagues (table 1).[23] Finally, we revised the model to the specific case-mix in this elderly suspected population. We refitted the Wells-model and D-dimer test within our data thereby re-estimating all coefficients and the intercept. As our study was not primarily powered to derive a new model, we did not add extra predictors to the model. Rather we applied stepwise backward selection within the Wells-model using a p-value of >0.1 on the likelihood ratio test as exclusion criterion.[24] As newly derived models tend to perform worse and overestimate the risk if applied in patients outside the study sample (i.e. overfitting),[25] we corrected the newly derived coefficients with a shrinkage factor, which was de-

Table 1 Clinical decision rules under study

Variables	Points on the original Wells rule[21]	Points on the modified Wells rule[23]	Points on the simplified Wells rule[23]
Clinical signs and symptoms of deep vein thrombosis	3.0	2.0	1.0
PE more likely than alternative diagnosis	3.0	2.0	1.0
Heart rate >100 beats/min	1.5	1.0	1.0
Immobilization (>3 days) or surgery in previous 4 weeks	1.5	1.0	1.0
Previous PE or deep vein thrombosis	1.5	1.0	1.0
Hemoptysis	1.0	1.0	1.0
Malignancy (receiving treatment, treated in past 6 months, or palliative)	1.0	1.0	1.0
Posttest probability based on the Wells rule			
Unlikely	≤4	≤2	≤1
Likely	>4	>2	>1
Low	<2	n.a.	n.a.
Moderate	2-6	n.a.	n.a.
High	>6	n.a.	n.a.

n.a.= not applicable

rived from internal validation within 1,000 bootstrap samples.[26,27] To construct an easily applicable diagnostic rule, the regression coefficients were transformed and rounded according to their relative contributions. We then calculated the numbers of patients and the 3-month incidence of PE across score categories according to this adapted diagnostic strategy.
All analyses were performed using R-2.15.3 for Windows.

RESULTS

Study participants

A total of 312 older suspected PE patients were evaluated of whom 18 were excluded as they fulfilled an exclusion criterion (n=17 anticoagulant use, n=1 declined providing informed consent) leaving 294 study participants. The mean age was 76 years, 129 participants (44%) resided in nursing homes, 36 had a history of coronary artery disease (12%) and 28 (10%) had an active malignancy (table 2).
According to our composite reference standard, PE was confirmed in 83 patients (28%); fatal PE presumed to have occurred in 11 of them (13%). Another 32 patients died within 3 months to causes not attributable to PE, resulting in a 3-month all-cause mortality rate of 15%. Major bleeding occurred in 2 patients and clinically relevant non-major bleeding in 3 patients (figure 1).

Patients with an unlikely risk of PE and a normal D-dimer test

Of the 294 study participants, 85 had an 'unlikely' Wells-score (≤4 points) in combination with a normal D-dimer test (efficiency 29%; 95% confidence interval 24 to 34%; figure 1). In five of these 85 patients, non-fatal PE occurred during 3-month follow-up (failure rate 5.9%; 2.5% to 13%). The characteristics of these five patients are described in table 3. One of these five patients had not undergone imaging examination but was adjudicated as PE present. If instead, for this patient it were adjudicated that PE was absent, the failure rate of the Wells-strategy would have been 4.7% (1.8 to 11%).

Scenario analyses

If physicians would have combined a normal D-dimer test with the Wells-score but using a lower threshold, i.e. <2 instead of ≤4, 2 extra former missed cases would have been detected. This would be at the expense of an extra 37 patients needing to be referred, resulting in an efficiency of 16% (13 to 21%) and a failure rate of 6.3% (2.1 to 17%; table 4).
If the modified Wells-score was applied instead of the original Wells-score (table 1), PE would still be missed in the same 5 patients (failure rate 6.0%; 2.6 to 13%). With the simplified Wells-score, 2 extra patients who were missed on the original Wells-score would be detected (failure rate of 4.2%; 1.4 to 12%) at the expense of 13 extra patients needing referral (efficiency 25%; 20 to 30%).

Table 2 Characteristics of the study participants

Patient characteristic	Frequency n (%)
Total study population	294 (100)
Patients with confirmed PE	83 (28.2)
Demographic characteristics	
Male	99 (33.7)
Age, years, mean (standard deviation)	75.6 (10.3)
Residing in nursing home	129 (43.9)
Symptoms	
Unexplained dyspnea	190 (64.6)
Pain on inspiration	144 (49.0)
Chest pain	110 (37.4)
Unexplained cough	77 (26.2)
Acute onset of symptoms	208 (70.8)
Duration of complaints, days, median (interquartile range)	3 (6)
Signs	
Concomitant suspicion of DVT*	41 (14.0)
Hemoptysis*	8 (2.7)
Tachycardia (>100 beats/minute)*	82 (27.9)
Mean heart rate (standard deviation)	86.9 (18.9)
Mean respiratory rate (standard deviation)	22.1 (7.9)
Crepitations	103 (35.0)
D-dimer abnormal	191 (65.0)
Medical history	
Previous episode of deep vein thrombosis*	28 (9.5)
Previous episode of PE*	37 (12.6)
Chronic obstructive pulmonary disease	54 (18.2)
Heart failure (diagnosed with ultrasonography of the heart)	39 (13.3)
Angina pectoris	36 (12.2)
Myocardial infarction	34 (11.6)
Active malignancy*	28 (9.5)
Immobilization or surgery in previous month*	88 (29.9)
Co medication	
Antiplatelet therapy	97 (33.0)
Prophylactic dose of low molecular weight heparin	12 (4.1)

n.a.= not applicable; * predictor in the Wells rule; ‡ including patients residing in homes for the elderly

Revised strategy to exclude PE in older patients

As the failure rate for the Wells-strategy (original, modified or simplified) when applied to older outpatients might be considered too high, we refitted a diagnostic model in combination with the D-dimer result within our study-population. With this revised strategy (adjusted for overfitting; shrinkage factor 0.89 (table 5)), a group of 69 patients with a 'low risk' of PE (<2 points) could be assigned (efficiency 24%; 19 to 29%; figure 2). PE was present in 2 of these 69 patients (failure rate 2.9%; 0.8 to 10%). Also, 53 patients (18% of the total population) with a 'high risk' of PE (>6 points) could be distinguished; 39 of these patients indeed had PE (74%; 60 to 84%). PE was confirmed in 42 (24%; 29 to 31%) of the remaining 172 patients (59% of the total population; 2 to 6 points).

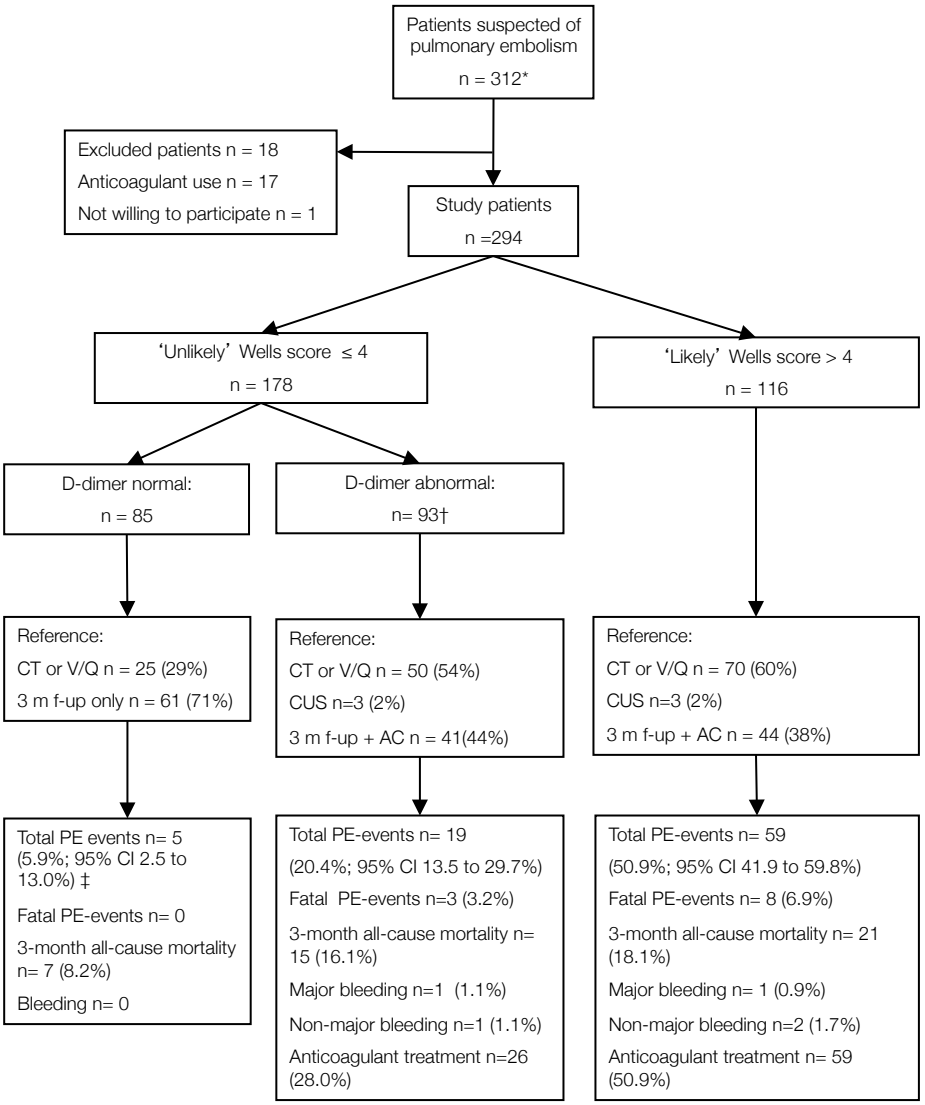
DISCUSSION

We assessed the accuracy of the Wells-strategy combined with a qualitative point-of-care D-dimer test to rule-out PE in frail older out-of-hospital patients.[21] The failure rate of this strategy was higher (6%) than expected based on previous validation studies conducted among younger aged suspected patients; a recent meta-analysis on the same strategy (Wells-score ≤4 combined with a normal D-dimer test) to exclude PE in - on average younger - suspected patients reported a failure rate below 1%.[15]

The difference between our and previously reported failure rates likely results from the much higher prevalence of PE in our older study population (almost 30%) as compared to prevalence in the previous studies (ranging from 9.5% to 23%). This substantially higher prevalence in our study resulted in a higher prior-probability for PE and thereby likely to a lower proportion of patients that could be correctly classified as PE absent (i.e. a higher failure rate).[13,14,28-33] Yet, though we cannot fully exclude the possibility that this higher prevalence reflects a somewhat lower awareness of PE among elderly care physicians, we stress that our study population represents a distinct population of frail old patients (mean age 76 years) with many co-morbidities (table 2), a short life expectancy (3-month all-cause mortality rate 15%) and almost half of the patients residing in nursing homes. As age, nursing home confinement and co-morbidity are all strong risk factors for PE, this higher prevalence of PE in our frail old population could thus have been expected.[2,4,34,35]

The higher failure rate in our study might also be (partly) explained by the application of a qualitative point-of-care D-dimer assay. This assay has a somewhat lower sensitivity than the high-sensitive ELISA assays.[36] In the current study, we found that in four of the five PE cases in the low risk category (based on a normal qualitative D-dimer test and a total Wells-score ≤4), the D-dimer test result would have been classified abnormal according to a quantitative D-dimer test (table 3). Nevertheless, two previous validation studies where the same D-dimer assay in combination with clinical decision rules were applied still yielded much lower failure rates (1.5% and 1.4%). But, as said, the prevalence and thereby the prior probability of venous thromboembolism was much lower in these studies (12% and 14%) as compared to our study.[14,37]

Figure 1 Flow of participants through the study, using the original Wells score[13]



*n=150 patients were entered in the study via the AMUSE2 –study; ‡ one of the missed patients did not undergo reference testing but was adjudicated as PE positive, if this patient were adjudicated as PE negative the failure rate would have been 4.7% (1.8 to 11.4%) ; †D-dimer result was invallid or uniterpretable in 7 patients.
VTE=venous thromboembolism; CT = computed tomography; V/Q = ventilation-perfusion; CUS= compressionultrasonography of the lower extremity, 3 m f-up = 3 months follow-up; AC= adjudication committee; D-Dimer positive= quantitive D-dimer ≥500 µg/L and/or POC DD test positive

Table 3 Detailed description of the 5 patients classified as unlikely risk (based on a Wells-score of ≤4) and with a normal D-dimer test but diagnosed with PE.

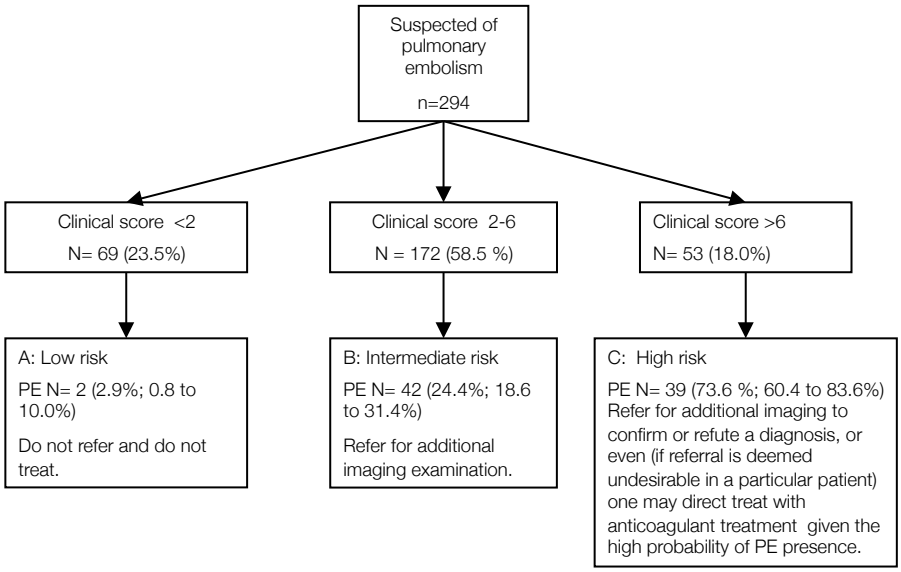
Patient No	Description	Reference test
1	80-years old female, community dwelling, subacute progressive shortness of breath after a flight. Painful and swollen leg, no chestpain. Wells-score*=3 points (immobilization and prior deep venous thromboembolism). Point of care D-dimer test normal. Quantitative D-dimer 4000 µg/L.	CUS + CT
2	75-years old male, community dwelling. Acute onset of pain on inspiration, no dyspnea. Wells-score*= 1.5 (prior venous thromboembolism). Point of care D-dimer test normal. Quantitative D-dimer 6820 µg/L.	CT
3	66-years old male community dwelling, acute onset of dyspnea, no chest pain. Wells-score*= 0 points. Point of care D-dimer test normal. Quantitative D-dimer 1530 µg/L.	CT
4	77-years old female, chair bound, nursing home resident. Dyspnea and cough. Wells-score*= 1.5 points (tachycardia). Point of care D-dimer test normal. Quantitative D-dimer 3600 µg/L. Passed away 6 weeks after suspicion of PE, supposed cause of death hearth failure.‡	Adjudication panel‡
5	63-years old female, community dwelling, acute dyspnea, pain on inspiration, chest pain and pain on inspiration, after a long haul flight. Wells-score*=3 points (tachycardia and immobilization). Point of care D-dimer test normal.	CT

* as scored by their physician; CUS= compression ultrasonography of the lower limb, ‡adjudicated as PE present but mortality not due to PE.

Table 4 Scenario analyses

n=294	**Number of patients** (% of total; 95% confidence interval)	**Prevalence of PE** (% of subgroup; 95% confidence interval)
Original Wells score ≤ 4, and normal D-dimer		
All study participants	85 (28.9; 24.0 to 34.3)	5 (5.9; 2.5 to 13.0)
Varying the threshold on the original Wells rule combined with D-dimer testing		
Low Wells score (<2) + normal D-dimer	48 (16.3; 12.5 to 21.0)	3 (6.3; 2.1 to 16.8)
Likely Wells score (>4) + abnormal D-dimer	98 (33.3; 28.2 to 38.9)	58 (59.2; 49.3 to 68.4)
High Wells score (>6) + abnormal D-dimer*	16 (5.4; 3.4 to 8.7)	13 (81.3; 57.0 to 93.4)
Modified Wells Rule[23]		
Low score on modified Wells-rule (≤2) + normal D-dimer	83 (28.2; 23.4 to 33.6)	5 (6.0; 2.6 to 13.3)
Simplified Wells Rule[23]		
Low score on simplified Wells-rule (≤1) + normal D-dimer	72 (24.5; 19.9 to 29.7)	3 (4.2; 1.4 to 11.6)

Figure 2 Revised diagnostic strategy for the elderly to refute or diagnose PE



Strengths and limitations of the study

To our knowledge, this is the first study on the accuracy of diagnostic strategies to exclude PE with particular focus on frail older patients.

However, some aspects of our study require comment. First, a combination of tests combined with 3-month follow-up were used to define the presence or absence of PE. Also, by protocol, the choice of the applied reference test was related to the score on the Wells-rule and the D-dimer result (differential disease verification).[38,39] For patients with an unlikely risk and normal D-dimer test we had to rely on clinical follow-up to detect any missed pulmonary emboli. This could have introduced small under- or overestimations of the failure rates as small (probably clinically less relevant) emboli may have been missed in these patients or de novo pulmonary emboli could have been developed within these 3 months.[38,39]

Second, to approach clinical practice, we used the clinical variables as scored by the physicians. As a result, there might have been some inter-rater variability in the interpretation and subsequent scoring of the more subjective items of the Wells' rule like the item "PE more likely than alternative diagnosis".

Furthermore, 85 patients (29%) with either a likely score on the Wells-rule (>4 points) or an abnormal D-dimer test were not referred for imaging examination. Since the physicians' decision to withhold imaging examination was related to patient-characteristics (referral was notably withheld

Table 5 Refitted diagnostic strategy for the elderly to refute or diagnose PE. C-statistic (optimism corrected) 0.80 (95% confidence interval 0.75 to 0.86). Correction factor slope 0.89, correction factor intercept -0.06.

Variables for PE (Wells strategy)	Regression coefficient in derivation cohort[20]	Points original rule[20]	Regression coefficient in VT-elderly study (retaining after backward selection)	Points based on VT-elderly (coefficients * 1.65)
Signs/ symptoms of DVT	1.8	3.0	1.14	2
PE most likely diagnosis	1.5	3.0	1.01	1.5
Heart rate >100 beats/min	1.1	1.5	0.90	1.5
Immobilisation or surgery	0.87	1.5	0.56	1
Previous VTE	0.92	1.5	1.21	2
Haemoptysis	0.87	1.0	-	
Malignancy	0.81	1.0	-	
D-dimer abnormal	-	Not in rule	1.75	3
Intercept	a		-3.76	

a No value for the intercept was reported in the publication describing the Wells score
Predicted probability of PE according to original Wells rule =1/(1+exp-(intercept a+ 1.8* signs and symptoms of DVT + 1.5*PE most likely + 1.1*tachycardia + 0.87*recent immobilization or surgery +0.92*previous VTE + 0.87*hemoptysis + 0.81*malignancy)).
Predicted probability of PE according to the updated rule =1/(1+exp-(-3.76+ 1.14* signs and symptoms of DVT + 1.01*PE most likely + 0.90*tachycardia +0.56*immobilization or surgery +1.21*previous VTE + 1.75*abnormal D-dimer)).

for the frailest patients and patients in terminal life-phase), we chose not to exclude these patients to avoid selection of only the 'fittest elderly'. Instead, an adjudication committee of experts in the field of venous thromboembolism decided on each of these 85 patients whether it was likely or unlikely that PE indeed was present. This might also have introduced some classification errors of the final diagnosis, but it highly reflects clinical practice. To avoid differential verification bias, we explicitly focused - according to recent methodological standards - on predictive values (i.e. the failure rate) rather than on estimates of the sensitivity and specificity as the former estimates are hardly affected by differential verification.[38,39]

Clinical implications

Though there is no consensus on what exact proportion of missed cases is still acceptable, many studies have considered a point-estimate of around 2% missed cases as acceptable as these values correspond with the proportion of missed cases given that all suspected patients were referred for the gold standard (CT pulmonary angiography).[13-15,28-33,40] Based on this safety standard of 2%, one has to consider the use of an unlikely Wells-score combined with normal qualitative D-dimer test as investigated in our study as an unsafe strategy to rule out PE in frail older out-of-hospital patients. Accordingly this would actually imply that all frail older out-of-hospital patients with suspected PE should be referred to undergo computed tomography; including those with a 5.9% risk of subsequent PE as based on an unlikely Wells score combined with a normal D-dimer test. Referring all suspected patients seems unappealing and unrealistic for this frail population. Indeed, referral was withheld in more than half (54%) of the nursing home patients who had a likely risk according to the Wells-rule or an abnormal D-dimer test. Clearly, the potential risks and burden of additional testing and hospital transfers for frail older patients such as the risk of contrast-induced nephropathy and functional decline implicitly played a role in this decision making.[10,41-44] These considerations and the higher failure rate in older patients as compared to the younger aged, may raise a discussion among elderly care professionals whether the original Wells-strategy might still be considered useful for frail elderly outpatients with suspected PE as it can contribute to avoidance of burdensome imaging examinations for 29% them. However, the medical professional may consider the failure rate still as too high or the efficiency of 29% as too low. This prompted us to perform several post-hoc analyses, to provide direction for future diagnostic work up of PE in this distinct population. We first assessed whether lowering the threshold or using the simplified or modified version of the Wells' strategy could improve the safety.[23] However, none of these strategies resulted in a substantial reduction of the failure rate. Secondly, we developed a revised strategy within our elderly study population resulting in an improved safety (2.9%), but still with an efficiency of 24%.[14]

Considering the possible harms of referral to a hospital for elderly patients, we assessed whether it was possible to further reduce the referral rate by considering a rule-in strategy for the frailest patients. For this purpose, our revised strategy can also be used to distinguish elderly patients (18% of the study population) with a high risk of PE (74%). In these patients anticoagulant treatment might be directly initiated if referral is deemed undesirable. The downside of this 'rule-in strategy' is that approximately 25% of the patients in this high-risk group would be exposed to the risks and burden of anticoagulant therapy while no PE is indeed present.[45] Yet, by using this combined rule-out and rule-in approach, clinicians would be able to make a decision for 42% of older patients with suspected PE (rule out the diagnosis in 24% and rule in the diagnosis in 18%; figure 2) and thereby to avoid he burden of referral to a radiology department and the subsequent risk of contrast induced nephropathy in these frail older patients for whom the disadvantages of further testing are of particular concern.

Conclusions and implications

The Wells-strategy for PE (original, modified simplified, or by using a lower threshold) in combination with a qualitative D-dimer test has a lower safety when applied in frail older out-of-hospital patients as compared to previous studies among younger ages. Our findings highlight that frail older out-of-hospital patients with suspected PE represent a distinct population in whom the use of a well-known and widely used Wells-strategy does not guarantee safe exclusion of PE. We therefore refitted a new diagnostic strategy for older suspected patients, resulting in an improved safety.[19] Our revised diagnostic model for the elderly was also able to distinguish patients with a very high probability of PE in whom treatment might be directly initiated if referral to a hospital is considered as too burdensome. This might enable clinicians' decision-making for 42% of older patients without the need for further diagnostic work-up. Before implementing our revised diagnostic strategy for the frail elderly in daily practice, its acceptability should be discussed among health-care-providers. Moreover, we worked with a relatively small dataset which made the updated model prone for overfitting. Though we corrected for this as much as possible with shrinkage methods, further validation of our revised strategy for the elderly suspected PE patients in larger study populations is needed.[17,19]

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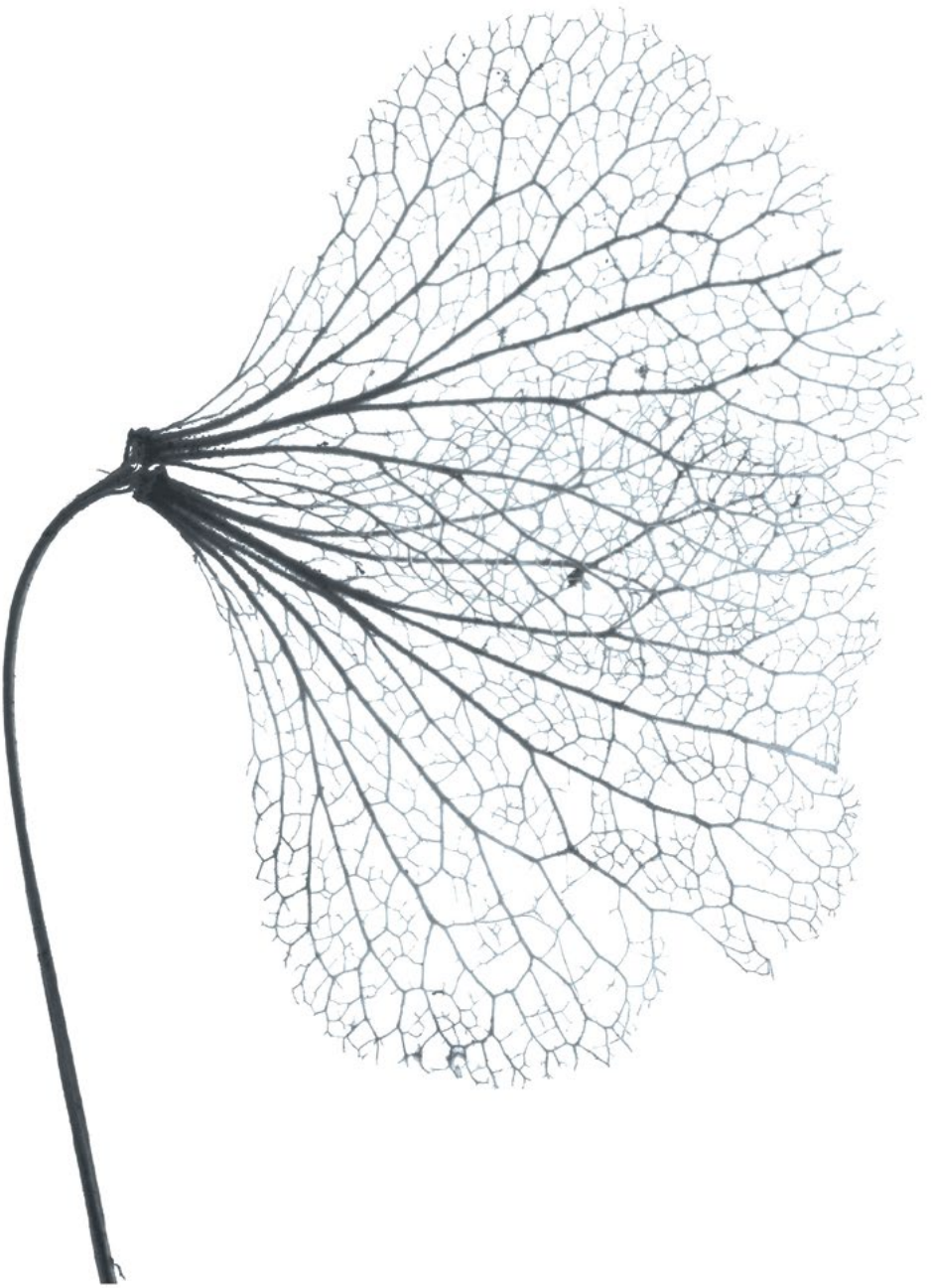

CHAPTER 5

VALIDATION OF TWO AGE DEPENDENT D-DIMER CUT-OFF VALUES FOR EXCLUSION OF DEEP VENOUS THROMBOSIS IN SUSPECTED ELDERLY PRIMARY CARE PATIENTS

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ABSTRACT

Objective To determine whether the use of age adapted D-dimer cut-off values can be translated to primary care patients who are suspected of deep vein thrombosis.

Design Retrospective, cross sectional diagnostic study.

Setting 110 primary care doctors affiliated with three hospitals in the Netherlands.

Participants 1,374 consecutive patients (936 (68.1%) aged >50 years) with clinically suspected deep vein thrombosis.

Main outcome measures Proportion of patients with D-dimer values below two proposed age adapted cut-off levels (age in years×10 µg/L in patients aged >50 years, or 750 µg/L in patients aged ≥60 years), in whom deep vein thrombosis could be excluded; and the number of false negative results.

Results Using the Wells score, 647 patients had an unlikely clinical probability of deep vein thrombosis. In these patients (at all ages), deep vein thrombosis could be excluded in 309 (47.8%) using the age dependent cut-off value compared with 272 (42.0%) using the conventional cut-off value of 500 µg/L (increase 5.7%, 95% confidence interval 4.1% to 7.8%). This exclusion rate resulted in 0.5% and 0.3% false negative cases, respectively (increase 0.2%, 0.004% to 8.6%).The increase in exclusion rate by using the age dependent cut-off value was highest in the oldest patients. In patients older than 80 years, deep vein thrombosis could be safely excluded in 22 (35.5%) patients using the age dependent cut-off value compared with 13 (21.0%) using the conventional cut-off value (increase 14.5%, 6.8% to 25.8%). Compared with the age dependent cut-off value, the cut-off value of 750 µg/L had a similar exclusion rate (307 (47.4%) patients) and false negative rate (0.3%).

Conclusions Combined with a low clinical probability of deep vein thrombosis, use of the age dependent D-dimer cut-off value for patients older than 50 years or the cut-off value of 750 µg/L for patients aged 60 years and older resulted in a considerable increase in the proportion of patients in primary care in whom deep vein thrombosis could be safely excluded, compared with the conventional cut-off value of 500 µg/L.

INTRODUCTION

Venous thromboembolism (pulmonary embolism and deep vein thrombosis) is a common disease in elderly people. In fact, the annual incidence of venous thromboembolism rises sharply with age, from an insignificant rate in children (less than five cases per 100000 people) to 450-900 cases per 100000 people in those older than 80 years.[1;2] Short term mortality of venous thromboembolism also increases with age, and can occur in more than 15% of elderly patients.[1;3] Hence, especially in this age group, accurate and timely diagnosis of venous thromboembolism can be lifesaving.[4] However, comorbidity often camouflages typical signs and symptoms of venous thromboembolism, and the diagnosis of deep vein thrombosis and pulmonary embolism is difficult and is often missed in elderly populations.[4]

Accurate exclusion of venous thromboembolism can be improved by the additional use of tests to measure the concentration of D-dimer (a degradation product of fibrin). Negative test results are commonly used to rule out patients with suspected venous thromboembolism and a low clinical probability.[5;6] However, D-dimer concentration increases with age and its specificity for venous thromboembolism decreases in elderly patients.[7;8] This effect leads to more false positive test results in elderly people (that is, detection of a lower proportion of these patients in whom venous thromboembolism can be excluded). As a result, many elderly patients could be referred to hospital unnecessarily for additional testing.[9;10;11] Many physicians would prefer to rule out venous thromboembolism (especially in frail elderly patients) without an often burdensome referral.

To improve the diagnostic strategy of suspected venous thromboembolism in elderly patients, Douma and colleagues[10] recently derived and internally validated an age dependent D-dimer cut-off value for those with clinically suspected pulmonary embolism in secondary care. The researchers defined this cut-off value as age (years)×10 µg/L in patients older than 50 years (for example, a patient aged 73 years would have a cut-off value of 73*10=730 µg/L). Use of this formula doubled the proportion of patients older than 70 years in whom pulmonary embolism could be excluded, without hampering the false negative rate of such an approach.[10] In addition, Haas and colleagues proposed an alternative, fixed cut-off value of 750 µg/L in patients aged 60 years and older who were referred to secondary care with symptoms of deep vein thrombosis.[12] This proposed cut-off value also yielded an increased proportion of patients in whom deep vein thrombosis could be correctly excluded.

The age dependent value and fixed value can both help safely exclude venous thromboembolism in a large proportion of frail elderly patients without the need for burdensome referrals for further diagnostic work-up. However, the age dependent cut-off value was not validated for use in patients suspected of deep vein thrombosis. Since deep vein thrombosis and pulmonary embolism can be seen as expressions of the same disease,[13] we hypothesised that use of the age dependent cut-off value could be extrapolated to patients with suspected deep vein thrombosis. Furthermore, both the age dependent value and the fixed value were not validated in primary care.

Before implementing these different cut-off values for patients with suspected deep vein thrombosis, a formal validation study would be needed.[14 15] Therefore, we aimed to compare the exclusion rate and false negative rate of both proposed cut-off values with those of the conventional cut-off value of 500 µg/L for the exclusion of deep vein thrombosis in a large cohort of patients with clinically suspected deep vein thrombosis in primary care.

METHODS

Patients

We performed a retrospective analysis of data from two originally prospective, diagnostic accuracy studies that included 2086 primary care patients suspected of deep vein thrombosis. The first study was a derivation study for a new diagnostic rule to determine the presence or absence of deep vein thrombosis in primary care patients (n=1,295).[16] On behalf of validation of the newly derived rule, researchers extended the study within the same setting and added 791 patients to the initial cohort[9;17] (so-called temporal validation).[18;19] The characteristics of these studies have been published previously.[9;16;17;20]

In short, the studies were conducted among 110 primary care physicians affiliated with three hospitals in the Netherlands, between 1 January 2002 and 1 January 2006. The three adhering hospitals participated in a diagnostic programme in which the primary care physicians used diagnostic facilities of the hospital without referring the patient to a hospital specialist. All consecutive adults with a clinical suspicion of deep vein thrombosis were eligible for inclusion. Suspicion of deep vein thrombosis was based on swelling, redness, or pain of the lower extremities. The study excluded patients if symptoms and signs lasted for more than 30 days and if there was a suspicion of pulmonary embolism. The study also excluded patients receiving anticoagulant treatment at presentation or who were unwilling to participate in the studies. Written informed consent was obtained from patients. The studies were approved by the local ethics review boards of the University Medical Center Utrecht, the Netherlands.

Each patient was assessed for the clinical probability score according to Wells,[21] and measured for plasma D-dimer (VIDAS (Biomerieux) or Tinaquant (Roche) assays). On the same day, all patients underwent reference testing by repeated compression ultrasonography of the symptomatic leg, performed with a real time, B-mode, linear array sonographic scanner at 5.0-7.5 MHz (system V GE/Sonotion).[22] The entire proximal deep vein system was explored for compressibility. In patients with a normal ultrasonography, the test was repeated at day seven. Deep vein thrombosis was established if at least one of the deep veins in the legs was not completely compressible at one of the two compression ultrasonography examinations, or excluded after two negative examinations (that is, revealing completely compressible veins of the legs). The performers and

Table 1 Baseline characteristics of study patients with clinically suspected deep vein thrombosis. Data are no (%) of patients unless specified otherwise

	No of patients (N=1374)
Age (years)*	59.3 (17.4)
Female	863 (62.8)
Active malignancy	61 (4.4)
Paresis	194 (14.1)
Recent surgery or bedridden	168 (12.2)
Localised tenderness in deep vein system	966 (70.3)
Entire leg swollen	596 (43.4)
Calf distension ≥3 cm	551 (40.1)
Pitting oedema	838 (61.0)
Vein distension	254 (18.5)
Alternative diagnosis present	672 (48.9)
History of deep vein thrombosis	284 (20.7)
Wells score*	1.66 (2.0)
Prevalence of deep vein thrombosis	270 (19.7)

*Data are mean (standard deviation).

interpreters of the examinations (board certified radiologists) were blinded to information on the patient's history, physical examination and D-dimer test results.

Data analysis

For the current analysis, we included only participants for whom D-dimer test results were available (n=1,374). We calculated the clinical probability of deep vein thrombosis for all patients using the Wells clinical prediction rule. Patients were classified according to the dichotomised Wells score as "likely" (≥2) or "unlikely" (≤1) to have deep vein thrombosis.[21] We dichotomised D-dimer concentrations by using the age dependent cut-off value proposed by Douma and colleagues in patients older than 50 years (age in years×10 µg/L)[10]; the fixed cut-off value of 750 µg/L in patients aged 60 years and older, as proposed by Haas and colleagues[12]; and the conventional cut-off value of 500 µg/L in patients of all ages.[21]

For patients with an unlikely clinical probability of deep vein thrombosis according to the Wells score, we calculated the proportion in whom deep vein thrombosis could be excluded (based on an unlikely clinical probability and a negative D-dimer test result using the different cut-off values). We also calculated the corresponding proportions of false negative results - that is, prevalence of deep vein thrombosis (as established by compression ultrasonography) among patients in the age group. We calculated the number of patients needed to undergo a D-dimer assay to exclude

Table 2 Proportion of patients with unlikely probability of deep vein thrombosis (Wells score ≤1) in whom deep vein thrombosis could be excluded, by age group. Data are no (%, 95% CI) of patients, unless stated otherwise

	Age group (years)				
	All ages	**50-60**	**60-70**	**70-80**	**>80**
Median age (years)	57	55	66	74	85
No (%) of patients	647 (100)	126 (19.5)	107 (16.5)	111 (17.2)	62 (9.6)
Conventional cut-off value (500 µg/L)					
Patients below value	272 (42.0, 38.2 to 46.0)	59 (46.8, 37.9 to 55.9)	35 (32.7, 24.0 to 42.5)	34 (30.6, 22.2 to 40.1)	13 (21.0 11.7 to 33.2)
Patients with false negative result	2 (0.3, 0.04 to 1.1)	0	1 (0.9, 0.02 to 5.1)	0	0
Number of patients needed to test	2.4	2.1	3.1	3.3	4.8
Age dependent cut-off value*					
Patients below value	309 (47.8, 43.9 to 51.7)	64 (50.8, 41.7 to 59.8)	42 (39.3, 30.0 to 49.2)	50 (45.0, 35.6 to 54.8)	22 (35.5, 23.7 to 48.7)
Patients with false negative result	3 (0.5, 0.01 to 1.3)	1 (0.8, 0.02 to 4.3)	1 (0.9, 0.02 to 5.1)	0	0
Number of patients needed to test	2.1	2.0	2.6	2.2	2.8
Cut-off value (750 µg/L)†					
Patients below value	307 (47.4, 43.5 to 51.4)	59 (46.8, 37.9 to 55.9)	45 (42.1, 32.6 to 52.0)	51 (45.9, 36.4 to 55.7)	21 (33.9, 22.3 to 47.0)
Patients with false negative result	2 (0.3, 0.04 to 1.1)	0	1 (0.9, 0.02 to 5.1)	0	0
Number of patients needed to test	2.1	2.1	2.4	2.2	3.0
Absolute increase in efficiency (% (95% CI))					
Using age dependent cut-off value‡	5.7 (4.1 to 7.8)	3.9 (1.3 to 9.0)	6.5 (2.7 to 13.0)	14.4 (8.5 to 22.3)	14.5 (6.8 to 25.8)
Using cut-off value (750 µg/L)§	5.4 (3.8 to 7.4)	Not applicable	9.3 (4.6 to 16.5)	15.3 (9.2 to 23.4)	12.9 (5.7 to 23.9)

*Age (years)*10 µg/L for patients older than 50 years; conventional cut-off value 500 µg/L for younger patients.
†Cut-off value 750 µg/L for patients aged 60 years and older; conventional cut-off value 500 µg/L for younger patients.
‡Calculated as percentage of patients in whom deep vein thrombosis can be excluded by use of age dependent cut-off value minus percentage of patients in whom deep vein thrombosis can be excluded by use of conventional cut-off value.

Table 3 Proportion of patients with unlikely probability of deep vein thrombosis (Wells score ≤1) in whom deep vein thrombosis could be excluded, by D-dimer assay used. Data are no (%, 95% CI) of patients, unless stated otherwise

	VIDAS test (n=323)	Tinaquant (n=324)	P
Median age (years)	60	54	<0.001
Conventional cut-off value (500 µg/L)			
Below value	106 (32.8, 27.7 to 38.2)	166 (51.2, 45.6 to 56.8)	<0.001
With false negative result	1 (0.3, 0.01 to 1.7)	1 (0.3, 0.01 to 1.7)	0.97
Age dependent cut-off value*			
Below value	128 (39.6, 34.2 to 45.2)	181 (55.9, 50.3 to 61.3)	<0.001
With false negative result	2 (0.6, 0.01 to 2.2)	1 (0.3, 0.01 to 1.7)	0.53
Cut-off value (750 µg/L)†			
Below value	128 (39.6, 34.2 to 45.2)	179 (55.2, 49.7 to 60.7)	<0.001
With false negative result	1 (0.3, 0.01 to 1.7)	1 (0.3, 0.01 to 1.7)	0.97
Absolute increase in efficiency (% (95% CI))			
Using age dependent cut-off value‡	6.8 (4.3 to 10.1)	4.6 (2.6 to 7.5)	Not significant
Using cut-off value (750 µg/L)§	6.8 (4.3 to 10.1)	4.0 (2.1 to 6.8)	Not significant

P values calculated by Pearson's Chi-square 2 two sided tests.
*Age (years)*10 µg/L for patients older than 50 years; conventional cut-off value 500 µg/L for younger patients.
†Cut-off value 750 µg/L for patients aged 60 years and older; conventional cut-off value 500 µg/L for younger patients.
‡Calculated as percentage of patients in whom deep vein thrombosis can be excluded by use of age dependent cut-off value minus percentage of patients in whom deep vein thrombosis can be excluded by use of conventional cut-off value.
§Calculated as percentage of patients in whom deep vein thrombosis can be excluded by use of cut-off value 750 µg/L minus percentage of patients in whom deep vein thrombosis can be excluded by use of conventional cut-off value.

deep vein thrombosis in one patient (that is, the number of patients needed to test) by dividing 1 by the proportion of patients with a negative test result and indeed without deep vein thrombosis (that is, the proportion of true negatives).[23] We did analyses with SPSS version 17.0, and calculated appropriate 95% confidence intervals using a programmable calculator application in Microsoft Office, Excel 2003.[24]

RESULTS

Table 1 shows the baseline characteristics of all included participants with available D-dimer results (n=1,374). Mean age was 59.3 years (standard deviation 17.4) and most participants were older than 50 years (936/1,374, 68.1%). Prevalence of deep vein thrombosis was 19.7% (270/1,374). Of 1,374 participants of all ages, 647 (47.1%) had an unlikely clinical probability of deep vein thrombosis (Wells score ≤1; table 2). Using the conventional D-dimer cut-off value of 500 µg/L, 272 of these 647 participants had negative test results (42.0%, 95% confidence interval

38.2% to 46.0%, number needed to test 2.4). Two of these 272 participants had deep vein thrombosis, a false negative proportion of 0.3% (0.04% to 1.1%).

Using the age dependent cut-off value (age in years×10 µg/L for patients aged >50 years), we could exclude deep vein thrombosis in 309 patients (47.8%, 95% confidence interval 43.9% to 51.7%; table 2), which was an additional 37 patients (absolute increase 5.7%, 4.1% to 7.8%, number needed to test 2.1) compared with the conventional cut-off value of 500 µg/L. The age dependent cut-off value missed one patient more than the conventional cut-off value (three missed cases (false negative proportion 0.5%, 0.01% to 1.3%) *v* two (0.3%, 0.04% to 1.1%), respectively; increase 0.2% (0.004% to 8.6%)).

Using the fixed cut-off value of 750 µg/L in participants aged 60 years and older, we could exclude deep vein thrombosis in 307 patients (47.4%, 95% confidence interval 43.5% to 51.4%, number needed to test 2.1; table 2). Compared with the conventional cut-off value of 500 µg/L, use of the fixed cut-off value could exclude deep vein thrombosis in an additional 35 patients (5.4%, 3.8% to 7.4%). The fixed cut-off value did not miss any extra cases, and the false negative rate remained at 0.3% (0.04% to 1.1%).

Effect of age on efficiency and safety of different D-dimer cut-off values

Use of the age dependent cut-off value (at age >50 years) and cut-off value of 750 µg/L (at age ≥60 years) instead of the conventional cut-off value of 500 µg/L (at all ages) showed an increasing efficiency (that is, a higher proportion of patients in whom deep vein thrombosis could be excluded) with increasing age, without compromising safety (that is, the false negative proportion of patients). The proportion of patients aged 70-80 years in whom deep vein thrombosis could be excluded increased from 30.6% (95% confidence interval 22.2% to 40.1%; table 2) using the conventional cut-off value to 45.0% (35.6% to 54.8%) using the age dependent cut-off value and 45.9% (36.4% to 55.7%) using the cut-off value of 750 µg/L. In patients older than 80 years, these proportions were 21.0% (11.7% to 33.2%), 35.5% (23.7% to 48.7%), and 33.9% (22.3% to 47.0%), respectively.

Performance of age adapted cut-off values with different D-dimer assays

Since the original studies used two different D-dimer assays (Tinaquant or VIDAS),[9;16;17;20] we did separate analyses for these two assays. We found no differences between the two assays in false negative rates for any of the studied cut-off values (table 3). However, irrespective of the cut-off value applied, deep vein thrombosis was ruled out more frequently in the Tinaquant assay group than in the VIDAS assay group.

DISCUSSION

This study showed that the use of an age dependent cut-off value (age*10 µg/L in patients aged >50 years) and a fixed cut-off value (750 µg/L in patients aged ≥60 years), combined with an unlikely clinical probability of deep vein thrombosis, resulted in a considerable increase in the proportion of suspected elderly patients in primary care in whom deep vein thrombosis could be safely and correctly excluded, compared with use of the conventional cut-off value (500 µg/L at all ages). Use of these proposed D-dimer cut-off values reduced the number needed to test by compression ultrasonography. This increase in diagnostic efficiency rose with age, notably in the eldest group of elderly patients. These findings are important, since further diagnostic testing can thus be avoided in these often frail elderly patients.

Strengths and limitations of the study

This study provides an external validation of two age adapted, D-dimer cut-off values previously proposed in secondary care patients with suspected venous thromboembolism, and translates these results to a large cohort of patients in primary care with suspected deep vein thrombosis.

This study had some limitations. D-dimer values were missing in 712 of 2,086 participants in the original studies, because only dichotomised D-dimer values (high *v* low) were displayed by the laboratories in the early inclusion phase. Therefore, the availability of the D-dimer values was time dependent. Time can change the nature of study populations. For example, a tendency for incidence of venous thromboembolism to fall in suspected patients over time has been reported.[2] Therefore, we analysed whether the absence versus presence of a D-dimer value was related to observed patient characteristics. Most baseline characteristics (11 of 14) were the same in patients with and without available D-dimer values (appendix 1); the prevalence of deep vein thrombosis and the mean Wells score also did not differ between the two groups (deep vein thrombosis 19.7% v 20.4%, P=0.698; mean Wells' score 1.66 (standard deviation 1.97) *v* 1.74 (2.20), P=0.658). Therefore, we believe that the exclusion of the patients with missing D-dimer values was probably not related to patient characteristics and thus did not bias our results.

We also repeated the entire analysis with the missing D-dimer values imputed, using multiple imputation techniques (appendix 2). This advanced strategy deals with missing values, and is generally preferred over complete case analysis. In short, we based a multiple imputation regression model on the observed D-dimer values and corresponding patient characteristics. We then used this model to estimate missing values according to the observed patient's characteristics.[25] This analysis yielded the same results sustaining the inferences of the complete case analysis, which further confirmed our assumption that the study findings would not change if the missing D-dimer values had been present.

Another limitation was that we used two different laboratory techniques - VIDAS, an enzyme linked immunosorbent assay (ELISA), and Tinaquant, a latex agglutation test. Although assay de-

pendent thresholds have been suggested previously,[26;27] we based our analysis on a conventional cut-off point of 500 µg/L for both assays. After stratifying for type of assay, we found no differences in safety between the two tests, irrespective of the cut-off level applied (table 3). However, deep vein thrombosis could be ruled out more frequently in patients in the Tinaquant assay group than in those in the VIDAS group. These findings accord with those of Di Nisio and colleagues,[27] who reported a higher safety at the expense of a lower efficiency when using the VIDAS test, compared with the Tinaquant test.

We also used serial compression ultrasonography as the reference test. Owing to its non-invasiveness and its accuracy running close to the gold standard, compression ultrasonography has largely replaced venography in current medical practice. However, ultrasonography has shown a missed diagnosis rate of 0.57% (pooled meta-analysis, 95% confidence interval 0.25% to 0.89%) in patients with deep vein thrombosis.[28] To lower this misclassification rate, we by design repeated the compression ultrasonography at day seven. However, the true safety of the proposed D-dimer cut-off values might be slightly lower than that based on the present analysis. Moreover, the misclassification rate is known to be lower in patients with a low clinical probability of deep vein thrombosis (0.29%, 0% to 0.70%).[28] The current analysis, however, included only patients with an "unlikely" clinical probability. Hence, any possible bias induced by our choice of reference test would probably not change the presented conclusions of our analysis.

We also caution the interpretation of our findings in patients older than 80 years, since the number of this subgroup was rather small. Finally, although the data were originally collected in a prospective manner, this study was a retrospective analysis.

Comparison with other studies

Douma and colleagues recently derived the age dependent cut-off value in three cohorts of patients with suspected pulmonary embolism (total of 5,132 participants). They found a similar increase in the proportion of patients in whom venous thromboembolism could be excluded (increases of 6.3%, 5.1%, and 6.2% in derivation set, and validation sets 1 and 2, respectively), compared with the current study (5.7%).[10]

Our results also accord with the findings of Haas and colleagues,[12] who found a similar although slightly higher increase in exclusion rate in suspected patients older than 60 years in secondary care (12.8%). This small difference in increase can probably be explained by differences in the spectrum of patients (the range of comorbidities, the clinical setting, and previous test probability) between our study and the Haas study. Variations in patient spectrum have been linked with variations in disease prevalence as well as variations in diagnostic test accuracy.[29;30] In the Haas-study, the prevalence of deep vein thrombosis in their hospital setting was twice as high as that found in our study (39.1% v 19.7%). This higher prevalence can emerge from a shift spectrum of patients, towards fewer patients with limited forms of deep vein thrombosis and more patients with more manifested forms. This effect in turn could have resulted in a somewhat lower exclusion rate with

the traditional cut-off value of 500 µg/L, and led to a higher increase in the exclusion rate after use of the age adapted cut-off value, compared with our study.

Implications for clinicians and other researchers

After derivation and validation in secondary care,[10;12] we showed that the two proposed age adapted strategies for excluding deep vein thrombosis using D-dimer measurement, have sustained external validation in a large cohort of patients with suspected deep vein thrombosis in primary care. Before implementing these strategies in daily practice, a formal, prospective impact study would need to assess the potential benefits of using an age adapted, D-dimer cut-off value in daily patient care.[31;32]

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APPENDIX 1

Baseline characteristics of patients with available D-dimer values versus patients with missing D-dimer values

Characteristic	Missing D-dimer values N= 712	Available D-dimer values N=1374	P-value
Age (years) Mean (standard deviation)	61.0 (17.6)	59.3 (17.4)	0.039
Female	459 (64.5)	863 (62.8)	0.456
Active malignancy	56 (7.9)	61 (4.4)	0.001
Paresis	107 (15.0)	194 (14.1)	0.575
Recent surgery or bedridden	108 (15.2)	168 (12.2)	0.060
Localised tenderness deep venous system	521 (73.2)	966 (70.3)	0.170
Entire leg swollen	344 (48.3)	596 (43.4)	0.032
Calf distension ≥3 cm	325 (45.6)	551 (40.1)	0.171
Pitting oedema	455 (63.9)	838 (61.0)	0.193
Vein distension	154 (21.6)	254 (18.5)	0.086
Alternative diagnosis present	416 (58.4)	672 (48.9)	0.000
History of deep venous thrombosis	168 (23.6)	284 (20.6)	0.124
Wells score mean (standard deviation)	1.74 (2.20)	1.66 (1.97)	0.658
Frequency of deep venous thrombosis	145 (20.4)	270 (19.7)	0.698

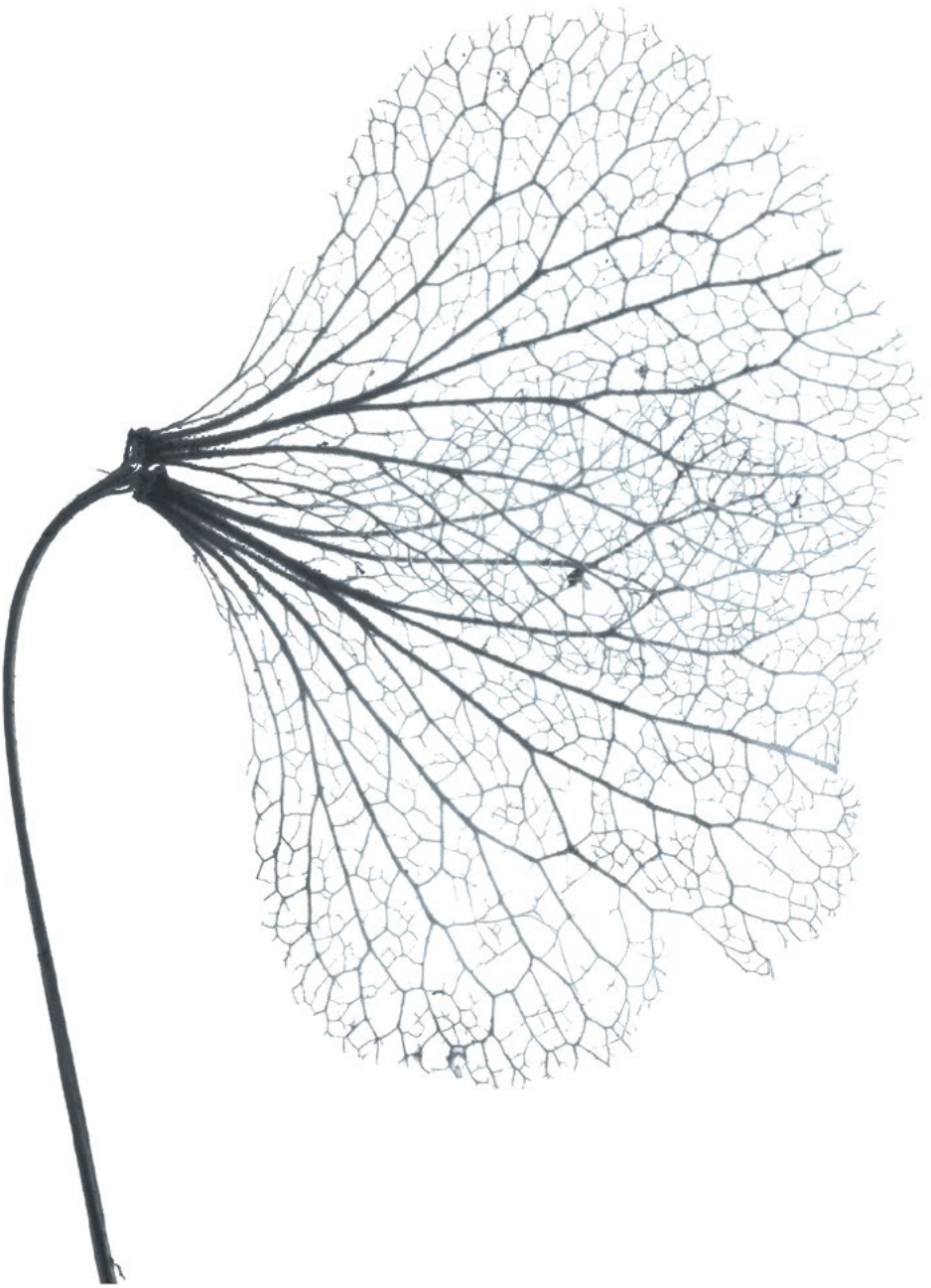
Values are numbers (percentages) of patients unless specified otherwise. P-values calculated by Pearson Chi-square 2-sided tests for dichotomous variables or independent T-tests for linear variables (age, Wells score).

APPENDIX 2

Proportion of patients with an unlikely probability for deep venous thrombosis (Wells clinical decision rule ≤1) in whom deep venous thrombosis could be excluded based on a D-dimer test below the cut-off value. Missing D-dimer values (n=712) imputated with multiple imputation. Variables used as imputation predictor: dichotomous D-dimer, presence of deep venous thrombosis, Wells-score and age.

Age (years)	All ages (57)	50-60	60-70	70-80	>80
No (%) of patients	1053 (100)	192 (18)	181 (17)	198 (19)	102 (9.7)
D-dimer cut-off value 500 µg/l					
No (%, 95%CI) of patients below cut-off value	419 (39.7, 36.8 to 42.8)	89 (46.4, 39.1 to 53.7)	61 (33.7, 26.9 to 41.1)	59 (29.8, 23.5 to 36.7)	24 (23.5, 15.7to 33.0)
With false negative result	3 (0.3, 0.05 to 0.8)	0	1 (0.6, 0.01 to 3.0)	0	0
Number needed to test	2.5	2.2	3.1	3.4	4.3
Age dependent cut-off value †					
No (%, 95%CI) of patients below cut-off value	467 (44.3, 41.3 to 47.4)	95 (49.5, 42.2 to 56.8)	70 (38.7, 31.5 to 46.2)	80 (40.4, 33.5 to 47.6)	36 (35.3, 26.1 to 45.4)
With false negative result	4 (0.4, 0.1 to 0.9)	1 (0.5, 0.01 to 2.9)	1 (0.6, 0.01 to 3.0)	0	0
Number needed to test	2.3	2.1	2.6	2.5	2.8
Cut-off value 750 µg/l *					
No (%, 95%CI) of patients below cut-off value	463 (44.0, 41.0 to 47.0)	89 (46.4, 39.1 to 53.7)	74 (40.9, 33.6 to 48.4)	82 (41.4, 34.5 to 48.6)	32 (31.4, 22.5 to 41.3)
With false negative result	3 (0.3, 0.06 to 0.8)	0	1 (0.6, 0.01 to 3.0)	0	0
Number needed to test	2.3	2.2	2.5	2.4	3.2
Absolute increase in efficiency					
by use of the age dependent cut off value (95%CI) §	4.6% (3.4 to 6.0)	3.1% (2.4 to 13.0)	5.0%(2.3 to 9.2)	10.6%(6.7 to 15.8)	11.8%(6.2 to 19.6)
by use of the cut off of 750 µg/l (95%CI) ‡	4.2% (3.1 to 5.6)	n.a.	7.2% (3.9 to 12.0)	11.6% (7.5 to 16.9)	7.8% (3.4 to 14.9)

95%CI: 95% confidence interval. n.a.: not applicable.
* Cut-off value = 750 µg/l for patients aged ≥60 years, in participants <60 years the conventional cut-off value for D-dimer test = 500 µg/l
† Age dependent cut-off value = (age*10 µg/l) for patients aged >50 years, in participants ≤50 years the conventional cut-off value for D-dimer test = 500 µg/l
§ Percentage of patients with excluded deep venous thrombosis based on the age dependent D-dimer cut-off value (age*10 µg/l for patients aged >50 years) minus percentage of patients with excluded deep venous thrombosis based on the conventional D-dimer cut-off value
‡ Percentage of patients with excluded deep venous thrombosis based on the D-dimer cut-off value 750 µg/l for patients aged ≥60 years minus percentage of patients with excluded deep venous thrombosis based on the conventional D-dimer cut-off value



CHAPTER 6

DIAGNOSTIC ACCURACY OF CONVENTIONAL OR AGE-ADJUSTED D-DIMER CUT-OFF VALUES IN OLDER PATIENTS WITH SUSPECTED VENOUS THROMBOEMBOLISM:

A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

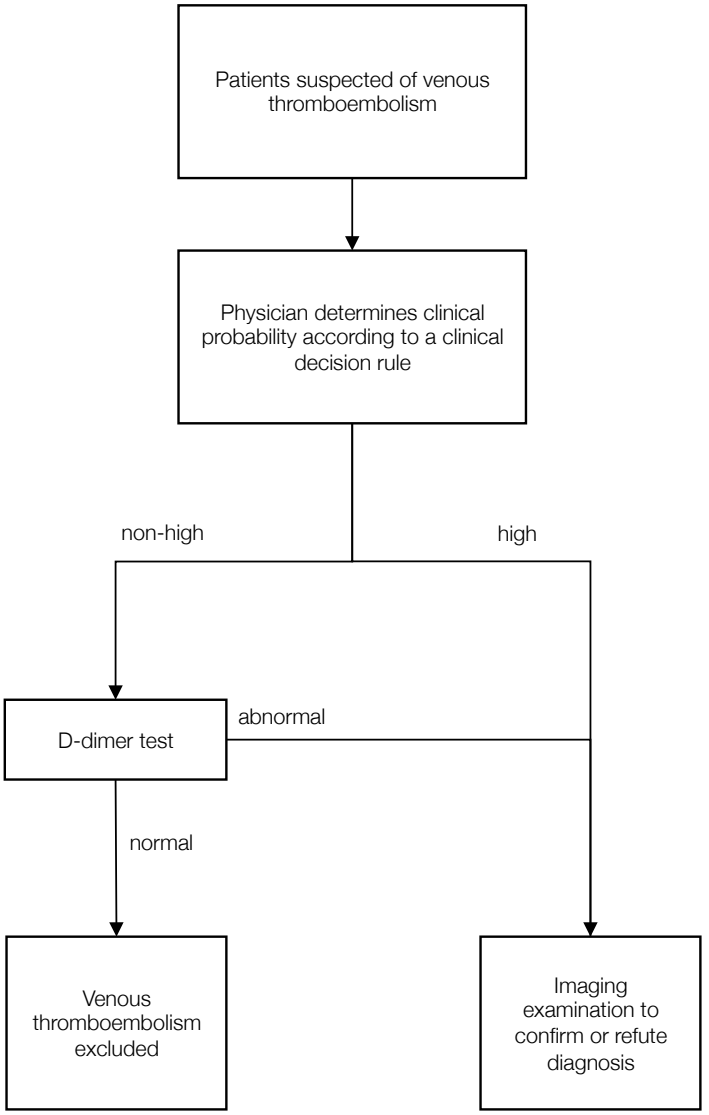
Objective To review the diagnostic accuracy of D-dimer testing in older patients (>50 years) with suspected venous thromboembolism, using conventional or age adjusted D-dimer cut-off values.
Design Systematic review and bivariate random effects meta-analysis.
Data sources We searched Medline and Embase for studies published before 21 June 2012 and we contacted the authors of primary studies.
Study selection Primary studies that enrolled older patients with suspected venous thromboembolism in whom D-dimer testing, using both conventional (500 µg/L) and age adjusted (age*10 µg/L) cut-off values, and reference testing were performed. For patients with a non-high clinical probability, 2×2 tables were reconstructed and stratified by age category and applied D-dimer cut-off level.
Results 13 cohorts including 12,497 patients with a non-high clinical probability were included in the meta-analysis. The specificity of the conventional cut-off value decreased with increasing age, from 57.6% (95% confidence interval 51.4% to 63.6%) in patients aged 51-60 years to 39.4% (33.5% to 45.6%) in those aged 61-70, 24.5% (20.0% to 29.7% in those aged 71-80, and 14.7% (11.3% to 18.6%) in those aged >80. Age adjusted cut-off values revealed higher specificities over all age categories: 62.3% (56.2% to 68.0%), 49.5% (43.2% to 55.8%), 44.2% (38.0% to 50.5%), and 35.2% (29.4% to 41.5%), respectively. Sensitivities of the age adjusted cut-off remained above 97% in all age categories.
Conclusions The application of age adjusted cut-off values for D-dimer tests substantially increases specificity without modifying sensitivity, thereby improving the clinical utility of D-dimer testing in patients aged 50 or more with a non-high clinical probability.

INTRODUCTION

D-dimer concentrations are highly sensitive for thrombus formation. Hence D-dimer tests are often used to rule-out venous thromboembolism (pulmonary embolism or deep vein thrombosis) in suspected patients with a non-high clinical probability. Patients with a high clinical probability do not require a D-dimer test. In these patients imaging examination is warranted to confirm or refute the diagnosis, irrespective of the D-dimer results (figure 1).[1-3] However, D-dimer concentrations increase with age, which leads to a high proportion of older patients with D-dimer concentrations higher than conventional cut-off values (500 µg/L).[4;5] This in turn leads to a low specificity (that is, more false positive results) of D-dimer testing in older patients suspected of having venous thromboembolism; the specificity is 49% to 67% for patients aged less than 50 years but in older old patients (≥80 years) between 0% and 18%.[4-8] As imaging is indicated in patients suspected of having venous thromboembolism with a D-dimer concentration above the cut-off value,[9] a high proportion of older patients with a non-high clinical probability undergo unnecessary diagnostic investigations. This can be burdensome, especially in older patients, and the yield of this imaging is relatively low (typically 20% or less of patients with clinically suspected venous thromboembolism are actually affected).[10;11] As a result of a low specificity of D-dimer testing in older patients, some authors dissuade doctors from D-dimer testing in very old patients.[4;8;12] Yet this would actually imply referring all suspected older patients for imaging, which is even less desirable.

Others have argued for increasing the D-dimer cut-off value in older patients to improve the specificity and thereby increase the number of patients in whom - based on a D-dimer level below the cut-off value - imaging could be avoided.[4;6;13-15] An age adjusted D-dimer cut-off value that increases gradually with age especially showed a promising increase in specificity without substantial loss of safety.[6] This age adjusted cut-off value was defined as age (years)×10 µg/L for patients aged over 50 years (for example, for a patient aged 78 years, the D-dimer concentration would be considered normal below 780 µg/L). The age adjusted cut-off value was derived from a cohort of secondary care patients with a non-high probability of pulmonary embolism. This cohort was subdivided into 10 year age groups and the optimal cut-off value was selected for each age group - that is, the cut-off value with a sensitivity of 100% and the highest accompanying specificity. This revealed an increase of the optimal cut-off value of approximately 100 µg/L per decade (10 µg/L per year). This age adjusted cut-off value was subsequently validated in secondary care patients with suspected pulmonary embolism,[16;17] and in both primary and secondary care cohorts of patients with suspected deep vein thrombosis.[18;19] However, higher cut-off values may also lead to an increased percentage of false negative cases (that is, missed cases of venous thromboembolism), which might make this strategy less safe.[20;21] Since venous thromboembolism has a high short term mortality rate in older patients, doctors do not always get the chance to reconsider a missed diagnosis.[22;23]

Figure 1 Diagnostic investigations in patients with suspected venous thrombembolism. Adapted from Wells 2007,[9] Le Gal et al 2006,[40] and Wells et al 2001[57]



Controversy therefore remains on the utility of D-dimer testing (either using the conventional or higher cut-off values) to safely exclude venous thromboembolism in a substantial proportion of older patients. A formal systematic review increases the evidence base on this topic; a meta-analysis can provide more precise estimates of the accuracy of D-dimer testing among clinically

relevant subgroups, whereby sources for interstudy heterogeneity can be considered.[24] We conducted a systematic review and meta-analysis to assess the diagnostic value of D-dimer testing for excluding suspected venous thromboembolism in older patients, with a particular interest in whether increasing the threshold for test positivity using the proposed age adjusted manner is a safe and more efficient strategy than using the conventional cut-off value.

METHODS

Data sources and searches

On 12 June 2012 we systematically searched Embase and Medline for studies evaluating the diagnostic value of D-dimer tests in diagnosing venous thromboembolism. The search query combined synonyms for "D-dimer" with synonyms for "venous thromboembolism" and "elderly" (see appendix 1 for the search strategy).[25] Duplicate articles were manually filtered using the "close match function" of Refworks 2.0.

Study selection

We included studies if they were original diagnostic studies and comprised a study population of consecutive patients with a clinical suspicion of venous thromboembolism, performed quantitative D-dimer testing using the age adjusted D-dimer cut-off value and the conventional cut-off value, and applied reference testing in all patients according to previously described methods.[26] No language restrictions were applied. To check cross referencing we used a previously published systematic review.[1] We excluded studies carried out exclusively in populations with a high risk for thrombosis - defined as perioperative patients or patients with previous thrombosis, cancer, or coagulation disorders. When a study cohort was described by more than one article, we included only the paper best meeting the inclusion criteria. Two reviewers (HJS and NV) independently selected the first batch of articles and a third reviewer (GJG) was consulted by HJS to agree on the final selection and to resolve discrepancies between the first two reviewers.

Data extraction and quality assessment

We reviewed the included studies in duplicate and extracted the study design, setting, number of patients, prevalence of venous thromboembolism, personal characteristics of the study population, clinical decision rule used to classify patients in risk categories, and reference standard and D-dimer assay applied. Using extracted numbers of true and false positive and negative results according to the reference tests, we reconstructed 2x2 tables for the patients with a non-high clinical probability and stratified them by predefined age categories (≤50 years, 51-60 years, 61-70 years, 71-80 years, and >80 years) and by the different D-dimer cut-off values (for the age category ≤50 years the conventional and age adjusted cut-off value are the same). If complete

reconstruction of 2x2 tables using the desired age categories was not possible based on the data presented in the papers, we contacted the authors and requested to reanalyse their data, if needed, according to the predefined age class categories and to complete the cross tables for all age categories and for both the conventional and age adjusted D-dimer cut-off level.
We assessed risk of bias and applicability at study cohort level, using the revised tool for quality assessment of diagnostic accuracy studies (QUADAS-2). This is a validated tool for assessment of methodological quality and applicability of diagnostic accuracy studies.[27] We appraised both the primary studies describing the included study cohorts and the publications included in this meta-analysis that were based on these cohorts.

Data synthesis and analysis

From the 2x2 tables we calculated the prevalence of venous thromboembolism and the D-dimer test sensitivity (the number of patients with venous thromboembolism and a D-dimer level above the tested cut-off value - that is, patients with true positive test results - divided by the total number of patients with venous thromboembolism) and specificity (the number of patients without venous thromboembolism and a D-dimer level below the tested cut-off level - that is, patients with true negative test results - divided by the total number of patients without venous thromboembolism). To graphically display the sensitivity and specificity measurements at study level we used Review Manager 5 software from the Cochrane collaboration. For the main analyses we stratified the data by age category and D-dimer cut-off value. We used random effects bivariate regression models to meta-analyse the logit transformed sensitivity and specificity of D-dimer to obtain pooled estimates and 95% confidence intervals of these variables.[28;29] The bivariate approach simultaneously models pairs of (logit transformed) sensitivity and specificity from studies, thereby incorporating any correlation that might exist between these measures. The model uses a random effects approach for both sensitivity and specificity to incorporate heterogeneity beyond chance as a result of remaining clinical and methodological differences between studies. We added covariates to the bivariate model to examine whether sensitivity and specificity were different for the following study characteristics: prevalence of venous thromboembolism within each study, the type of applied D-dimer assay, and whether the initial suspicion was deep vein thrombosis or pulmonary embolism in the included studies. We fitted the bivariate random effects models using the NLMIXED (non-linear mixed effect) procedure of SAS version 9.2 (SAS Institute, Cary, NC, USA).
For each age category and D-dimer cut-off level we constructed hypothetical classification tables including 1000 hypothetical patients per table. We calculated the total number of venous thromboembolism cases by multiplying 1000 with the estimated median prevalence of venous thromboembolism within the particular age category based on the studies included in this meta-analysis. We calculated the number of patients with true positive test results by multiplying the total number of hypothetical venous thromboembolism cases with the estimated sensitivity of the D-dimer test in the particular age category (or with the lower or upper 95% confidence interval

border of the estimated sensitivity to extract a measure of uncertainty). To obtain the number of patients with true negative test results we multiplied the total number of hypothetical non-cases by the estimated specificity (or with the lower or upper limits of the 95% confidence interval of this estimate). To examine the influence of the prevalence on these numbers, we repeated these analyses using the minimum and maximum prevalence of venous thromboembolism within each age group based on this meta-analysis. These analyses were performed in Microsoft Office Excel version 2010.

RESULTS

Selection, characteristics, and quality of studies

Our search yielded 2696 unique publications (see flowchart in appendix 2). After we had screened the titles and abstracts, 307 publications were selected for full text review. Of these publications, 302 were excluded, mainly because they did not concern consecutive patients, applied no (quantitative) D-dimer test, or did not apply age adjusted D-dimer cut-off levels. Finally, five publications were included concerning a total of 22,608 patients of whom 12,630 had a non-high clinical probability of venous thromboembolism.[6;16-19] All these publications concerned retrospective analyses on one or more cohorts of patients with suspected venous thromboembolism. One publication[19] separately analysed and presented five different cohorts;[(Tan et al, unpublished);30-33] two publications[6;16] separately analysed and presented three different cohorts[34-39] and the other two publications concerned one cohort each.[17;18] Hence the five included publications concerned a total of 13 different study cohorts, which we considered as separate cohorts in this meta-analysis. All authors granted our requests to reanalyse their data and provided 2x2 tables for each predefined age category and both D-dimer cut-off levels.

Table 1 summarises the characteristics of the included study cohorts. Seven cohorts concerned patients with suspected pulmonary embolism[17;34-39] and the other six concerned patients with suspected deep vein thrombosis[(Tan et al, unpublished),18;30-33] All studies analysed and presented only patients with non-high clinical probability scores on clinical decision rules as this is the indicated population for the application of D-dimer tests.[3;9] To select these patients with a non-high clinical probability, either a revised Geneva score[40] of ≤10 or a Wells score[41] of ≤4 was applied in the pulmonary embolism cohorts; and for the deep vein thrombosis cohorts, a Wells score[9] of either ≤2 or ≤1 was applied. In one study,[31] a clinical probability of <80% of deep vein thrombosis as estimated by the treating doctor - instead of a formal clinical decision rule - was used to select the patients with a non-high clinical probability.

One study was performed in primary care,[18] whereas all other cohorts concerned patients presenting at emergency departments or in outpatients clinics; in two studies, inpatients were also included.[17;35] Overall, the quality of the included study cohorts was good (see the results of QUA-

Table 1 Characteristics of included study cohorts. Data were sorted according to primary suspicion of pulmonary embolism (PE) or deep vein thrombosis (DVT) and setting. All studies used D-dimer cut-off value of 500 ug/L and age*10 µg/L

Reference*	PE or DVT	No of patients (% male)	Mean age (SD)	Prevalence of VTE (%)	Setting	Reference test to rule out VTE	D-dimer assay†	CDR used (cut-off)
Douma 2010, derivation set[6;34]	PE	1721 (41)	61 (19)	24	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) D-dimer <500 µg/L; or (b) negative results from CUS and from HCT in patients with non-high CDR; or (c) normal VQ scan or normal pulmonary angiogram) and (3 month event free follow-up)	ELFA	Wells[54] (≤4)
Douma 2010, validation set [26;36]	PE	1819 (49)	59 (19)	21	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) Non-high CDR and D-dimer <500 µg/L; or (b) negative HCT) and (3 month event free follow-up)	ELFA	Revised Geneva score[40] (≤10)
Penaloza 2012, French cohort[16;38]	PE	1529 (39)	Not given	28	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) D-dimer <500 µg/L; or (b) normal pulmonary angiogram; or (c) negative VQ scan; or (d) negative HCT; or (e) low CDR and non-diagnostic VQ or HCT and negative CUS) and (3 month event free follow-up)	ELFA or quantitative latex agglutination assay	Revised Geneva score[40] (≤10)
Penaloza 2012, European cohort[16;37]	PE	1645 (42)	59	18	Hospital; outpatients presenting in emergency department or outpatient clinics	(a) Non-high CDR and D-dimer ELISA <500 µg/L; or (b) non-high CDR and negative moderate sensitivity D-dimer test; or (c) low CDR and low probability VQ scan or negative computed tomography angiography; or (d) negative multidetector HCT	ELFA or quantitative latex agglutination assay	Revised Geneva score[40] (≤10)
Penaloza 2012, US cohort[16;42]	PE	7940 (33)	49	5.1	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) D-dimer <500 µg/L; or (b) normal VQ scan; or (c) non-diagnostic VQ scan and negative CUS and/or negative D-dimer (d) negative multidetector CT angiography) and (45 days follow-up)	ELFA or quantitative latex agglutination assay	Revised Geneva score[40] (≤10)
Douma 2010, validation set [16;35]	PE	3306 (43)	53 (18)	20	Hospital: inpatients and outpatients	((a) Unlikely clinical probability and D-dimer ≤500 µg/L; or (b) negative HCT) and (3 month event free follow-up)	ELFA or quantitative latex agglutination assay	Wells[54] (≤4)

Van Es 2012[17;55]	PE	456 (46)	65	27	Hospital: inpatients and outpatients	((a) Unlikely clinical probability and D-dimer ≤500 µg/L; or (b) negative HCT) and (3 month event free follow-up)	ELFA or quantitative latex agglutination assays	Wells[54] (≤4)
Schouten 2012‡[18;56]	DVT	1374 (27)	59 (17)	20	Primary care patients	Normal first and repeated CUS	ELFA or quantitative latex agglutination assay	Wells[9] (≤1)
Douma 2012, cohort 1[7;19]	DVT	812 (36)	59 (17)	39	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) Non-high CDR and D-dimer <500 µg/L; or (b) negative results from first CUS and D-dimer <500 µg/L; or (c) normal results from repeated CUS) and (3 month event free follow-up)	Quantitative latex agglutination assay	Wells[9] (≤2)
Douma 2012, cohort 2[19;31]	DVT	474 (38)	61 (19)	23	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) D-dimer <500 µg/L; or (b) normal CUS in combination with a non-high clinical probability; or (c) normal phlebography) and (3 month event free follow-up)	ELFA	Clinical probability estimated by treating doctor[31] (<80%)
Douma 2012, cohort 3[19;32]	DVT	359 (41)	66 (17)	23	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) Low CDR and D-dimer <500 µg/L and 3 month event free follow-up; or (b) normal CUS or impedance plethysmography. Patients with intermediate CDR and D-dimer <500 µg/L imaged at treating doctor's discretion) and (3 month event free follow-up)	Quantitative latex agglutination assay	Wells[9] (≤2)
Douma 2012, cohort 4[19;33]	DVT	556 (38)	65 (16)	10	Hospital; outpatients presenting in emergency department or outpatient clinics	((a) Non-high CDR and normal D-dimer test and 3 month event free follow-up; or (b) normal repeated CUS) and (3 month event free follow-up)	Quantitative latex agglutination assay	Wells[9] (≤2)
Douma 2012, cohort 5[19;(Tan et al, unpublished)]	DVT	617 (52)	58 (18)	37	Hospital; outpatients presenting in emergency department or outpatient clinics	(a) Unlikely CDR and D-dimer <500 µg/L; or (b) negative results from (first) leg venous CUS in combination with normal D-dimer <500 µg/L; or (c) normal repeated CUS	Quantitative latex agglutination assay	Wells[9] (≤1)

PE=pulmonary embolism; DVT=deep vein thrombosis; VTE=venous thromboembolism; CDR=clinical decision rule; ELFA=enzyme linked fluorescent assay; CUS=compression ultrasonography of leg (if repeated; 6-8 days after initial presentation); HRCT=helical computed tomography of chest; VQ=ventilation perfusion.
*Second reference refers to primary studies describing cohort.
†Classified according to Heim et al and Di Nisio et al.[2;48]
‡Study also presented data for cut-off value of 750 ug/L in patients aged >60 years.[18] These data were not included in this meta-analysis.

DAS-2 in appendix 3). All but one cohort[42] included prospectively collected data of consecutive patients with suspected venous thromboembolism. However, in 12 of the 13 study cohorts, three month event free follow-up (no signs or symptoms of recurrence) instead of imaging investigation was used as the reference test in patients with a negative D-dimer result and a non-high clinical probability, so not all patients underwent the same sequence of reference tests in these studies. Hence differential verification could have introduced bias. Furthermore, there were concerns about the applicability of the studies, as unstratified data for different applied D-dimer assays (enzyme linked fluorescent assays as well as quantitative latex assays) within one study cohort was presented for six of the 13 study cohorts.

Prevalence of venous thromboembolism and effect of age on specificity and sensitivity of D-dimer testing with a conventional cut-off value

The median prevalence of venous thromboembolism in patients not at high risk ranged from 12.3% in patients aged less than 50 years, to 21.5% in patients aged 71-80 (table 2). The pooled specificity of D-dimer testing decreased substantially with increasing age from 66.8% (95% confidence interval 61.3% to 72.0%) in patients aged less than 50 years to 14.7% (11.3% to 18.6%) in patients aged more than 80 years when the conventional cut-off value was applied (table 2). The pooled sensitivity hardly differed between the age groups.

Table 2 Pooled estimates of diagnostic accuracy of D-dimer testing in older patients with suspected venous thromboembolism and non-high clinical probability per age category and cut-off value in 13 study cohorts

Age (yrs)	No of patients	Median (range) prevalence within studies (%)	Pooled sensitivity (95% CI)			Pooled specificity (95% CI)		
			Conventional cut-off (%)	Age adjusted cut-off (%)	P value	Conventional cut-off (%)	Age adjusted cut-off (%)	P value
≤50	5528*	12.3 (3.09 to 28.6)	97.6 (95.0 to 98.9)	not applicable†	-	66.8 (61.3 to 72.0)	not applicable†	-
51-60	2043*	13.4 (5.00 to 33.3)	100.0 (NA)	99.4 (97.3 to 99.9)	0.97	57.6 (51.4 to 63.6)	62.3 (56.2 to 68.0)	0.005
61-70	1815	15.6 (6.58 to 26.2)	99.0 (96.6 to 99.7)	97.3 (93.8 to 98.8)	0.14	39.4 (33.5 to 45.6)	49.5 (43.2 to 55.8)	<0.001
71-80	1842	21.5 (6.78 to 34.5)	98.7 (96.5 to 99.5)	97.3 (94.3 to 98.8)	0.20	24.5 (20.0 to 29.7)	44.2 (38.0 to 50.5)	<0.001
>80	1269	15.2 (5.88 to 26.9)	99.6 (96.9 to 99.9)	97.0 (92.9 to 98.8)	0.06	14.7 (11.3 to 18.6)	35.2 (29.4 to 41.5)	<0.001

*Additional data of cohort 5 of Douma 2012 study (Tan et al, unpublished), were not provided for these age categories (89 patients aged <50 years and 44 patients aged 51-60 years).
†Age adjusted cut-off value (age×50 µg/L) does not apply to patients aged ≤50 years.

Performance of age adjusted D-dimer cut-off values

The use of the age adjusted D-dimer cut-off value (age*10 µg/L in patients aged >50 years) still showed a decrease in specificity with increasing age, which was 35.2% (29.4% to 41.5%) in patients aged more than 80 years, but noticeably less pronounced compared with the application of the conventional cut-off value. The specificity of D-dimer testing by application of the age adjusted D-dimer cut-off value instead of the conventional cut-off value was higher in all age categories and was more than doubled in patients aged more than 80 years (table 2).

The use of age adjusted cut-off values instead of the conventional cut-off value was at the expense of a decrease in sensitivity (albeit small and not statistically significant), which stayed above 97% for both cut-off levels in all age categories.

Table 3 Overall and covariate analysis for D-dimer testing stratified by use of conventional and age adjusted cut-off levels in patients with a non-high clinical probability of venous thromboembolism (all age categories except <50 years)

Analyses	No of cohorts	Sensitivity conventional cut-off	Sensitivity age adjusted cut-off	Specificity conventional cut-off	Specificity age adjusted cut-off
Overall analyses: age-categories >50 years	13	99.3 (98.4 to 99.7)	97.8 (95.9 to 98.9)	36.1 (30.8 to 41.7)	48.8 (42.9 to 54.7)
Prevalence in cohort (overall):					
<23%	7	99.4 (98.2 to 99.8)	97.9 (95.3 to 99.1)	37.5 (30.4 to 45.2)	49.9 (42.0 to 57.7)
>23%	6	99.1 (97.0 to 99.7)	97.7 (94.2 to 99.1)	34.2 (26.7 to 42.5)	47.8 (39.1 to 56.5)
P value	—	0.64	0.89	0.56	0.73
D-dimer assay:					
Only ELFA	3	100 (NA)	99.6 (98.2 to 99.9)	28.69 (20.6 to 38.5)	40.8 (30.8 to 51.7)
Quantitative latex assay (and ELFA)†	10	98.7 (97.5 to 99.3)	96.4 (94.6 to 97.6)	35.6 (32.9 to 42.5)	51.3 (45.2 to 57.4)
P value	—	0.97	0.005	0.08	0.10
Clinical suspicion:					
Pulmonary embolism	7	99.2 (97.9 to 99.7)	97.5 (94.7 to 98.8)	34.0 (27.7 to 40.9)	45.7 (38.5 to 53.1)
Deep vein thrombosis	6	99.8 (97.8 to 99.97)	99.3 (96.6 to 99.8)	36.0 (34.0 to 38.0)	48.0 (45.8 to 50.2)
P value	—	0.31	0.15	0.58	0.55

ELFA=enzyme linked fluorescent assay; NA=not applicable.
*Covariate analysis for setting was not possible as only one study was performed in primary care.
†This stratum contains studies wherein quantitative latex agglutination assays were used, or latex agglutination assays indifferently with ELFA assays.

Table 4 Classification table for 1000 hypothetical patients based on median prevalence of venous thromboembolism (VTE) in each age subgroup* and on pooled estimates of sensitivity and specificity

Variables	Age (years)														
	≤50			51-60			61-70			71-80			>80		
Conventional cut-off value	VTE+	VTE-	Total	VTE+	VTE-	Total	VTE+	VTE-	Total	VTE+	VTE-	Total	VTE+	VTE-	Total
D-dimer high	120	291	411	134	367	501	154	512	666	212	593	805	151	724	876
D-dimer low	3	586	589	0	499	499	2	332	334	3	192	195	1	124	124
Total	123	877	1000	134	866	1000	156	844	1000	215	785	1000	152	848	1000
Sensitivity/specificity	97.6	66.8	—	100.0	57.6	—	99.0	39.4	—	98.7	24.5	—	99.6	14.6	—
Age adjusted cut-off value	—	—	—	VTE+	VTE-	Total	VTE+	VTE-	Total	VTE+	VTE-	Total	VTE+	VTE-	Total
D-dimer high	—	—	—	133	327	460	152	427	578	209	438	647	147	550	697
D-dimer low	—	—	—	1	539	540	4	417	422	6	347	353	5	298	303
Total	—	—	—	134	866	1000	156	844	1000	215	785	1000	152	848	1000
Sensitivity/specificity	—	—	—	99.4	62.3	—	97.3	49.5	—	97.3	44.2	—	97.0	35.2	—
No of avoided unnecessary imaging examinations	—	—	—	—	40	—	—	85	—	—	155	—	—	175	—
Additional No of cases missed	—	—	—	1	—	—	2	—	—	3	—	—	4	—	—

*12.3% in patients aged ≤50, 13.4% in patients aged 51-60, 15.6% in patients aged 61-70, 21.5% in patients aged 71-80, and 15.2% in patients aged >80 years.

Covariates

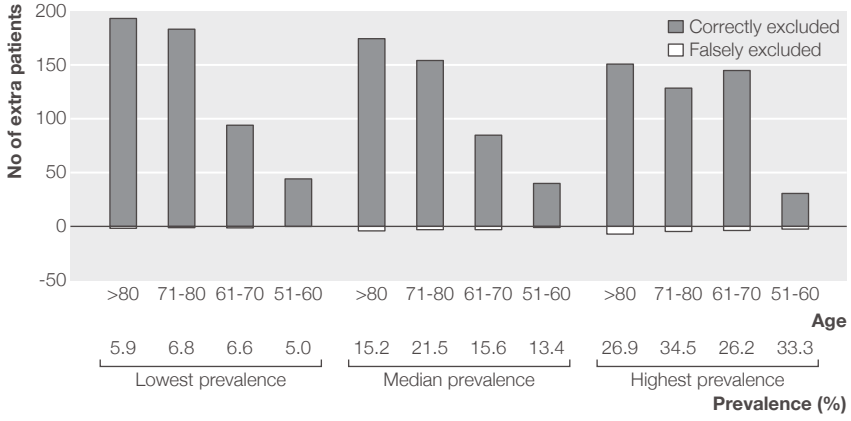
The forest plot in appendix 4 depicts the sensitivity and specificity of D-dimer testing stratified by cohort, age group, and D-dimer cut-off level. We analysed the effect of covariates (the venous thromboembolism prevalence in each total cohort, applied D-dimer assays, and whether the patients were initially suspected of having pulmonary embolism or deep vein thrombosis) on the D-dimer sensitivity and specificity (table 3). We found no association between the sensitivity and specificity of D-dimer testing and the prevalence of venous thromboembolism in the study populations or whether patients were suspected of having either pulmonary embolism or deep vein thrombosis.

D-dimer testing revealed a higher sensitivity and a trend towards lower specificity in the three cohorts in which only enzyme linked fluorescent assays were applied, compared with the cohorts in which quantitative latex assays were also used. Besides, the enzyme linked fluorescent assays showed less decrease in sensitivity by application of the age adjusted cut-off value instead of the conventional cut-off.

Hypothetical cohort

Based on hypothetical cohorts of 1000 patients for each age category, we calculated the numbers of extra patients in whom imaging examination would, correctly or wrongly, be avoided by using the age adjusted instead of the conventional D-dimer cut-off value (table 4). This would result in a correct exclusion of venous thromboembolism in 40 (95% confidence interval 38 to 41), 85 (81 to 86), 155 (141 to 164), and 175 (153 to 194) extra patients at the expense of 1 (0 to 4) extra missed cases for those aged 51-60 years, 2 (2 to 5) for those aged 61-70 years, 3 (2 to 4), for those aged 71-80 years, and 4 (2 to 6) for those aged more than 80 years. D-dimer testing would rule

Figure 2 Number of extra patients per 1000 patients with non-high clinical probability in whom venous thromboembolism would be correctly or falsely excluded by application of age adjusted D-dimer cut-off values instead of conventional cut-off values



out venous thromboembolism in 124 per 1000 non-high risk patients aged more than 80 years if the conventional cut-off value would be applied, whereas the application of the age adjusted D-dimer cut-off value results in exclusion of venous thromboembolism in 303 per 1000 of these patients. The positive predictive value was 21.2% (95% confidence interval 19.1% to 23.2%) in patients aged more than 80 years and 29.1% (25.3% to 33.1%) in patients aged 50 years or less. To examine the influence of the prevalence on this figure we also compared these numbers for the lowest and highest prevalence of venous thromboembolism of the non-high risk patients within each age category of the studies in this meta-analysis (figure 2). The relative merit of application of the age adjusted cut-off value instead of the conventional cut-off value was higher in the case of a low prevalence (44-194 correct *v* 0-2 falsely excluded cases) compared with a high prevalence (31-150 correctly *v* 2-7 falsely excluded cases) (see figure 2 and appendix 5).

DISCUSSION

We performed a systematic review and meta-analysis on the diagnostic value of D-dimer testing to exclude venous thromboembolism in older patients aged 50 or more years. Generally, in combination with a non-high clinical probability, D-dimer testing is used as a rule-out test in patients with suspected venous thromboembolism. Using such a rule-out approach, unnecessary burdensome and more costly imaging can be avoided in about 1 in 3 patients.[1;2;30;33-35] However, this proportion of patients in whom imaging can be safely withheld by using D-dimer testing seemed to be low (around 10%) in the eldest patients (>80 years).[4;8;12] This has led to controversy over the diagnostic value of D-dimer testing in older old patients (>80 years) with clinically suspected venous thromboembolism. In particular old, fragile patients, who would benefit if an unnecessary referral to a radiology department could be safely avoided.[43] In fact, this was the main reason for the development of age adjusted cut-off values for D-dimer testing[6] and thereby the reason for this aggregated meta-analysis.

Indeed we found a sharp decrease in the specificity of D-dimer testing to rule out venous thromboembolism in older patients with a non-high clinical probability using the conventional D-dimer cut-off value, although the sensitivities of D-dimer testing were high across all age categories. The proportion of patients with a non-high clinical probability in whom D-dimer testing could exclude venous thromboembolism was only 12.4% in those aged more than 80 years. This finding underlines the arguments of several authors that D-dimer testing in this conventional way is of limited value in the eldest patients.[4;8;12] Yet the application of the age adjusted D-dimer cut-off value[6] would result in the exclusion of venous thromboembolism in almost 1 out of 3 (30.3%) of the eldest patients (>80 years), while the sensitivity stayed above 97% in all age categories. This would lead to one identified and treated patient for every five patients undergoing imaging examinations in the eldest patients, or in other words a positive predictive value of 21.1%. This positive predic-

tive value of D-dimer testing in the eldest patients is almost comparable to the positive predictive value of 29.2% in the youngest patients (<50 years, cut-off value of 500 µg/L). The small number of missed cases from applying the age adjusted cut-off value instead of the conventional cut-off (1 to 4 per 1000) is largely outnumbered by the large number of patients in whom imaging would be avoided (303 to 540 per 1000). Moreover, this number of missed cases from using the age adjusted cut-off value is comparable to the failure rate in the youngest age category (≤50 years) in whom 3 per 1000 patients would be missed if D-dimer testing using conventional cut-off levels was used. Even in case of a high prevalence of venous thromboembolism (when the relative merit of application of the age adjusted cut-off value is lowest) the additional number of patients missed (2 to 7 per 1000) would be outweighed by the number of avoided unnecessary imaging examinations (31 to 150 per 1000).

Currently, broadly available imaging techniques for the detection of venous thromboembolism have replaced burdensome and time consuming techniques bringing about high radiation exposure (repeated two point compression ultrasonography replaced venography for the detection of deep vein thrombosis, and contrast enhanced computed tomography of the pulmonary arteries replaced pulmonary angiography for pulmonary embolism).[35;44] Still, the burden and risks of imaging, such as attending a hospital, extension of hospital stay, waiting at a radiology department are of particular concern for old patients.[43] Moreover, contrast enhanced computed tomography of the pulmonary arteries is associated with a 14% risk of nephropathy, which might be even higher in older patients in whom renal impairment is more common.[45] Therefore it would (notably for older patients) be beneficial to safely withhold imaging investigations based on negative D-dimer test results.

Strengths and limitations of this review

This is the first systematic review and meta-analysis on the diagnostic utility of D-dimer testing in older patients. We were able to include 13 large cohorts involving over 12,000 patients wherein both the conventional adjusted and the age adjusted cut-off values were studied in different age categories. However, the included publications were from only three research groups. Our search yielded another 107 publications in which the diagnostic accuracy of quantitative D-dimer testing had been examined in consecutive patients, but as this was not done in an age adjusted manner these publications were not included in our meta-analysis. Yet given the robustness, precision, and consistency of our results over the 13 included cohorts, we expect that the addition of more studies to the meta-analysis would not have changed our inferences. Moreover, funnel plots of estimates of the effect size (differences in logit specificities within studies as a result of the application of the different cut-off levels) against the study size, gave (although based on a small number of studies) no indication for publication bias (analysis not presented).

Other strategies to adjust the D-dimer cut-off value to exclude venous thromboembolism in older patients have been suggested - for example, a fixed cut-off of 750 µg/L in all patients aged over

60 or 70 years.[14;21;46;47] Owing to the heterogeneity of the applied D-dimer assays, methodology, and categorization of age (for example, >60 or >70 years instead of 61-70 years, 71-80 years, and >80 years), we were unable to provide pooled estimates of the studies that analysed alternative D-dimer cut-off levels. This hampered the comparison of the different adjusted D-dimer cut-off values.

We also found some heterogeneity in the sensitivity and specificity of D-dimer tests among the studies, partly explained by the application of different assays. Our covariate analysis suggests that the application of age adjusted instead of conventional cut-off values was most favourable in the cohorts in which enzyme linked fluorescent assays were only applied, as the high sensitivity remained constant in these cohorts. These findings are consistent with previous studies: enzyme linked fluorescent assays turned out to have a higher sensitivity at the expense of a lower specificity compared with second generation latex assays.[2;48] However, as a result of between study variation of covariates and their potential multicollinearity (linear relation between explaining variables), we are unable to draw firm conclusions on the differences between various D-dimer assays based on our current meta-analysis.

Another limitation might be that we included studies both with populations suspected of having pulmonary embolism and with populations suspected of having deep vein thrombosis, and primary as well as secondary care patients, which might have introduced some extra between study variation. Furthermore, there was a variation in the prevalence of venous thromboembolism in the included cohorts, ranging from 5.1% to 39%. However, although previous studies revealed an association between the prevalence of venous thromboembolism and the diagnostic accuracy of D-dimer testing,[49] our covariate analysis did not show such an association. Moreover, there was a fair similarity of study design and patient selection over the included cohorts; in all studies only patients with a non-high clinical probability were selected. Therefore we assumed that the conditions for pooling were met.

Finally, the reference standards used to diagnose or exclude venous thromboembolism differed between the included studies. In all but one study[18] differential verification was of concern; in these studies venous thromboembolism was excluded without confirmation by imaging in patients with a negative D-dimer test result and without recurrence of symptoms during follow-up. Hence the false negative cases from using the conventional cut-off value were patients presenting with worsening or recurrence of their symptoms within 45 days or three months, leading to further examinations and the detection of venous thromboembolism. Although this is common practice, this could have introduced small overestimations of the diagnostic accuracy of the D-dimer test, as small thrombi may have been missed in these patients.

Conclusions and implications for further research

D-dimer testing has limited utility in older patients when the conventional cut-off value is applied. The application of the age adjusted cut-off value combined with a non-high clinical probability

greatly increases the utility of a D-dimer test for the exclusion of venous thromboembolism in older patients, while hardly affecting the sensitivity. D-dimer levels below the age adjusted cut-off value correctly avoided imaging examinations in 30% to 54% of older patients with a non-high probability. This meta-analysis shows the robustness of our findings for patients with suspected deep vein thrombosis or pulmonary embolism, as well as for different age groups, D-dimer assays, and prevalence of venous thromboembolism.

Given that the age adjusted cut-off level could be easily implemented in routine laboratory practice it may have an immediate impact in clinical practice and serve the needs of older patients with a non-high clinical probability of venous thromboembolism by sparing a substantial proportion the burden of imaging investigations. Our results are not, however, applicable to patients with a high clinical probability of venous thromboembolism as additional imaging examination is warranted in these patients, irrespective of the D-dimer test results. Furthermore, since this strategy has only been confirmed in retrospective analyses, it could be argued that a formal cost effectiveness modeling study[50;51] or even a prospective impact study[52;53] is needed to further confirm the cost effectiveness and ease of use and acceptability of this diagnostic strategy in daily patient care before its implementation in clinical practice.

ACKNOWLEDGEMENTS

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APPENDIX 1

Search strategy

Pubmed query 21-06-2012

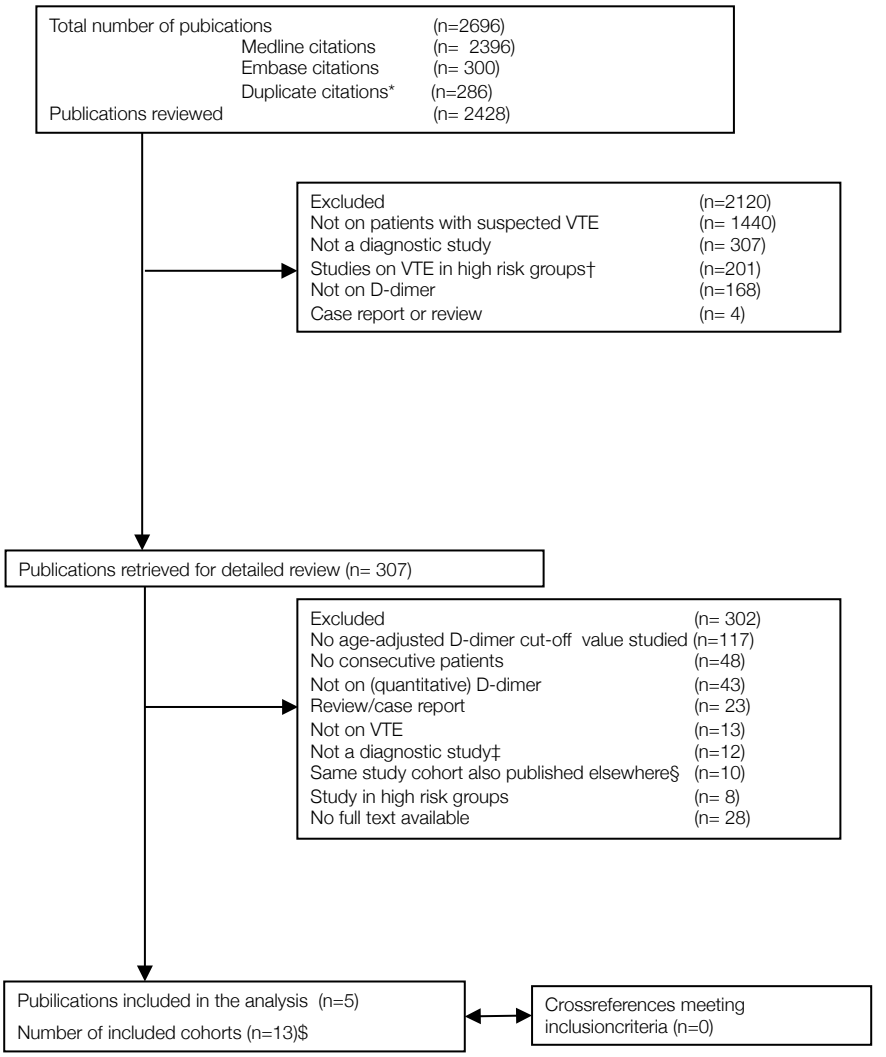
("embolism"[MeSH Terms] OR "embolism"[Title/Abstract] OR "emboli"[Title/Abstract] OR "embolic"[Title/Abstract] OR "embolus"[Title/Abstract] OR "pe"[Title/Abstract] OR "dvt"[Title/Abstract] OR "thrombosis"[Title/Abstract] OR "thrombose"[Title/Abstract] OR "thrombosed"[Title/Abstract] OR "thromboemboli"[Title/Abstract] OR "thromboembolic"[Title/Abstract] OR "vte"[Title/Abstract] OR "Venous Thrombosis"[Mesh] OR "Pulmonary Embolism"[Mesh]) AND (d dimer[Substance Name] OR "dimer"[Title/Abstract] OR "fibrinogen"[Title/Abstract] OR "fibrin"[Title/Abstract] OR "fibrin fragment D "[Substance Name]) AND ("aged"[Title/Abstract] OR "elderly"[Title/Abstract] OR "geriatric"[Title/Abstract] OR "nursing home"[Title/Abstract] OR "nursing homes"[Title/Abstract] OR "nursing care"[Title/Abstract] OR "old persons"[Title/Abstract]) OR age group[Title/Abstract] OR "age groups"[Title/Abstract] OR "older adult"[Title/Abstract] OR "older adults"[Title/Abstract] OR "older patient"[Title/Abstract] OR "older patients"[Title/Abstract] OR "senior"[Title/Abstract] OR "seniors"[Title/Abstract] OR "psychogeriatric"[Title/Abstract] OR "psychogeriatrics"[Title/Abstract] OR "elder population"[Title/Abstract] OR "Aged"[Mesh] OR "Health Services for the Aged"[Mesh] OR "Homes for the Aged"[Mesh] OR "Aged, 80 and over"[Mesh] OR "Frail Elderly"[Mesh] OR "Housing for the Elderly"[Mesh] OR "Nursing Homes"[Mesh] OR "Nursing Care"[Mesh] OR "age groups"[Title/Abstract] OR "elderly care"[Title/Abstract])

Embase query 21-06-2012

(embolism:ab,ti OR emboli:ab,ti OR embolic:ab,ti OR embolus:ab,ti OR pe:ab,ti OR dvt:ab,ti OR thrombosis:ab,ti OR thrombose:ab,ti OR thrombosed:ab,ti OR thromboemboli:ab,ti OR thromboembolic:ab,ti OR vte:ab,ti) AND (dimmer:ab,ti OR fibrinogen:ab,ti OR fibrin:ab,ti) AND [embase]/lim AND (aged:ab,ti OR elderly:ab,ti OR geriatric:ab,ti OR 'nursing home':ab,ti OR 'nursing homes':ab,ti OR 'nursing care':ab,ti OR 'old persons':ab,ti OR 'age group':ab,ti OR 'older adult':ab,ti OR 'older adults':ab,ti OR 'older patient':ab,ti OR 'older patients':ab,ti OR senior:ab,ti OR seniors:ab,ti OR psychogeriatric:ab,ti OR psychogeriatrics:ab,ti OR 'elder population':ab,ti OR 'age groups':ab,ti OR 'elderly care':ab,ti)

APPENDIX 2

Flowchart of search strategy and included studies



Search June 21th 2012.
* Duplicates between Medline and Embase or within Medline
† These publucations concern selected patients; for example, only patients with confirmed pulmonary embolism.
‡ Not a diagnostic, but rather a therapeutic, etiologic or prognostic study
§ Two citations based on same studypopulation
$ Three studies separately presented data derived from >1 studypopulation (3, 3 and 5 study populations).

APPENDIX 3

Critical appraisal according to the QUADAS-2 tool[27]

Study cohort[a]	Risk of Bias				Concerns regarding Applicability		
	Patient selection[b]	Index test[c]	Reference standard[d]	Flow and timing[e]	Patient selection[b]	Index test[c]	Reference standard[d]
Douma 2010, Derivation set [6;34]	Low	Low	High	Low	Low	Low	Low
Douma 2010 Validation set 2 [6;36]	Low	Low	High	Low	Low	Low	Low
Penaloza 2012, French cohort [16;38]	Low	Unclear	High	High	Low	Unclear	Low
Penaloza 2012, European cohort [16;37]	Low	Unclear	High	High	Low	Unclear	Low
Penaloza 2012, USA cohort [16;42]	High	Unclear	High	Low	High	Unclear	Low
Douma 2010 Validation set 1 [6;35]	Low	Low	High	Low	Low	Low	Low
Es, van 2012 [17;55]	Low	Low	High	Low	Low	Unclear	Low
Schouten 2012 [18;56]	Low	Low	Low	Unclear	Low	Unclear	Low
Douma 2012, cohort 1 [7;19]	Low	Low	High	Low	Low	Low	Low
Douma 2012, cohort 2 [19;31]	Low	Low	High	Low	Low	Low	Low
Douma 2012, cohort 3 [19;32]	Low	Low	High	Low	Low	Low	Low
Douma 2012, cohort 4 [19;33]	High*	Low	High	Low	Low	Low	Low
Douma 2012, cohort 5 [19, Tan et al, unpublished]	Low	Low	High	Low	Low	Unclear	Low

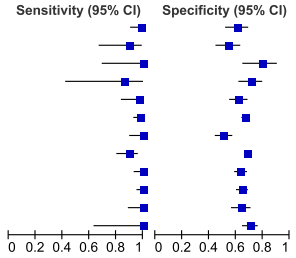
a. Second given reference refers to primary studies describing the cohort
b. If a consecutive sample of patients suspected of having venous thromboembolism was enrolled, the risk of bias was considered low. Studies including only patients in whom D-dimer testing and/or imaging investigations were performed or wherein >10% of patients were excluded using inappropriate exclusion criteria (e.g. unable to follow up)* were considered as having a high risk of bias. If there were concerns that the patients included in the study would differ from patients that are targeted by the review question, applicability concerns were considered high.
c.If there was no roam for subjective interpretation of the index-test (D-dimer result), the risk of bias was considered low. If there was no clear description of the type of D-dimer assay used, the risk of bias was considered unclear. For cohorts wherein two or more D-dimer assays were used from which results were presented unstratified, the applicability was considered unclear.
d. If all patients in the sample underwent imaging investigation (reference standard), the risk of bias was considered low. However, if only patients with a high D-dimer test and/or a non-high clinical probability underwent imaging investigation, the risk of (differential verification) bias was considered high.
e. If all patients who were enrolled in the studies were presented in the 2x2 tables, the risk of bias was considered low. If D-dimer results were missing for 10% or more of the enrolled patients, the risk of bias was 'unclear'. The risk of bias was considered high if not all patients underwent the same algorithm of reference testing.

APPENDIX 4

Sensitivity and specificity of individual included cohorts, with prevalence, pre-test probability and applied D-dimer assay.

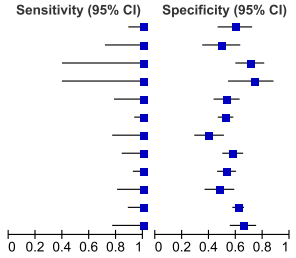
D-dimer tests in patients aged <= 50, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 1	53	53	1	82	DVT	outpatients	Quantitative latex aglutination assay	39.0	0.98 [0.90, 1.00]	0.61 [0.52, 0.69]
Douma 2012, cohort 2	17	56	2	66	DVT	outpatients	Quantitative latex aglutination assay	23.0	0.89 [0.67, 0.99]	0.54 [0.45, 0.63]
Douma 2012, cohort 3	10	9	0	35	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.69, 1.00]	0.80 [0.65, 0.90]
Douma 2012, cohort 4	6	32	1	79	DVT	outpatients	Quantitative latex aglutination assay	10.0	0.86 [0.42, 1.00]	0.71 [0.62, 0.79]
Schouten, 2012	30	80	1	130	DVT	primary care	Quantitative latex or ELFA	19.7	0.97 [0.83, 1.00]	0.62 [0.55, 0.69]
Douma 2010, valid.set 1	91	339	2	687	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.98 [0.92, 1.00]	0.67 [0.64, 0.70]
Es, van 2012	33	120	0	124	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.89, 1.00]	0.51 [0.44, 0.57]
Penaloza 2012, USA cohort	61	575	7	1262	PE	outpatients	Mixed assays	5.1	0.90 [0.80, 0.96]	0.69 [0.67, 0.71]
Douma 2010, derivationset	49	153	0	266	PE	outpatients	ELFA	24.2	1.00 [0.93, 1.00]	0.63 [0.59, 0.68]
Douma 2010, valid.set 2	69	169	0	307	PE	outpatients	ELFA	20.7	1.00 [0.95, 1.00]	0.64 [0.60, 0.69]
Penaloza 2012, Eur cohort	30	66	0	116	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.88, 1.00]	0.64 [0.56, 0.71]
Penaloza 2012, French coh	8	74	0	177	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.63, 1.00]	0.71 [0.64, 0.76]



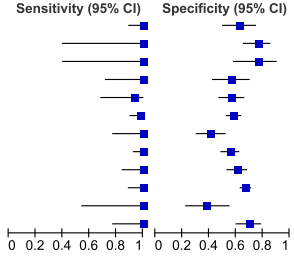
D-dimer tests in patients aged 51-60, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 1	31	25	0	37	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.89, 1.00]	0.60 [0.46, 0.72]
Douma 2012, cohort 2	11	27	0	26	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.72, 1.00]	0.49 [0.35, 0.63]
Douma 2012, cohort 4	4	22	0	54	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.40, 1.00]	0.71 [0.60, 0.81]
Douma 2012, cohort 3	4	8	0	22	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.40, 1.00]	0.73 [0.54, 0.88]
Schouten, 2012	15	52	0	59	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.78, 1.00]	0.53 [0.43, 0.63]
Douma 2010, valid.set 1	52	146	0	160	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.93, 1.00]	0.52 [0.47, 0.58]
Es, van 2012	14	50	0	33	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.77, 1.00]	0.40 [0.29, 0.51]
Douma 2010, derivationset	21	71	0	97	PE	outpatients	ELFA	24.2	1.00 [0.84, 1.00]	0.58 [0.50, 0.65]
Douma 2010, valid.set 2	45	97	0	110	PE	outpatients	ELFA	20.7	1.00 [0.92, 1.00]	0.53 [0.46, 0.60]
Penaloza 2012, Eur cohort	17	45	0	41	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.80, 1.00]	0.48 [0.37, 0.59]
Penaloza 2012, USA cohort	30	193	0	311	PE	outpatients	Mixed assays	5.1	1.00 [0.88, 1.00]	0.62 [0.57, 0.66]
Penaloza 2012, French coh	14	34	0	65	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.77, 1.00]	0.66 [0.55, 0.75]



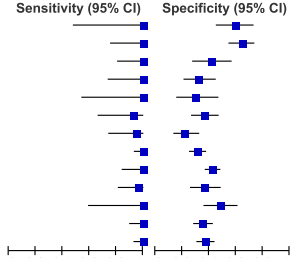
D-dimer tests in patients aged 51-60, cut-off age*10 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 1	31	23	0	39	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.89, 1.00]	0.63 [0.50, 0.75]
Douma 2012, cohort 4	4	18	0	58	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.40, 1.00]	0.76 [0.65, 0.85]
Douma 2012, cohort 3	4	7	0	23	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.40, 1.00]	0.77 [0.58, 0.90]
Douma 2012, cohort 2	11	23	0	30	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.72, 1.00]	0.57 [0.42, 0.70]
Schouten, 2012	14	48	1	63	DVT	primary care	Quantitative latex or ELFA	19.7	0.93 [0.68, 1.00]	0.57 [0.47, 0.66]
Douma 2010, valid.set 1	51	128	1	178	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.98 [0.90, 1.00]	0.58 [0.52, 0.64]
Es, van 2012	14	49	0	34	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.77, 1.00]	0.41 [0.30, 0.52]
Douma 2010, valid.set 2	45	92	0	115	PE	outpatients	ELFA	20.7	1.00 [0.92, 1.00]	0.56 [0.49, 0.62]
Douma 2010, derivationset	21	66	0	102	PE	outpatients	ELFA	24.2	1.00 [0.84, 1.00]	0.61 [0.53, 0.68]
Penaloza 2012, USA cohort	30	166	0	338	PE	outpatients	Mixed assays	5.1	1.00 [0.88, 1.00]	0.67 [0.63, 0.71]
Penaloza 2012, Eur cohort	6	23	0	14	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.54, 1.00]	0.38 [0.22, 0.55]
Penaloza 2012, French coh	14	30	0	69	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.77, 1.00]	0.70 [0.60, 0.79]



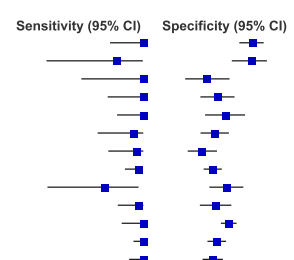
D-dimer tests in patients aged 61-70, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 3	5	21	0	31	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.48, 1.00]	0.60 [0.45, 0.73]
Douma 2012, cohort 4	13	37	0	67	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.75, 1.00]	0.64 [0.54, 0.74]
Douma 2012, cohort 1	17	28	0	20	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.80, 1.00]	0.42 [0.28, 0.57]
Douma 2012, cohort 2	12	44	0	21	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.74, 1.00]	0.32 [0.21, 0.45]
Douma 2012, cohort 5	6	26	0	11	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.54, 1.00]	0.30 [0.16, 0.47]
Schouten, 2012	13	59	1	34	DVT	primary care	Quantitative latex or ELFA	19.7	0.93 [0.66, 1.00]	0.37 [0.27, 0.47]
Es, van 2012	18	63	1	18	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	0.95 [0.74, 1.00]	0.22 [0.14, 0.33]
Douma 2010, valid.set 1	50	151	0	69	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.93, 1.00]	0.31 [0.25, 0.38]
Penaloza 2012, USA cohort	21	171	0	127	PE	outpatients	Mixed assays	5.1	1.00 [0.84, 1.00]	0.43 [0.37, 0.48]
Penaloza 2012, Eur cohort	26	48	1	28	PE	outpatients	Quantitative latex or ELFA	18.0	0.96 [0.81, 1.00]	0.37 [0.26, 0.49]
Penaloza 2012, French coh	7	34	0	32	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.59, 1.00]	0.48 [0.36, 0.61]
Douma 2010, derivationset	33	115	0	63	PE	outpatients	ELFA	24.2	1.00 [0.89, 1.00]	0.35 [0.28, 0.43]
Douma 2010, valid.set 2	48	133	0	79	PE	outpatients	ELFA	20.7	1.00 [0.93, 1.00]	0.37 [0.31, 0.44]



D-dimer tests in patients aged 61-70, cut-off age*10 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 4	13	29	0	75	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.75, 1.00]	0.72 [0.62, 0.80]
Douma 2012, cohort 3	4	15	1	37	DVT	outpatients	Quantitative latex aglutination assay	23.0	0.80 [0.28, 0.99]	0.71 [0.57, 0.83]
Douma 2012, cohort 5	6	23	0	14	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.54, 1.00]	0.38 [0.22, 0.55]
Douma 2012, cohort 2	12	35	0	30	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.74, 1.00]	0.46 [0.34, 0.59]
Douma 2012, cohort 1	17	23	0	25	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.80, 1.00]	0.52 [0.37, 0.67]
Schouten, 2012	13	52	1	41	DVT	primary care	Quantitative latex or ELFA	19.7	0.93 [0.66, 1.00]	0.44 [0.34, 0.55]
Es, van 2012	18	53	1	28	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	0.95 [0.74, 1.00]	0.35 [0.24, 0.46]
Douma 2010, valid.set 1	48	126	2	94	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.96 [0.86, 1.00]	0.43 [0.36, 0.50]
Penaloza 2012, French coh	5	31	2	35	PE	outpatients	Quantitative latex or ELFA	28.0	0.71 [0.29, 0.96]	0.53 [0.40, 0.65]
Penaloza 2012, Eur cohort	26	42	1	34	PE	outpatients	Quantitative latex or ELFA	18.0	0.96 [0.81, 1.00]	0.45 [0.33, 0.57]
Penaloza 2012, USA cohort	21	135	0	163	PE	outpatients	Mixed assays	5.1	1.00 [0.84, 1.00]	0.55 [0.49, 0.60]
Douma 2010, valid.set 2	48	115	0	97	PE	outpatients	ELFA	20.7	1.00 [0.93, 1.00]	0.46 [0.39, 0.53]
Douma 2010, derivationset	33	102	0	76	PE	outpatients	ELFA	24.2	1.00 [0.89, 1.00]	0.43 [0.35, 0.50]



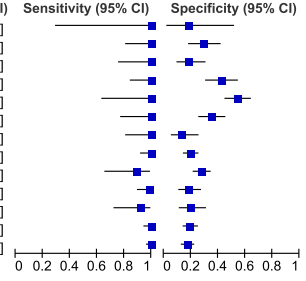
Additional data of cohort 5 of the Douma 2012 study (Tan et al), were not provided for the age-categories <50 years and 51-60 years (89 patients and 44 patients respectively)

APPENDIX 4 (CONTINUED)

Sensitivity and specificity of individual included cohorts, with prevalence, pre-test probability and applied D-dimer assay (continued)

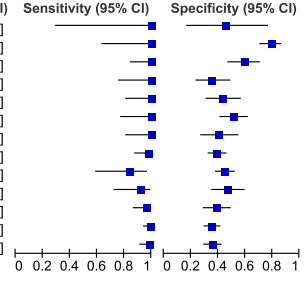
D-dimer test in patients aged 71-80, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 5	3	9	0	2	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.29, 1.00]	0.18 [0.02, 0.52]
Douma 2012, cohort 1	17	44	0	18	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.80, 1.00]	0.29 [0.18, 0.42]
Douma 2012, cohort 2	13	48	0	11	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.75, 1.00]	0.19 [0.10, 0.31]
Douma 2012, cohort 3	21	41	0	30	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.84, 1.00]	0.42 [0.31, 0.55]
Douma 2012, cohort 4	8	50	0	60	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.63, 1.00]	0.55 [0.45, 0.64]
Schouten, 2012	14	63	0	34	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.77, 1.00]	0.35 [0.26, 0.45]
Es, van 2012	17	45	0	7	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.80, 1.00]	0.13 [0.06, 0.26]
Douma 2010, valid.set 1	41	164	0	40	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.91, 1.00]	0.20 [0.14, 0.26]
Penaloza 2012, USA cohort	16	138	2	53	PE	outpatients	Mixed assays	5.1	0.89 [0.65, 0.99]	0.28 [0.22, 0.35]
Penaloza 2012, Eur cohort	48	76	1	17	PE	outpatients	Quantitative latex or ELFA	18.0	0.98 [0.89, 1.00]	0.18 [0.11, 0.28]
Penaloza 2012, French coh	21	56	2	14	PE	outpatients	Quantitative latex or ELFA	28.0	0.91 [0.72, 0.99]	0.20 [0.11, 0.31]
Douma 2010, derivationset	58	167	0	40	PE	outpatients	ELFA	24.2	1.00 [0.94, 1.00]	0.19 [0.14, 0.25]
Douma 2010, valid.set 2	85	205	0	43	PE	outpatients	ELFA	20.7	1.00 [0.96, 1.00]	0.17 [0.13, 0.23]



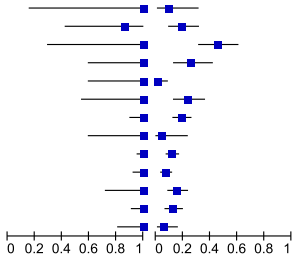
D-dimer test in patients aged 71-80, cut-off age*10ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 5	3	6	0	5	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.29, 1.00]	0.45 [0.17, 0.77]
Douma 2012, cohort 4	8	23	0	87	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.63, 1.00]	0.79 [0.70, 0.86]
Douma 2012, cohort 3	21	29	0	42	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.84, 1.00]	0.59 [0.47, 0.71]
Douma 2012, cohort 2	13	38	0	21	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.75, 1.00]	0.36 [0.24, 0.49]
Douma 2012, cohort 1	17	35	0	27	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.80, 1.00]	0.44 [0.31, 0.57]
Schouten, 2012	14	47	0	50	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.77, 1.00]	0.52 [0.41, 0.62]
Es, van 2012	17	31	0	21	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.80, 1.00]	0.40 [0.27, 0.55]
Douma 2010, valid.set 1	40	124	1	80	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.98 [0.87, 1.00]	0.39 [0.32, 0.46]
Penaloza 2012, USA cohort	15	105	3	86	PE	outpatients	Mixed assays	5.1	0.83 [0.59, 0.96]	0.45 [0.38, 0.52]
Penaloza 2012, French coh	21	37	2	33	PE	outpatients	Quantitative latex or ELFA	28.0	0.91 [0.72, 0.99]	0.47 [0.35, 0.59]
Penaloza 2012, Eur cohort	47	57	2	36	PE	outpatients	Quantitative latex or ELFA	18.0	0.96 [0.86, 1.00]	0.39 [0.29, 0.49]
Douma 2010, valid.set 2	84	160	1	88	PE	outpatients	ELFA	20.7	0.99 [0.94, 1.00]	0.35 [0.30, 0.42]
Douma 2010, derivationset	57	133	1	74	PE	outpatients	ELFA	24.2	0.98 [0.91, 1.00]	0.36 [0.29, 0.43]



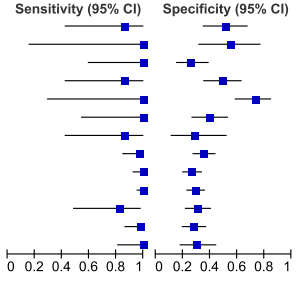
D-dimer test in patients aged >80, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 5	2	18	0	2	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.16, 1.00]	0.10 [0.01, 0.32]
Douma 2012, cohort 3	6	43	1	10	DVT	outpatients	Quantitative latex aglutination assay	23.0	0.86 [0.42, 1.00]	0.19 [0.09, 0.32]
Douma 2012, cohort 4	3	26	0	22	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.29, 1.00]	0.46 [0.31, 0.61]
Douma 2012, cohort 1	7	29	0	10	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.59, 1.00]	0.26 [0.13, 0.42]
Douma 2012, cohort 2	7	57	0	1	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.59, 1.00]	0.02 [0.00, 0.09]
Schouten, 2012	6	43	0	13	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.54, 1.00]	0.23 [0.13, 0.36]
Douma 2010, valid.set 1	33	108	0	25	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.89, 1.00]	0.19 [0.13, 0.26]
Es, van 2012	7	20	0	1	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.59, 1.00]	0.05 [0.00, 0.24]
Douma 2010, valid.set 2	68	163	0	22	PE	outpatients	ELFA	20.7	1.00 [0.95, 1.00]	0.12 [0.08, 0.17]
Douma 2010, derivationset	43	144	0	11	PE	outpatients	ELFA	24.2	1.00 [0.92, 1.00]	0.07 [0.04, 0.12]
Penaloza 2012, USA cohort	11	83	0	15	PE	outpatients	Mixed assays	5.1	1.00 [0.72, 1.00]	0.15 [0.09, 0.24]
Penaloza 2012, Eur cohort	37	92	0	13	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.91, 1.00]	0.12 [0.07, 0.20]
Penaloza 2012, French coh	17	47	0	3	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.80, 1.00]	0.06 [0.01, 0.17]



D-dimer test in patients aged >80, cut-off age*10 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 1	6	19	1	20	DVT	outpatients	Quantitative latex aglutination assay	39.0	0.86 [0.42, 1.00]	0.51 [0.35, 0.68]
Douma 2012, cohort 5	2	9	0	11	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.16, 1.00]	0.55 [0.32, 0.77]
Douma 2012, cohort 2	7	43	0	15	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.59, 1.00]	0.26 [0.15, 0.39]
Douma 2012, cohort 3	6	27	1	26	DVT	outpatients	Quantitative latex aglutination assay	23.0	0.86 [0.42, 1.00]	0.49 [0.35, 0.63]
Douma 2012, cohort 4	3	13	0	35	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.29, 1.00]	0.73 [0.58, 0.85]
Schouten, 2012	6	34	0	22	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.54, 1.00]	0.39 [0.26, 0.53]
Es, van 2012	6	15	1	6	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	0.86 [0.42, 1.00]	0.29 [0.11, 0.52]
Douma 2010, valid.set 1	32	86	1	47	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.97 [0.84, 1.00]	0.35 [0.27, 0.44]
Douma 2010, derivationset	43	114	0	41	PE	outpatients	ELFA	24.2	1.00 [0.92, 1.00]	0.26 [0.20, 0.34]
Douma 2010, valid.set 2	68	131	0	54	PE	outpatients	ELFA	20.7	1.00 [0.95, 1.00]	0.29 [0.23, 0.36]
Penaloza 2012, USA cohort	9	68	2	30	PE	outpatients	Mixed assays	5.1	0.82 [0.48, 0.98]	0.31 [0.22, 0.41]
Penaloza 2012, Eur cohort	36	76	1	29	PE	outpatients	Quantitative latex or ELFA	18.0	0.97 [0.86, 1.00]	0.28 [0.19, 0.37]
Penaloza 2012, French coh	17	35	0	15	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.80, 1.00]	0.30 [0.18, 0.45]



Additional data of cohort 5 of the Douma 2012 study (Tan et al), were not provided for the age-categories <50 years and 51-60 years (89 patients and 44 patients respectively)

APPENDIX 5

Hypothetical 2x2 tables for patients with suspected venous thromboebolism (VTE) within hypothetical cohorts with a median, low and high prevalence of VTE

With a median prevalence in patients with a non-high clinical probability of VTE

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE+	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	120	291	411	29.2	134	367	501	26.7	154	512	666	23.2	212	593	805	26.4	151	724	876	17.3
D-dimer low	3	586	589	99.5	0	499	499	100.0	2	332	334	99.5	3	192	195	98.5	1	124	124	99.5
Total	123	877	1,000		134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000	
Sensitivity/specificity	97.6	66.8			100.0	57.6			99.0	39.4			98.7	24.5			99.6	14.6		
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					133	327	460	28.9	152	427	578	26.2	209	438	648	32.3	147	550	697	21.2
D-dimer low					1	539	540	99.8	4	417	422	99.0	6	347	352	98.4	5	298	303	98.5
Total					134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000	
Sensitivity/specificity					99.4	62.3			97.3	49.5			97.3	44.2			97.0	35.2		
Number of reclassified patients					1	40			2	85			3	155			4	175		

SCENARIO HYPOTHETICAL 2X2; LOWER LIMIT CONFIDENCE INTERVALS SENS/SPEC

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	117	340	456	25.6	134	421	555	24.1	151	561	712	21.2	207	628	835	24.8	147	752	899	16.4
D-dimer low	6	537	544	98.9	0	445	445	100.0	5	283	288	98.1	8	157	165	95.4	5	96	101	95.3
Total	123	877	1000		134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000	
Sensitivity/specificity	95.0	61.3			100.0	51.4			96.6	33.5			96.5	20.0			96.9	11.3		

Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					130	380	510	25.6	146	480	626	23.4	203	487	689	29.4	141	599	740	19.1
D-dimer low					4	486	490	99.2	10	364	374	97.4	12	298	311	96.0	11	249	260	95.9
Total					134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000	
Sensitivity/specificity					97.3	56.2			93.8	43.2			94.3	38.0			92.9	29.4		
Number of reclassified patients					4	41			5	81			4	141			6	153		

SCENARIO HYPOTHETICAL 2X2; UPPER LIMIT CONFIDENCE INTERVALS SENS/SPEC

Hypothetical 2x2 tabs	**≤50 years**				**51-60 years**				**61-70 years**				**71-80 years**				**>80 years**			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	122	246	368	33.1	134	315	449	29.8	156	459	615	25.3	214	552	766	27.9	152	690	842	18.0
D-dimer low	1	631	632	99.8	0	551	551	100.0	0	385	385	99.9	1	233	234	99.6	0	158	158	99.9
Total	123	877	1000		134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000	
Sensitivity/specificity	98.9	72.0			100.0	63.6			99.7	45.6			99.5	29.7			99.9	18.6		
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					134	277	411	32.6	154	373	527	29.2	212	388	601	35.4	150	496	647	23.2
D-dimer low					0	589	589	100.0	2	471	473	99.6	3	397	399	99.3	2	352	353	99.5
Total					134	866.0	1,000		156	844	1,000		215	785	1,000		152	848	1,000	
Sensitivity/specificity					99.9	68.0			98.8	55.8			98.8	50.5			98.8	41.5		
Number of reclassified patients					0	38			2	86			2	164			2	194		

APPENDIX 5 (CONTINUED)

Hypothetical 2x2 tables for patients with suspected venous thromboebolism (VTE) within hypothetical cohorts with a median, low and high prevalence of VTE

With the lowest (MINIMAL) prevalence in patients with a non-high clinical probability of VTE

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	30	322	352	8.6	50	403	453	11.0	65	566	631	10.3	67	703	771	8.7	59	804	863	6.8
D-dimer low	1	647	648	99.9	0	547	547	100.0	1	368	369	99.8	1	229	229	99.6	0	137	137	99.8
Total	31	969	1000		50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000	
Sensitivity/specificity	97.6	66.8			100.0	57.6			99.0	39.4			98.7	24.5			99.6	14.6		
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					50	359	408	12.2	64	472	536	12.0	66	520	587	11.3	57	610	667	8.6
D-dimer low					0	591	592	99.9	2	462	464	99.6	2	412	413	99.6	2	331	333	99.5
Total					50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000	
Sensitivity/specificity					99.4	62.3			97.3	49.5			97.3	44.2			97.0	35.2		
Number of reclassified patients					0	44			1	94			1	183			2	194		

SCENARIO HYPOTHETICAL 2X2; LOWER LIMIT CONFIDENCE INTERVALS SENS/SPEC

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	29	375	405	7.3	50	462	512	9.8	64	621	685	9.3	66	746	811	8.1	57	835	892	6.4
D-dimer low	2	594	595	99.7	0	488	488	100.0	2	313	315	99.3	2	186	189	98.7	2	106	108	98.3
Total	31	969	1000		50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000	
Sensitivity/specificity	95.0	61.3			100.0	51.4			96.6	33.5			96.5	20.0			96.9	11.3		

Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					49	416	465	10.5	62	531	593	10.4	64	578	642	10.0	55	665	720	7.6
D-dimer low					1	534	535	99.7	4	403	407	99.0	4	354	358	98.9	4	276	280	98.5
Total					50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000	
Sensitivity/specificity					97.3	56.2			93.8	43.2			94.3	38.0			92.9	29.4		
Number of reclassified patients					1	46			2	90			2	168			2	170		

SCENARIO HYPOTHETICAL 2X2; UPPER LIMIT CONFIDENCE INTERVALS SENS/SPEC

Hypothetical 2x2 tabs	**≤50 years**				**51-60 years**				**61-70 years**				**71-80 years**				**>80 years**			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	31	272	302	10.1	50	346	396	12.6	66	508	574	11.5	68	655	723	9.4	59	766	825	7.1
D-dimer low	0	697	698	99.9	0	604	604	100.0	0	426	426	100.0	0	277	277	99.9	0	175	175	100.0
Total	31	969	1000		50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000	
Sensitivity/specificity	98.9	72.0	1000		100.0	63.6			99.7	45.6			99.5	29.7			99.9	18.6		
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					50	304	354	14.1	65	413	478	13.6	67	461	528	12.7	58	551	609	9.6
D-dimer low					0	646	646	100.0	1	521	522	99.9	1	471	472	99.8	1	390	391	99.8
Total					50	950.0	1,000		66	934	1,000		68	932	1,000		59	941	1,000	
Sensitivity/specificity					99.9	68.0			98.8	55.8			98.8	50.5			98.8	41.5		
Number of reclassified patients					0	42			1	95			1	194			1	215		

APPENDIX 5 (CONTINUED)

Hypothetical 2x2 tables for patients with suspected venous thromboebolism (VTE) within hypothetical cohorts with a median, low and high prevalence of VTE

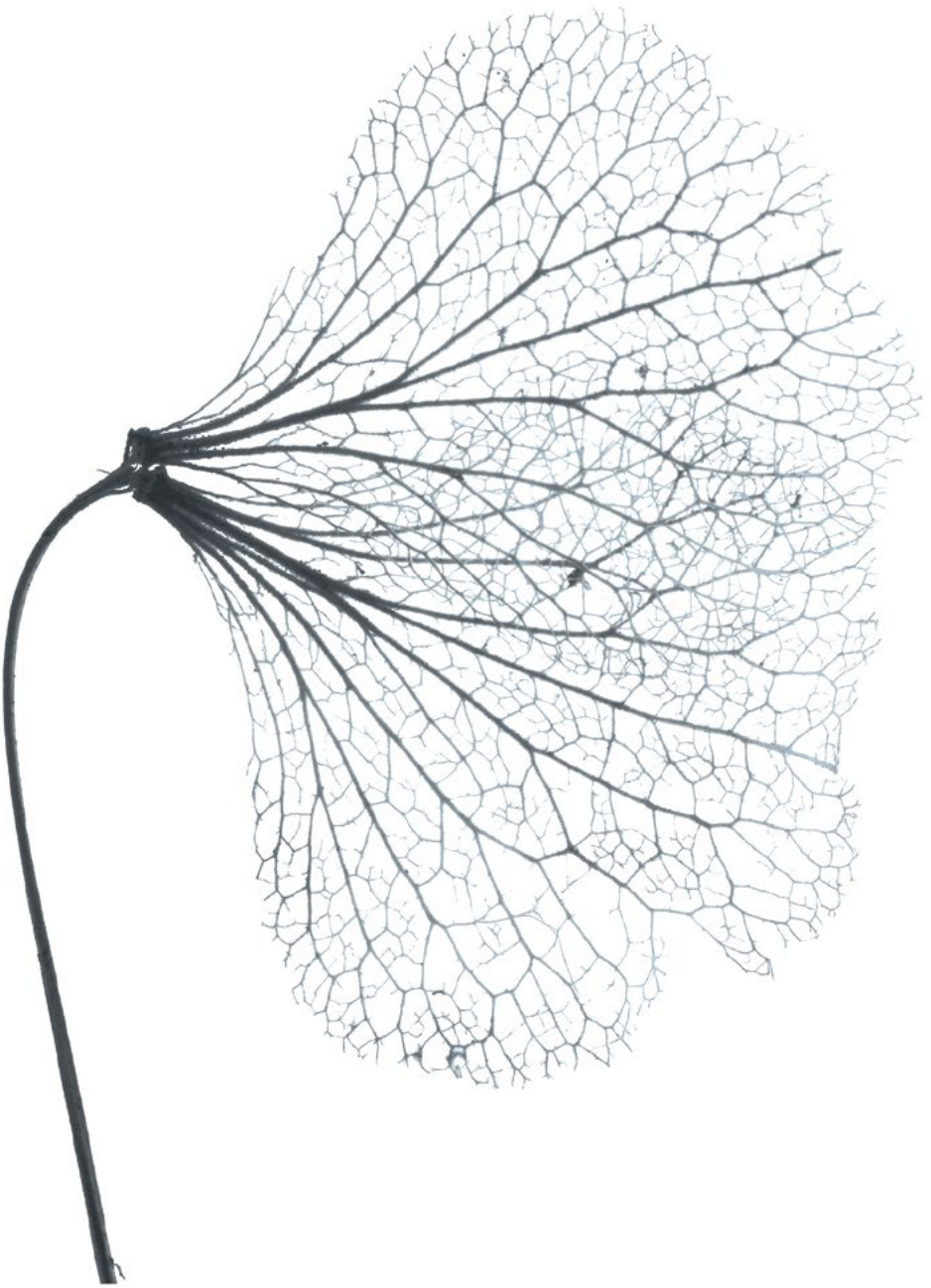
With the highest (MAXIMAL) prevalence in patients with a non-high clinical probability of VTE

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	279	237	516	54.1	333	283	616	54.1	259	557	816	31.7	340	494	835	40.8	268	624	892	30.0
D-dimer low	7	477	484	98.6	0	384	384	100.0	3	181	184	98.1	5	161	165	97.2	1	107	108	99.0
Total	286	714	1000		333	667	1,000		262	738	1,000		345	655	1,000		269	731	1,000	
Sensitivity/specificity	97.6	66.8			100.0	57.6			98.7	24.5			98.7	24.5			99.6	14.6		
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					331	252	583	56.8	255	412	667	38.2	336	366	702	47.9	261	474	735	35.5
D-dimer low					2	415	417	99.5	7	326	333	97.9	9	289	298	96.9	8	257	265	97.0
Total					333	667	1,000		262	738	1,000		345	655	1,000		269	731	1,000	
Sensitivity/specificity					99.4	62.3			97.3	44.2			97.3	44.2			97.0	35.2		
Number of reclassified patients					2	31			4	145			4	128			7	150		

SCENARIO HYPOTHETICAL 2X2; LOWER LIMIT CONFIDENCE INTERVALS SENS/SPEC

Hypothetical 2x2 tabs	**≤50 years**				**51-60 years**				**61-70 years**				**71-80 years**				**>80 years**			
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	272	277	548	49.6	333	324	657	50.7	265	580	845	31.4	292	558	850	34.4	261	648	909	28.7
D-dimer low	14	437	452	96.8	0	343	343	100.0	10	145	155	93.7	11	139	150	92.9	8	83	91	90.9
Total	286	714	1000		333	667	1,000		275	725	1,000		303	697	1,000		269	731	1,000	
Sensitivity/specificity	95.0	61.3			100.0	51.4			96.5	20.0			96.5	20.0			96.9	11.3		

Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					324	292	616	52.6	259	449	709	36.6	286	432	718	39.8	250	516	766	32.6
D-dimer low					9	375	384	97.6	16	276	291	94.6	17	265	282	93.8	19	215	234	91.9
Total					333	667	1,000		275	725	1,000		303	697	1,000		269	731	1,000	
Sensitivity/specificity					97.3	56.2			94.3	38.0			94.3	38.0			92.9	29.4		
Number of reclassified patients					9	32			6	131			6	126			11	132		
SCENARIO HYPOTHETICAL 2X2; UPPER LIMIT CONFIDENCE INTERVALS SENS/SPEC																				
Hypothetical 2x2 tabs		**≤50 years**				**51-60 years**				**61-70 years**				**71-80 years**				**>80 years**		
Conventional cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high	283	200	483	58.5	333	243	576	57.8	274	510	784	34.9	302	490	792	38.1	269	595	864	31.1
D-dimer low	3	514	517	99.4	0	424	424	100.0	1	215	217	99.4	1	207	208	99.3	0	136	136	99.9
Total	286	714	1000		333	667	1,000		275	725	1,000		303	697	1,000		269	731	1,000	
Sensitivity/specificity	98.9	72.0			100.0	63.6			99.5	29.7			99.5	29.7			99.9	18.6		
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV	VTE +	VTE-	Total	PPV/ NPV
D-dimer high					333	214	546	60.9	272	359	630	43.1	299	345	644	46.5	266	428	694	38.3
D-dimer low					0	453	454	99.9	3	366	370	99.1	4	352	356	99.0	3	303	306	98.9
Total					333	667.0	1,000		275	725	1,000		303	697	1,000		269	731	1,000	
Sensitivity/specificity					99.9	68.0			98.8	50.5			98.8	50.5			98.8	41.5		
Number of reclassified patients					0	29			2	151			3	145			3	167		



CHAPTER 7

NON-DIAGNOSIS DECISIONS AND NON-TREATMENT DECISIONS IN ELDERLY PATIENTS WITH CARDIOVASCULAR DISEASES, DO THEY DIFFER?

A SYSTEMATIC REVIEW

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ABSTRACT

The growth in the number of possible medical interventions in the past decennia necessitates physicians to consider whether to use them. Contrary to decisions to withhold treatment, little is known about 'non-diagnosis decisions' (NDD) although their consequences seem to be more uncertain. Hence we hypothesized that "determinants" and "reasons" for NDD are different from those that are associated with non treatment decisions (NTD). We performed a systematic review on research on physicians' decisions to withhold or withdraw diagnostic or therapeutic interventions. A total of 11,773 unique citations published either in Medline, Embase or the Cochrane databases were screened, of which 45 papers - including 4 papers describing NDD in elderly patients suspected of cardiovascular diseases - were considered relevant and analysed in detail. "Determinants" and "reasons" for NDD and NTD were extracted, categorized into predefined categories and compared to each other. Besides several similarities, we found various differences between NDD and NTD. The proportionality of an intervention -i.e. the risk or burden of an intervention opposed to that of no intervention- was associated with NTD but not with NDD. Physician- and care institution related characteristics, such as age of the physician or the employment of physician extenders, were more frequently associated with NDD than with NTD. Furthermore, the presence of non-resuscitate directives was correlated with NDD but not with NTD. This systematic review shows that there is little information on NDD in the current literature. Yet, there is not enough evidence to conclude whether NDD can be seen as a separate entity distinct from NTD. More research focusing on NDD seems needed.

BOX - NON DIAGNOSIS DECISIONS

Case 1

A 91 years old immobile nursing home resident complains of a heavy feeling in the right leg. Physical examination reveals some redness and swelling of the calf. The physician considers a deep venous thrombosis and performs a D-dimer test which has an abnormal result. Although referral for a compression ultrasonography examination is the proper way to establish a deep venous thrombosis, the physician regards this procedure too burdensome for the patient and starts with anticoagulation treatment.

Case 2

A 89 year old mildly demented female with multiple comorbidities presents to her general practitioner with loss of weight and constipation. Laboratory testing reveals a microcytic anemia and a high erythrocyte sedimentation rate. The general practitioner considers referring the patient for colonoscopy to exclude a colon carcinoma. However, due to the need for a burdening preparation, the invasive character of the colonoscopy procedure itself and the risk that this certain patient will develop a delirium due to this procedure, the physician decides to wait and see and to refrain from further diagnostic interventions.

INTRODUCTION

In current medical practice, the number of treatment possibilities is rapidly increasing. Yet, the availability of these interventions does not necessarily imply that physicians always use them. In fact, notably in older patients, physicians often decide to forgo treatment.[1-5] Reasons that physicians give for these non-treatment decisions (NTD) include advanced age, a short life expectancy after treatment, or a decreased physical condition of the patient.[4;6] Besides these self reported reasons, investigators have studied factors that are statistically correlated with NTD. These "determinants" include increasing patient's age, decreased quality of life and co-morbidity.[1;6]

In addition to NTD, decisions to withhold diagnostic procedures (hereinafter referred to as 'non-diagnosis decisions', NDD) are frequent in daily practice. Although several studies have focused on NTD in elderly patients,[1-5] little research was performed on the "determinants" of NDD and "reasons" for NDD in this group. From a clinical point of view, the consequences of NDD compared to these of NTD are less clear: By withholding diagnostic procedures there is a chance that a potentially manageable disease remains unknown and thus untreated. Hence, we hypothesized that "determinants" of and given "reasons" for NDD are different from NTD, and performed a sys-

tematic review to detect similarities and differences between non diagnosis- and non treatment decision processes with the focus on older patients with a (suspected) cardiovascular disease.

METHODS

Data sources and searches

A systematic search was performed in Medline, Embase and the Cochrane Review databases (2011-05-24; Appendix 1, search syntax). Synonyms for NTD and NDD were combined with synonyms for "elderly"[7] to identify articles reporting on NDD and NTD in the old patients. Duplicate articles were removed by hand using the "close match" function in Refworks 2.0.

Study selection

Articles were manually screened on title, abstract and full text using predefined in- and exclusion criteria (Figure 1, flowchart). Studies meeting the following criteria were included:

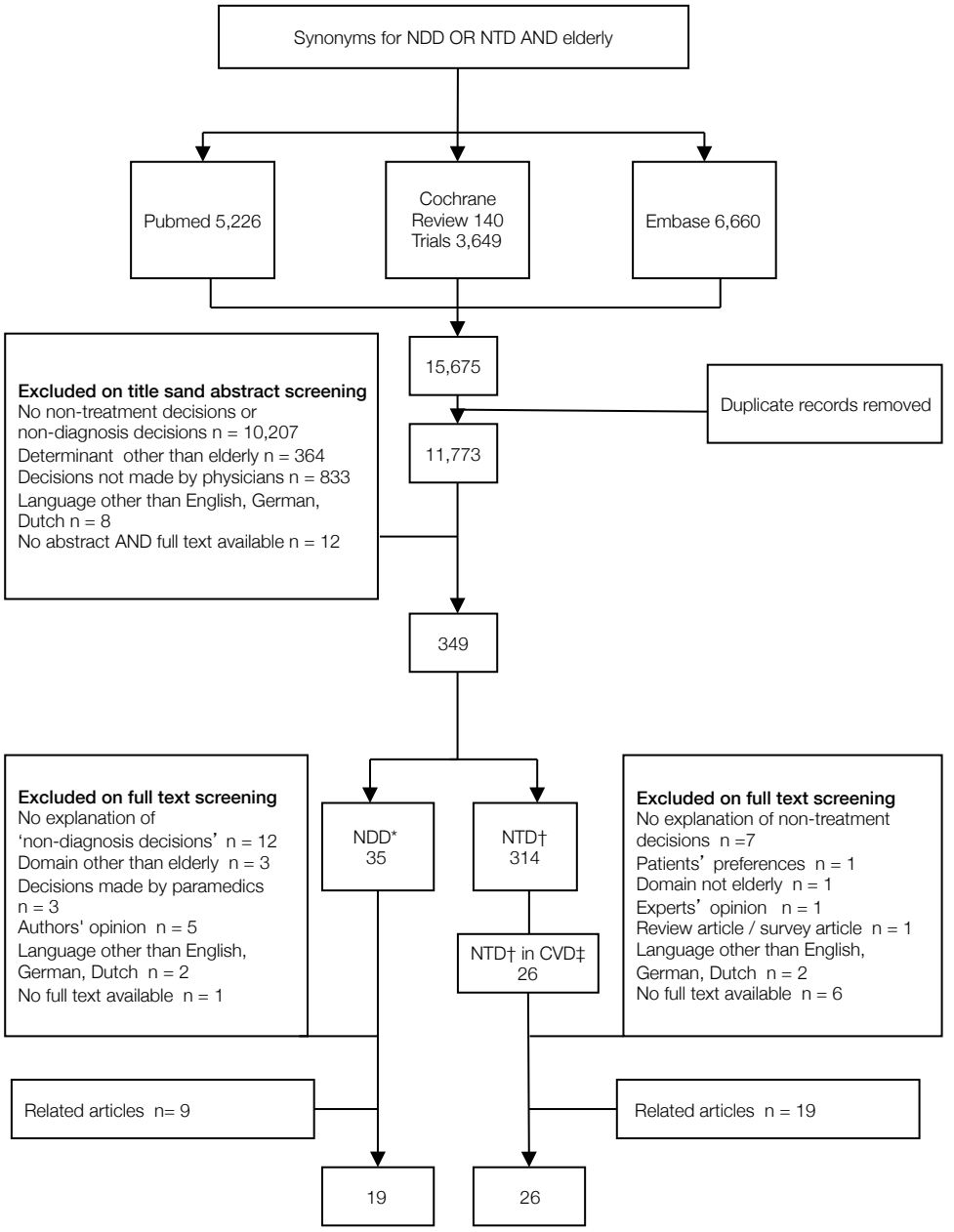
1. Described "determinants" of and/or "reasons" for NDD by physicians OR described "determinants" of and/or "reasons" for NTD made by physicians
2. Study (sub)population existed of patients aged ≥ 65 years with cardiovascular diseases or physicians involved with the care of patients aged ≥ 65 years with cardiovascular diseases
3 Language was English, German or Dutch.

Reviews and meta-analyses were excluded (but the reference lists were checked for studies suitable for inclusion), as well as studies concerning 'do not resuscitate' decisions as we aimed to focus on actual problems rather than decisions anticipating probable events in the future. If studies fulfilled the inclusion criteria but were unavailable as full text article in all Dutch libraries, the authors of the concerning studies were contacted and were asked to send a full text article. Reference lists of finally included articles were screened for additional papers satisfying the inclusion criteria.

Data extraction

Two reviewers (HJS, SG) independently extracted the following characteristics from each study: subject of the study; study design; setting; country; total number, mean age and percentage of males of the included patients and/or physicians. "Determinants" influencing physicians in making NDD or NTD in elderly patients and "reasons" that were given by physicians for such decisions were also extracted. If studies described decisions made by physicians as well as by paramedics, only data concerning physicians' decisions were used. To enable a comparison between the

Figure 1 Flowchart, literature search performed on 2011-05-24



* Given this small number of NDD papers, we decided to broaden the domain of the NDD papers to elderly patients suspected of any disease which resulted in 19 articles focusing on NDD.
† NTD: Non-treatment descisions
‡ CVD: Cardiovascular diseases

"determinants" and "reasons" of NDD with those of NTD, the "determinants" and "reasons" were classified into predefined categories by two independent authors (SG, HJS). The following eight categories were defined: 1) patients' preferences, 2) condition of the patient before intervention including age and co-morbidity, 3) expected quality of life after intervention, 4) proportionality of an intervention (i.e. the risk or burden of an intervention opposed to the risk or burden of no intervention), 5) physician related characteristics, 6) care institution related characteristics 7) non-medical patient-bound characteristics and 8) the presence of a 'no-resuscitate order' or a 'no-hospitalization order' 9) 'other "determinants" or "reasons".[8] Inconsistencies between the reviewers were discussed until consensus was reached.

Definitions

"NDD" were defined as decisions of physicians not to perform diagnostic procedures (e.g. imaging, exercise tolerance tests or biopsy). Decisions to withhold procedures with possibly both diagnostic and therapeutic purposes (e.g. hospitalization or axillary's lymph node dissection in patients with breast cancer) were also classified as NDD.

"*NTD*" are defined as decisions of physicians to withhold or withdraw therapy in patients with a certain disease or certain symptoms.

"Determinants" were defined as variables (i.e. characteristics) associated with NDD or with NTD as based on e.g. a univariable or multivariable regression analyses. When multivariable associations were available, we selected the variables that were reported as significantly (p-value <0.05) and independently associated with NDD or NTD. From studies were only univariable associations with NDD or NTD were available, those variables were selected.

"Reasons" were defined as the justifications for NDD or NTD as given by physicians. Hence – in contrast to "determinants" where the associations needed to be based on formal statistical correlations – this was not needed for "reasons" as they included motivations as given by physicians in interviews, surveys or in patient charts.

Cardiovascular diseases included arrhythmias, heart valve diseases, thrombotic or ischemic diseases as well as hemorrhagic cerebrovascular accidents.

RESULTS

Identification and selection of studies

Our search yielded 11,773 unique citations (Figure 1-flowchart). After applying our a priori defined in- and exclusion criteria, our search yielded of total of 26 NTD articles and 4 NDD articles. Given this small number of NDD papers, we decided to broaden the domain of the NDD papers to elderly patients suspected of any disease which resulted in 19 articles focusing on NDD. These in total 45 papers fulfilling the inclusion criteria and were further analyzed.

NDD

Characteristics of studies reporting on NDD

A total of 19 studies concerning 129,596 patients (range 72 to 91,521 per paper) of whom 111,561 nursing home residents and 72 electronic fictional patients, and 925 physicians (range 6 to 656 per study) were included. "Determinants" for NDD were investigated in 18 studies and "reasons" for NDD in 4 studies; 4 articles investigated both. Ten studies were performed in hospitals, 8 in nursing homes, and 1 in both hospital and general practitioner setting. Included studies investigated NDD in elderly patients suffering cancer (n=5), cardiovascular diseases (n=4), dementia (n=5) or elderly patients without specified diseases (n=5). A detailed description of the included articles is given in table 1.

"Determinants" associated with NDD

Considering studies on "determinants" associated with NDD (table 2), all studies demonstrated an association between the patient's condition before ordering a diagnostic test and NDD.[9-25] Within this category, twelve studies showed a positive correlation of the patient's age and the prevalence of withholding diagnostic procedures.[9-17;19;21;25] Seven studies associated co-morbidity with NDD.[12;18-20;22-25] Five of these studies included patients with dementia or cognitive impairment[18;22-25] and showed that depressive disorders were underdiagnosed (OR=0.61[95% CI,0.38–0.98])[18] and hospitalizations were more frequently omitted in patients with cognitive impairment (OR=0.69 [95%CI,0.49-0.89]).[24]

In the category "non-medical patient-bound determinants", female gender and non-white race were associated with NDD.[17;23-25] Female nursing home residents showed to have lower odds for hospitalization than men (OR=0.67[95%CI 0.47-0.89]).[24]

Two studies showed that nursing home residents with 'non-resuscitate orders' were less likely to be hospitalized (Mor et al, OR=0.48[95%CI,0.38-0.59]).[23;24] One study showed a relation between the patient's preference and NDD.[11]

Several studies showed an association between various physician-related "determinants" and NDD:[11;15;20] Edge et al showed that patients with mamma carcinoma treated by surgeons with subspecialty training in oncology were less likely to undergo axillary lymph node dissection compared with patients who were cared for by other surgeons (OR=0.41 [95% CI, 0.25– 0.68]).[11]

Finally, characteristics of care institutions[19;23;24] were associated with NDD. Residents were less likely to be hospitalized when they lived in a nursing home that had more staffing care hours per resident (OR=1.50 [95%CI,1.18–1.91] for residents with ≥ 4.44 staffing hours per day compared to <2.75 staffing hours/resident/day)[19;24] or in a nursing home that employed a physician-extender (e.g. nurse practitioners, OR=0.59 [95%CI,0.39-0.97]).[19;23;24]

"Reasons" given for NDD

Four studies investigated "reasons" given by physicians for NDD (table 2). In all four studies the expected quality of life after the diagnostic testing as well as the proportionality of a diagnostic procedure were stated reasons for NDD.[15;20;26;27] More specific, the following "reasons" were given: expected benefit and risks of potential treatment,[15;26;27] cost-effectiveness[20;26] and the expected discomfort due to diagnostic testing.[26] The patient's condition - including old age, quality of life and mental or physical disabilities - before diagnostic testing[15;26;27] were named by physicians to influence their decision-making. Another given reason for NDD is the perceived lack of adequate care in hospitals for elderly patients after the diagnosis.[26] Finally, the patient's preference and the patient's coping are mentioned as a "reason" to withhold diagnostic procedures.[15;26]

NTD

Characteristics of studies reporting on NTD

A total of 371,786 patients (range 2 to 350,755 per article) and 1,146 physicians (range 25 to 450 per article) were included. "Determinants" were investigated in 22 studies and "reasons" in 12 studies; 8 studies investigated both. Seventeen studies were performed in hospitals, 3 in nursing homes, 5 in primary care and 1 in both hospitals and primary care. Studies investigated older patients with aortic valve stenosis (AVS, n=7),[2;28-33] atrial fibrillation (AF, n=10),[34-43] or myocardial infarction (MI, n=9).[44-53] A list of characteristics of the included articles is given in table 1.

"Determinants" associated with NTD

"Reasons" of and "determinants" for NTD are listed in table 3. The patient's condition before treatment is the most frequently associated with physicians' decisions to withhold treatment.[2;28;30;31;33;34;36-38;42;43;45-47;47-53] Nineteen studies showed a relation between the patient's age and the frequency of NTD.[2;30;31;33;36-39;43;45-53] Eight studies demonstrated a relation between co-morbidity and NTD.[2;28;33;34;38;39;48;51] For example, neurological dysfunction was associated with decisions to withhold aorta valve replacement in patients with severe AVS (Iung et al, OR=3.82 [95%CI 1.23-12.27]).[2]

Non-medical patient bound characteristics were associated with NTD in six studies.[36;46;49;51-53] Females[36;46;49;52] and patients of a minority ethnicity[46;52] were found to be less frequently treated than males and patients of a non-minor ethnicity. Revascularization was less frequently performed in MI patients of an ethnic minority (risk ratio(RR)=0.65 [95%CI 0.58-0.72]) and females (0.71 [95% CI 0.65-0.78]).[46;52] Furthermore, a late presentation in a hospital after the onset of symptoms was associated with NTD.[51-53]

Three studies showed a relation between physician or care institution related characteristics and NTD.[41;43;49] Beyt et al[43] showed that physicians with a favorable opinion about - or a good experience with warfarin more often prescribed warfarin to patients with AF (respectively OR=3.4 [95%CI 1.2-9.7] and OR=2.6[95%CI 1.3-5.2]).

Finally, the proportionality of an intervention – i.e. the risk of treating opposed to the risk of non treating - was associated with NTD.[30;34;39-41;48] In all six studies in this category, trombolytic or anticoagulation therapy was withheld as result of a higher expected bleeding risk (OR=0.18 [95%CI 0.04-0.53]).[48]

"Reasons" given by physicians for NTD

Three "reasons" for NTD were frequently given by physicians (table 3). First, patient's preference regarding withholding treatment is mentioned by physicians in 8 studies.[28-32;35;38;40]

Second, old age[31;38;41;51] and a low physical and mental condition before treatment were frequently mentioned reasons for withholding therapy.[28;30-32;35;36;38;41;42;51]

Finally, physicians frequently cited the proportionality of an intervention as a reason to forgo treatment.[28-32;35;36;38;40;41] Specific "reasons" within this final category are diverse, including mild symptoms,[29;32;51] non-critical or stable disease,[28;29;31;32] high risk of falls when considering anti-thrombotic therapy,[35;36;38;41] high costs[40;41] and high (mortality) risk due to treatment.[28-30;40] In one study, the expected quality of life after intervention was a reason for NTD.[40]

Comparison of NDD with NTD

Differences and similarities concerning factors that were statistically correlated with NDD (i.e. "determinants") and "reasons" given by physicians for NDD were compared to those for NTD. We found similarities in NDD and NTD in the following categories: The patient's condition before an intervention - including age and co morbidity - was the most frequently associated "determinant" and most often mentioned "reason" for both NDD[9-15;15-27] and NTD.[2;28;30-43;45-53] Furthermore, the expected quality of life after the intervention was a "reason" for both NDD[15;26;54] and NTD[40] but the statistical association between the expected quality of life after the intervention was investigated in neither NDD nor in NTD articles. Several physician related characteristics were statistically associated with NDD (e.g. training, age of the physician),[11;20;27;43] and NTD[40;43] though it was not mentioned as reason in any of the analyzed articles. "Determinants" considering care institution (e.g. the presence of physician extenders) were found in NDD articles[19;23;24] as well as in NTD articles.[41;49] In neither NDD nor NTD papers, the patient's ethnicity and gender were given "reasons" for decision-making by physicians. In contrast, these characteristics were statistically correlated with both NDD and NTD in several studies.[17;19;23-25;66;46;49;52;53] Given "reasons" for both NDD and NTD were the patient's preference[28-32;35;38;40] and the proportionality of intervention.[15;20;26;28-32;35;36;38;40;41]

Concerning differences in related "determinants" of NDD compared to NTD, the presence of a 'no-resuscitate order' was associated with NDD in two articles,[23;24] as opposed to none of the NTD articles. Furthermore, though the proportionality of an intervention was a given "reason" for both NDD and NTD, it was only statistically correlated with NTD[30;34;38-41;48] and not with NDD. "Reasons" considering care institution related characteristics were given in one NDD article[26] and in none of the NTD articles.

DISCUSSION

This is the first systematic review on 'non diagnosis decisions'. We summarized and compared the literature on differences in non diagnosis decision making and non treatment decisions in elderly patients. Despite our extensive search, only four articles describing NDD in older patients suspected of having a cardiovascular disease were found,[14-17] which suggests that there is little attention for NDD as such in elderly patients.

Several similarities in decisions to withhold interventions in general (both NDD and NTD) were found. The condition of the patient before an intervention (old age and comorbidity),[15;26-28;30-32;35;36;38;40-42;51] female gender and non-white race were - though gender and race were mentioned as reason in none of the studies - statistically associated with both types of decisions.[17;19;23-25;36;46;49;52] Furthermore, the proportionality of an intervention was a mentioned reason for NDD as well as NTD in the majority of papers.[15;20;26;28-32;35;36;38;40;41] Besides similarities, we found differences between NDD and NTD. First, though it was a given reason in both NDD and NTD papers, the proportionality of an intervention was only statistically associated with decisions to withhold interventions in NTD papers[30;34;38-41;48] but not in NDD papers. Second, physician and care institution related characteristics[11;20;27;43] were more frequently associated with NDD[19;23;24] than with NTD.[41;49] Furthermore, advance care planning was associated with NDD,[19;20;23;24]but not with NTD.

Strengths and limitations

Some limitations have to be acknowledged. First, as only four articles describing NDD in elderly patients suspected of having a cardiovascular disease were found,[14-17] we decided to broaden the domain of the NDD papers to elderly patients suspected of any disease. This resulted in a notable heterogeneity and broader domain for NDD papers as compared to NTD papers. This was done because we assume that the physicians' considerations in the diagnostic process will be comparable within several diseases and will depend mostly on the features of the diagnostic procedure. Second, some of the included studies investigated the influence of only a few and easy measurable variables - such as age and gender - on decision making processes, while more difficult to measure variables might be underrepresented which may have biased the results that were found. Furthermore, most of the included studies had a cross sectional and observational design, and some studies only investigated univariable associations between "determinants" and decisions to withhold interventions (NDD or NTD). This means that we could not draw conclusions about the causality of the associations that were found. Yet, in a lot of studies that adjusted for confounding, the presented associations were still found. For example, after adjustment for co-morbidity or functional status, higher age still turned out to be associated with NDD and NTD.[2;11;12;18;31;39;48;52] Nevertheless, this does not exclude the possibility of residual confounding. However, these methodological issues may affect both the papers on NDD and the papers on NTD, and are therefore not likely to change our inferences from in the comparison between NTD and NDD.

Third, we found a substantial additional number of relevant articles by screening of reference lists of included articles. The original search did not contain these articles as a result of the absence of any synonym for the word “elderly” in titles and/or abstracts though a subgroup analysis in patients aged 65 years and over was performed. Hence, there is a possibility that more relevant articles were missed. However, we performed a very extensive and broad search which contained many synonyms for NDD and for NTD, as well as a validated search query including synonyms for “elderly”[7] yielding numerous of articles. Therefore, we believe this systematic review represents virtually all of the current literature concerning NDD in elderly patients, and NTD in older patients with cardiovascular diseases.

Implications

In this systematic review we found that - though there were several differences - there is a lot of overlap in NDD and NTD in the literature.

However, in clinical practice NDD tends to go with more uncertainties, a different (often earlier) moment in the patients’ illness course and possibly a different (more involved) role of the patient than in NTD. When a physician decides to refrain from diagnostic procedures - thus makes a non diagnosis decision - he/she will use all the available clinical information to asses the probability of the particular diagnosis. Seemingly, the physician in case 1 (Box) considered that the probability and moreover the possible consequences of deep venous thrombosis were that high that it would outweigh the (bleeding)risks of the treatment, though it was possible that the patient would not have thrombosis at all. In case 2 the non-diagnosis decision also implied a non-treatment decision; no physician will treat a patient as having a colon carcinoma when he/she is not confident about the presence of it. Yet, the prognosis of this patient is very uncertain. Probably the patient has colon carcinoma. In that case, the patient will lack treatment probably implying a shortened life-expectancy due to the NDD. On the other hand, when the patient does not have colon carcinoma her life expectancy will not be affected. Thus, whereas the uncertainty which goes with an eventual treatment (i.e. chance of curing as a consequence of the treatment versus the chance of complications due to the treatment) has a role in both NTD and NDD, the uncertainty about the actual presence or absence of a certain disease only applies in NDD.

To support physicians in their clinical ethical decisions concerning initiating versus refraining from (curative) treatment, standardized ethical decision algorithms have been proposed. Van der Steen et al developed a ‘Checklist of considerations’ which was specifically designed for treatment decision making in demented elderly patients with pneumonia.[55] Also, more global theoretical frameworks standardizing medical decision making processes have been developed.[56] The principles of such guidelines can provide underpinning in difficult decision making processes (both NDD and NTD) in older or mentally incompetent patients.

Conclusion

This systematic review yielded a small amount off NDD papers. On theoretical grounds we assume that NDD are clinically different than NTD but at present we are unable to confirm or to reject our hypothesis that NDD can be seen as a separate entity distinct from NTD based on the literature. Further research focusing on NDD and on the differences between NDD and NTD is needed to position the entity of NDD as distinct from NTD.

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APPENDIX 1

Search syntax

Search Query	Database	Date	Result
((diagno* [Title/Abstract]) AND (decision*[Title/Abstract] OR discussion*[Title/Abstract] OR dilemma*[Title/Abstract OR (withdrawing [Title/Abstract] OR withholding[Title/Abstract]) OR ("under reporting"[Title/Abstract] OR "under reported"[Title/Abstract] OR "under diagnose"[Title/Abstract] OR "under diagnosed"[Title/Abstract] OR "under diagnoses" [Title/Abstract] OR "under diagnosing"[Title/Abstract] OR "under diagnosis"[Title/Abstract] OR "under diagnostic"[Title/Abstract]) OR underreport*[Title/Abstract] OR underdiagno*[Title/Abstract] OR "decision making process" [Title/Abstract] AND (elderly[tiab] OR community-dwelling[tiab] OR geriatric[tiab] OR "mini-mental state"[tiab] OR alzheimer[tiab] OR alzheimer's[tiab] OR alzheimers[tiab] OR mmse[tiab] OR caregivers[tiab] OR falls[tiab] OR Adl[tiab] OR Frailty[tiab] OR Gds[tiab] OR Ageing[tiab] OR "hip fractures"[tiab] OR elders[tiab] OR Frail[tiab] OR Mci[tiab] OR Demented[tiab] OR Psychogeriatrics[tiab] OR "cognitive impairment"[tiab] OR "postmenopausal women"[tiab] OR comorbidities[tiab] OR dementia[tiab] OR aging[tiab] OR older[tiab] OR "daily living"[tiab] OR "cognitive decline"[tiab] OR "cognitive impairment"[tiab] OR residents[tiab] OR "cognitive functioning"[tiab] OR "old people"[tiab] OR nursing homes[mh] OR Geriatric assessment[mh] OR aging[mh] OR frail elderly[mh] OR Alzheimer disease[mh] OR homes for the aged[mh] OR cognition disorders[mh] OR dementia[mh] OR Activities of daily living[mh] OR aged, 80 and over[mh])	MEDLINE	2011/05/24	5226
	Embase*	2011/05/24	66660
	Cochrane*	2011/05/24	3789

* The displayed search query represents the search performed in MEDLINE. The same strategy was performed in Embase and Cochranedatabases, with adapted brackets and search-denotations for these databases.

APPENDIX 2

Table 1 Characteristics of included studies

Study	Design	Setting	Country*	Participants (n)	Participants age (years)†‡	Male (%)†	Analyses	Analyses adjusted for
NON-DIAGNOSIS STUDIES								
Cancer								
Litvak 2006 [9]	R D	H	US	Ph 0; Pt 354	38% 70 – 74 Y ; 33% 75 – 79 Y; 29% ≥ 80 Y	0	U	-
Truong 2002 [10]	R D	H	CA	Ph 0 ; Pt 8,038	35% 64-75 Y; 19% ≥ 75 Y	0	U	-
Edge 2002 [11]	R Ipt Iph Ch	H	US	Ph 158; Pt 464	14% 65-69Y; 37% 70-74Y; 42% 75-79Y; 20% ≥ 80Y	0	M	age, stage, education, functional status, region, year of surgery
Bennett 1991 [12]	R Ch	H	US	Ph 0; Pt 242	Mean 70 Y ± 9.1	100	M	symptoms, stage, co morbidity index, hospital
Chu 1987 [13]	R Ch	H	US	Ph 0; Pt 1,680	25% 65-74 Y; 21% ≥ 75 Y	100	U	-
Cardiovascular diseases								
Barrios 2010 [14]	Cr	H	ES	Ph 0; Pt 1,038	Mean 65 Y ± 10.7	71	U	-
Harries 2007 [15]	J	H	UK	Ph 85; Pt 72	Mean 39 Y; mean 72 Y	62; na	U	-
Fairhead 2006[16]	Cr	H	UK	Ph 0; Pt 639	na	na	U	-
Dudley 2002[17]	R Ch	H	UK	Ph 0; Pt 1,790	22% 65-74 Y; 10% 75-79 Y; 21% ≥ 80 Y	51	U	-
Dementia								
Baller 2010 [18]	Cr	N	NL	Ph 0; NHr 776	Mean 84 Y ± 7.8	26	M	ADL-dependency
Mitchell 2007 [19]	Cr	N	US	Ph 0; NHr 91,521	11% 65 – 74 Y; 37% 75 – 84 Y; 43% 85 - 94 Y; 16% ≥ 95 Y	na	M	Patient-, facility- and regional characteristics
Cohen-Mansfield 2006 [20]	R D	N	US	Ph 6; NP1; NHr 52	Na; na; Mean 89 Y, range 63-102Y	100; 0; 27	U	-
Lamberg 2005 [21]	R D	N	US	Ph 0; NHr 240	Median 92 .75 Y	24.2	M	Factors significantly associated with DNH orders inbivariate analyses (P< 0.10)
Burton 2001 [22]	P C	N	US	Ph 0; NHr 2,153	Demented mean 83 ± 7.3, no dementia mean 80 ± 7.51	24-33	M	case mix, age, sex, education, race, marital status, number of comorbid diseases, ADL score

Elderly patients without specified disease								
Pedersen 2008 [26]	Iph	H	NO	Ph 20; Nurses 25; Pt 0	Range 32 – 64Y; Range 26-59Y; -	75; 82; -	U	-
Hurst 2006 [27]	Iph	H+G	NO, CH, It, UK	Ph 656; Pt 0	Mean 51, range 28-82 Y; -	85	M	personal attitudes toward rationing as well as perceptions of rationing at the system-wide level
Mor 2005 [23]	R D	N	US	Ph 0; NHr 15,640	Median 82 – 87 Y	74	M	NHr- and facility characteristics, presence of a DNH- or DNR order
Intrator 1999 [24]	R D	N	US	Ph 0; NHr 2,080	Mean 81 Y	24	M	NHr demographics, presence of a DNH order or DNR-order, type of payer.
Fried 1997 [25]	Ct	N	US	Ph 0; Pt 3,782	Mean 83 Y ± 7.3	25	U	-
NON TREATMENT STUDIES								
Aortic valve stenosis								
Faggiano 2011 [28]	P Ch	H	IT	Ph 0; Pt 240	Mean 78.5 Y ± 8.9	40	U	-
Geldorp 2009 [29]	R Ch	H	NL	Ph 0; Pt 179	AVR, mean 67.9 Y ± 12.4; No AVR mean 73.3 Y± 12.3	50	U	-
Bach 2009 [30]	R Ch	H	US	Ph 0; Pt 369	Mean 72.8 Y ± 13.1	62	U	-
Charlson 2006 [31]	R Ch	H	US	Ph 0; Pt 124	Mean 81.5 Y ± 8.3	35	M	gender, comorbidity, baseline functioning
Iung 2005 [2]	R Ch	H	**	Ph 0; Pt 216	AVR mean 79.5 Y ± 3.7, no AVRmean 81.7 Y ± 4.8	43; 49	M	Co morbidities
Bouma 2001 [33]	J	H	NL	Ph 275; fictional Pt 32	Mean 45.5 ± 7.7; Range 72 – 87 Y	92; 50	U	-
Abdul-Hamid 1999 [32]	R	H	UK	Ph 0; Pt 40	75-84 Y 60%; ≥ 85 Y 40%	30	U	-

Y- years ; na- not available; DNH order- Do not hospitalize order; DNR- Do not resuscitate order
Design: R- Retrospecive studydesign; Cr- Crossectonal; P- Prospective study; D- Database review; Ch- Chartstudy; Ct- Cohorstudy; J- Judgement analysis in electronical (fictional) patients; Iph- interview phycician
Setting: H- Hospital(s); N- nursing home(s); G- Primary care/ General practiotioner. Analysis:; U- Univariable/ Bivariate; M- Multivariable. Participants: Ph- Physicians; Pt- Patients; NHr- Nursinghome residents (characteristics were presented for resp Ph, nurse, Pt/NHr if the study had >1 studygroup). *Conform the official short names in English as stated in the ISO 3166-1-alpha-2 code elements.(Ref: http://www.iso.org/iso/country_codes/iso_3166_code_lists/country_names_and_code_elements.htm), ** - ≥ 10 participating European countries; ‡ Only data of the eldest subgroups (age ≥ 65 years) were displayed; † In case of studypopulation of physicians, nurse(practiotioner)s and/or patients/ nursinghomeresidents; age and percentage of males were given for these respectively groups.

Table 1 (continued) Characteristics of included studies

Study	Design	Setting	Country*	Participants (n)	Participants age (years)†‡	Male (%)†	Analyses	Analyses adjusted for
Atrial fibrillation								
Abdel- Latif 2005 [34]	R Ch	N	US	Ph 0; Pt 117	Mean 84.6 ± 8.0	29	M	Prior stroke and prior gastrointestinal bleeding
Lew 2002 [35]	P	H	SG	Ph 0; Pt 56	Mean 83.3 ± 6.8	39	U	-
Sudlow 1998 [36]	C	G	UK	Ph 0; Pt 207	23% 65-74 Y; 77% ≥75 Y	60	U	-
Lip 1997 [37]	Cr Ch	G	UK	Ph 0; Pt 111	Mean 76.6 Y ± 9.1	38	U	-
Gurwitz 1997 [39]	R Ch	N	US + CA	Ph 0; Pt 413	9.0 % < 75 Y; 24.9% 75-84 Y; 66.1% ≥ 85 Y	34	M	age ≥ 85, history of stroke, dementia
Monette 1997 [41]	J	N	CA	Ph 182; fictional Pt 2	Na; 80Y and 94 Y	na	U	-
Antani 1996 [38]	Cr Ch	G	US	Ph 0; Pt 189	Mean 76 Y	42	M	status (in- or outpatient), appropriat-ness of warfarin therapy (determined by expertpanel)
Lip 1996 [42]	J	H	UK	Ph 214; Pt 0	Na	na	U	-
Beyt 1996 [43]	J	G	USA	Ph 25; Pt 0	Na	81	M	physicians' opinions and experience
McCrory 1995 [40]	J	G+H	US	Ph 450; Pt 0	Na	na	U	-
Myocardial Infarction (MI)								
Chandra 1997 [50]	R Ch	G	USA	Ph 0; Pt 3,824	Thromolysis mean 60.8 Y ; No thrombolysis mean 70.7 Y	60; 70	M	gender, medical history, duration of prehospital delay, survival status, acute MI characteristics
Krumholz 1997 [51]	R Ch	H	USA	Ph 0; Pt 753	47% 65-74 Y; 38% 75-84; 15% ≥ 85	54	M	demographic, clinical and electro-graphic variables
Woods 1998 [45]	R Ch	H	**	Ph 0; Pt 4,035	65-74 Y 28%; > 74 Y 33%	67%	M	sex, age and centre.
Stone 1996 [46]	P Ch	H	USA	Ph 0; Pt 3,318	Mean 63.8 Y	50.6	M	Interaction terms age, race, sex-
Gurwitz 1996 [47]	R Ch	H	USA	Ph 0; Pt 350,755	28% 65-74; 20.3% 75-84; 6.4% ≥ 85	62; 50; 36	M	gender, diagnosis by initial electrocar-diogram, Infarct description, time to hospital presentation, period of study enrollment

Oka 1996 [52]	P Ch	H	USA	Ph 0; Pt 3,016	Male 60 Y ± 10.0; Female 64 Y ± 8	67	M	stepwise including al variables with p-value of ≤ 0.01
McLaughlin 1996 [49]	R Ch	H	USA	Ph 0; Pt 2,490	40% < 65; 27% 65-74Y; 32% > 74Y	62	M	patient- and hospital characteristics
Ketley 1995 [48]	R Ch	H	UK	Ph 0;Pt 420	Mean 68 Y	67	U	adjustment via selective exclusion of patients from analysis for: history of stroke or peptic ulcer
Hannaford 1994 [53]	P Ch	H	UK	Ph 0; Pt 880	43 % < 65 Y; 33% 65 – 74; 21% 75 – 84; 4% ≥ 85	67	M	age, sex, smoking habits, interval between onset and admission.

Y- years ; na- not available; DNH order- Do not hospitalize order; DNR- Do not resuscitate order
Design: R- Retrospecive studydesign; Cr- Crossectonal; P- Prospective study; D- Database review; Ch- Chartstudy; Ct- Cohorstudy; J- Judgement analysis in electronical (fictional) patients; Iph- interview phycician
Setting: H- Hospital(s); N- nursing home(s); G- Primary care/ General practiotioner. Analysis:; U- Univariable/ Bivariate; M- Multivariable. Participants: Ph- Physicians; Pt- Patients; NHr- Nursinghome residents (characteristics were presented for resp Ph, nurse, Pt/NHr if the study had >1 studygroup). *Conform the official short names in English as stated in the ISO 3166-1-alpha-2 code elements.(Ref: http://www.iso.org/iso/country_codes/iso_3166_code_lists/country_names_and_code_elements.htm), ** - ≥ 10 participating European countries; ‡ Only data of the eldest subgroups (age ≥ 65 years) were displayed; † In case of studypopulation of physicians, nurse(practiotioner)s and/or patients/ nursinghomeresidents; age and percentage of males were given for these respectively groups.

APPENDIX 2 (CONTINUED)

Table 2 "Reasons" given for 'non-diagnosis decisions' and "determinants" associated with 'non-diagnosis decisions' in elderly patients - Reconstruction of given "reasons" and associated "determinants" which contributed to a decision not to perform diagnostic tests. "Reasons" and "determinants" where divided into predefined categories. Only "determinants" significant related (at a 5% level, if applicable after correction for potential confounders) are displayed; given odds ratio's represent the odds for receiving (no) diagnostic procedure in wherein patients with the characteristic concerned were compared to patients without this characteristic unless stated otherwise.

Study	Subject	"Reasons" given for NDD*	"Determinants" associated with NDD*
		1. Patients'preferences 2. Condition before intervention 3. Expected quality of life after intervention 4. Proportionality of an intervention 5. Physician related characteristics 6. Care institution related characteristics 7. Non-medical patient bound characteristics 8. The presence of a 'do not resuscitate order' or a 'do not hospitalize order' 9. Other	
Cancer			
Litvak 2006 [9]	Relation between patients' age and tumor characteristics with chosen method for diagnosing, and completeness of staging in patients with breast cancer.	No "reasons" studied	2. Complete staging was more commonly omitted in women in the eldest age-group
Truong 2002 [10]	Age-related variations in the use of axillary lymph node dissection in patients with T1-2 breast cancer.	No "reasons" studied	2. Age ≥ 75Y
Edge 2002 [11]	Association of patient-, clinical- and surgeon characteristics with the use of axillary lymph node dissection after breast conserving surgery.	No "reasons" studied	1. Preference of no treatment after surgery (OR 0.49 [95% CI 0.24 to 0.99] for receiving axillary lymph node dissection) 2. Older age (OR 0.11[95% CI 0.05 to 0.27] for receiving axillary lymph node dissection, patients aged > 80 Y compared to patients aged 65-69 Y); Lower physical function (OR 0.63 [0.25 to 0.68] for receiving axillary lymph node dissection, women in the lowest quartile of physical functioning compared to women in the highest quartile) 5. Subspecialty training of surgeon in oncology (OR 0.41 [95% CI 0.25 to 0.68] for receiving axillary lymph node dissection)
Bennett 1991 [12]	The influence of age and co-morbidity on diagnostic management strategies (invasive versus noninvasive) in patients with prostate cancer.	No "reasons" studied	2. Age ≥ 75 Y (treatment coefficient 12.20(p 0.03) for patients 50-64 compared to patients a age ≥ 75 Y)

Chu1987 [13]	Effect of age on the diagnostic process in women with breast cancer.	No "reasons" studied	2. Fewer mammograms, biopsies, lymph node dissection, medical oncologist consultations and hospital admissions in older patients
Cardiovascular diseases			
Barrios 2010 [14]	Differences according to age in the diagnostic management of patients with chronic heart diseases	No "reasons" studied	2. patients >65 Y underwent less exercise tests and coronary angiographies
Harries 2007 [15]	Examines the influence of electronic patients' age on frequency of performed diagnostic tests in patients with angina pectoris as ordered by physicians working in primary care, care for the older patients or cardiology wards.	1. Patient's wishes 2. Old age of patients, frailty, co morbidity, quality of life 3. Duration of potential benefit 4. Nature of potential treatment, risk of complications	2. Older age 5. Older physicians were less likely to perform blood test, angiograms or exercise tolerance tests in older patients
Fairhead 2006 [16]	Identifies under investigation in older patients with a transient ischemic attack (TIA)	No "reasons" studied	2. Age ≥ 80 Y (RR 0.36 [95% CI 0.26 to 0.46] for carotid imaging at age > 80 Y compared to participants <80 Y)
Dudley 2002 [17]	The effect of age and gender on use of cardiovascular investigations (exercise tolerance tests, echocardiogram).	No "reasons" studied	2. Age ≥ 75 Y 7. Female gender
Dementia			
Baller 2010 [18]	The influence of dementia on the prevalence of diagnosed depressive disorders in patients with mood symptoms.	No "reasons" studied	2. Demented patients with mood-symptoms were less frequently diagnosed with depressive disorders (OR 0.61[95% CI 0.38 to 0.98], demented- compared to non-demented residents)

OR- Odds ratio; RR- Relative risk; Y- Years; NHr- Nursing home resident; QoL- Quality of life; DNR order- 'do not resuscitate order'; fte- fulltime equivalent

Table 2 (continued) "Reasons" given for 'non-diagnosis decisions' and "determinants" associated with 'non-diagnosis decisions' in elderly patients - Reconstruction of given "reasons" and associated "determinants" which contributed to a decision not to perform diagnostic tests. "Reasons" and "determinants" where divided into predefined categories. Only "determinants" significant related (at a 5% level, if applicable after correction for potential confounders) are displayed; given odds ratio's represent the odds for receiving (no) diagnostic procedure in wherein patients with the characteristic concerned were compared to patients without this characteristic unless stated otherwise.

Study	Subject	"Reasons" given for NDD*	"Determinants" associated with NDD*
Mitchell 2007 [19]	"Determinants" associated with the presence of a do-not-hospitalize order in NHr with advanced dementia aged > 65 years	No "reasons" studied	2.Older patients (OR 1.67 [95% CI 1.44 to 1.91] 85-94 Y compared to 65-74 Y); Total functional dependence (OR 1..42 [95% CI 1.32 to 1.52]) absence of diabetes mellitus (diabetes OR 0.86 [0.79 to 0.95]) 6. Physician extenders employed (no hospitalization order OR 1..28 [95% CI 1.13 to 1.44]); more staffing care hours per resident (OR 1.5 [95% CI 1.18 to 1.91] ≥ 4.44 hours versus <2.75 hours); NH providing less subacute care (OR 1.30 [95% CI 1.09-1.53]); NH delivering more clinically complex care (OR 1.15 [1.03 to 1.29]); NH with few blacks residents (OR 2.04 [95% CI 1.54 to 2.69] percentage ≤2.4% black residents, reference group > 30.0% black residents), NH that is not part of a chain (OR 1.30 [95% CI 1.16 to 1.46]), NH with relatively more resource possibilities (OR 1.28 [95% CI 1.09 to 1.52]) 7. Nonwhite race (no hospitalization order OR black versus white race 0.40 [95% CI 0.34 to 0.46]); living in an urban location (OR 1.79[95% CI 1.54 to 2.07]), living in a special care dementia unit (OR 1.17 [95% CI 1.03 to 1.33]) 8. Do not hospitalize order OR 1.20 [95% CI 1.09 to 1.31])
Cohen- Mansfield 2006 [20]	"Determinants" influencing decision-making in hospitalization of mentally impaired nursing home residents with an acute health status change.	3. Negative effect on quality of life 4. High costs	2. Comorbidity, life expectancy < 3 months 5. Identity of the physician 8. Do not hospitalize order
Lamberg 2005 [21]	"Determinants" associated with orders not to hospitalize NHr with advanced dementia who are dying.	No "reasons" studied	2. Age > 92 Y (no hospitalization order OR 2.78 [95% CI 1.29 to 5.96] compared to age < 92), eating problems (OR 4.17 [95% CI 1.52 to 11.47]) 7. Length of stay in nursing home ≥ 2 Y (no hospitalization order OR 2.34 [95% CI 1.11 to 4.94]), having a surrogate decision-maker other than a patient's child (OR 4.39 [95% CI 1.52 to 12.66])
Burton 2001 [22]	Compares recorded medical service use (physician visits, hospitalization, emergency department visits) following detection of fever or infection between NHr with dementia and those without dementia.	No "reasons" studied	2. Dementia (medical care utilization RR 0.8 [95% CI 0.7 to 0.9])

Elderly patients without specified disease			
Pedersen 2008 [26]	Explores what kind of criteria, values and considerations are important in the diagnostic decision making process in healthcare services for older patients	1. Patients' wishes 2. Very old age of patients, mental disabilities, general functional disabilities, terminal phase of life, contra-indications, prognosis 3. Potential for rehabilitation, effect of potential treatment 4. Mild symptoms, diagnosis and seriousness of the condition, expected discomfort due to transport, long travel distances to hospital, expected discomfort due to hospitalization, negative cost-effectiveness 6. Lack of adequate care and adjustments for patients in hospital 7. Patients' coping	No "determinants" studied
Hurst 2006 [27]	Examines the frequency, criteria and strategies used in bedside rationing.	2. Age > 85Y, low QoL 4. Small expected benefit, low chances of success	5. Perceived pressure to ration (rationing OR 2.14 [95% CI 1.52 to 3.01]), perceived scarcity (OR 1.11 [95% CI 1.06 to 1.16]) agreement with rationing (OR 1.13 [1.05 to 1.23]), physicians from Norway, Italy and Switzerland (OR respectively 2.61[95% CI 1.34 to 5.06]; 3.62 [95% CI 1.65 to 7.91] and 5.1 [95% CI 2.28 to 11.68] as compared to physicians in the UK).
Mor 2005 [23]	Association between race, a nursing home's racial mix, and end of life hospitalization	No "reasons" studied	2. Cancer (hospitalization OR 0.68 [95% CI 0.62 to .075]), poorer cognitive status (OR 0.74 [95% CI 0.70 to 0.80]) 6. Presence of a physician extender (hospitalization OR 0.69 [95% CI 0.59 to 0.81]) 7. Female gender (hospitalization OR 0.86 [95% CI 0.81 to 0.93]) 8 DNR order (hospitalization OR 0.49 [95% CI 0.29 to 0.55])
Intrator 1999 [24]	Investigates the effect of selected resident and facility characteristics on hospitalization.	No "reasons" studied	2. Cognitive impairment (OR 0.69 [95% CI 0.49 to 0.98]) 6. NH with physician extenders employed (OR 0.59 [95% CI 0.39 to 0.97]) 7. Female gender (OR 0.67 [95% CI 0.47 to 0.89]) 8. DNR order (OR 0.65 [95% CI 0.47 to 0.89])
Fried 1997 [25]	Relationship between characteristics of older, long-term stay nursing home residents and hospitalization rate.	No "reasons" studied	2. Older age, moderate to severe cognitive impairment, dementia 7. Female gender

OR- Odds ratio; RR- Relative risk; Y- Years; NHr- Nursing home resident; QoL- Quality of life; DNR order- 'do not resuscitate order'; fte- fulltime equivalent

APPENDIX 2 (CONTINUED)

Table 3 "Reasons" given for 'non-treatment decisions' and "determinants" associated with 'non-treatment decisions' in elderly patients - Reconstruction of given "reasons" and associated "determinants" which contributed to a decision to withhold treatment. "reasons" and "determinants" where divided into predefined categories. Only "determinants" significant related (at a 5% level, if applicable after correction for potential confounders) are displayed; given odds ratio's represent the odds for receiving (no) treatment in wherein patients with the characteristic concerned were compared to patients without this characteristic unless stated otherwise.

Study	Subject	"Reasons" given for NTD*	"Determinants" associated with NTD*
		1. Patients'preferences 2. Condition before intervention 3. Expected quality of life after intervention 4. Proportionality of an intervention 5. Physician related characteristics 6. Care institution related characteristics 7. Non-medical patient bound characteristics 8. The presence of a 'do not resuscitate order' or a 'do not hospitalize order' 9. Other	
Aortic valve stenosis			
Faggiano 2011 [28]	"Determinants" associated with treatment choices (conventional versus surgical) in patients with symptomatic aortic valve stenosis	1. Valve replacement refusal 2. Active cancer 4. Non critical aorta valve stenosis; Mortality considered too high	2.Cerebrovascular disease; Carotid stenosis
Geldorp 2009 [29]	"Reasons" for treatment choices in patients with symptomatic severe aortic valve stenosis. (conservative treatment versus aorta valve replacement (AVR))	1. Patients' preference 4. Operation risk considered too high; Mild symptoms; Non-severe stenosis 8. Decisions not final yet; reasons unclear	No "determinants" studied
Bach 2009 [30]	"Reasons" and derterminants (symptoms and calculated operative risk) for treatment choices in patients with symptomatic severe aortic valve stenosis. (conservative treatment versus AVR)	1. Refusal of AVR 2. Comorbidities; Symptoms not related to aortic valve stenosis; Subvalvular stenosis 4. Perceived prohibitive operative risk	2. Older age 4. Operation risk considered too high
Charlson 2006 [31]	"Reasons" and "determinants" associated with physicians' decision-making not to offer an AVR to older patients with severe symptomatic aortic valve stenosis.	1. Preferred non-surgical treatment 2. Comorbidity; Older age 4. Clinically stable stenosis 9. Reason unclear	2. Age ≥ 80 Y (treatment OR 0.19[95% CI 0.07 to 0.51], patients aged >80 years versus patients aged 60-79 years)
Iung 2005 [2]	"Determinants" associated with decisions not to operate in older patients with severe aortic valve stenosis.	No "reasons" studied	2. Older age (non-treatment OR 3.60 [95% CI 1.47 to 8.82] Age ≥85 versus 75-80 years); LVEF ≤30%, (OR 7.09 [95% CI 2.42 to 20.82] LVEF ≤30% versus > 50%); Neurological dysfunction (OR 3.82 [95% CI 1.23 to 12.27])

Bouma 2001 [33]	Relation of age, cardiac signs and symptoms and comorbidity to treatment decisions (conservative versus AVR) in patients with aortic valve stenosis.	No “reasons” studied	2. Older age; Comorbidity; Less severe aortic valve stenosis; Lower LVEF; Smaller aortic valve area
Abdul-Hamid 1999 [32]	“Reasons” for non-referral policy forspecialistic assessment intended to workup for AVR in older people with symptomatic aortic stenosis.	1. Refusal of surgery 2. Comorbidity; Frailty; Symptoms considered not related to aortic valve stenosis 4. Non severe symptoms	No “determinants” studied
Atrial fibrillation			
Abdel- Latif 2005 [34]	Characteristic of NHr with atrial fibrillation determining no- treatment policy with oral anticoagulation	No “reasons” studied	2. History of gastrointestinal bleeding (non-treatment OR 5.6[95% CI 1.1 t 29.4]) 4. Absence of prior stroke (presence of stroke; non-treatment OR 0.02 [95% CI 0.09 to 0.47])
Lew 2002 [35]	“reasons” for withholding anticoagulation therapy in older patients with atrial fibrillation.	1. Objection of anticoagulation 2. Peptic ulcer disease ; Unsupervised dementia; Unexplained anemia; Terminal illness ; (Intracranial) bleeding; Dyspepsia 4. Risk of falls 9. No “reasons” documented	No “determinants” studied
Sudlow 1998 [36]	“Reasons” and “determinants” associated with withholding anticoagulants in patients with atrial fibrillation.	2. Uncontrolled hypertension; Non compliance with medication 4. Risk of falls	2./7.Females aged ≥ 75 Y
Lip 1997 [37]	“Determinants” associated with withholding anti-coagulants in patients with atrial fibrillation.	No “reasons” studied	2. Older age
Gurwitz 1997 [47]	Clinical and functional characteristics of institu-tionalized older patients associated with the use of warfarin in patients with atrial fibrillation.	No “reasons” studied	2. Older age(treatment OR 0.58 [95% CI 0.38 to 0.89]patients aged ,75 y versus patients aged ≥85 yr);Dementia (OR 0.59 [95% CI 0.38 to 0.90]). 4. No history of stroke (history of stroke treatment OR 1.87 [95% CI 1.20 to 2.91])
Monette 1997 [41]	Attitudes of physicians regarding use of warfarin in patients with atrial fibrillation in long term care facilities	2. History of stroke; Moderate to severe cognitive deficits; Older age; Poor functional status; Poor quality of life 4. Risk of falls; Poor prognosis	4. Estimated higher intracranial bleeding /stroke risk (non-treat-ment OR 1.9 [95% CI 1..5 to 2.4] for each unit of higher estimated risk) 5. Physician no geriatrician (geriatrician OR 1.27 [1.03 to 1.55])

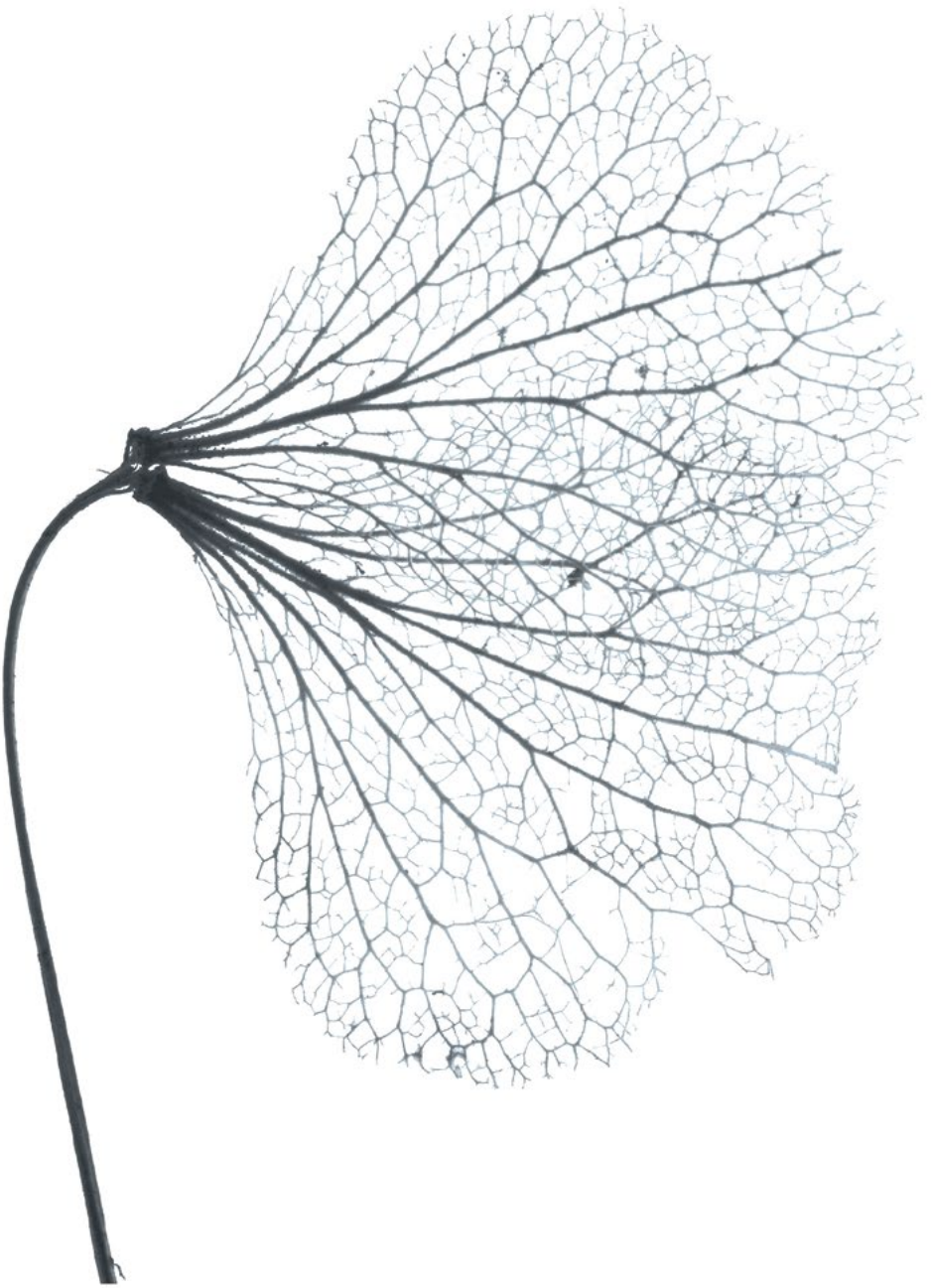
OR- Odds ratio; LVEF- left ventricular ejection fraction; NHr- Nursing home residen

Table 3 (continued) "Reasons" given for 'non-treatment decisions' and "determinants" associated with 'non-treatment decisions' in elderly patients - Reconstruction of given "reasons" and associated "determinants" which contributed to a decision to withhold treatment. "reasons" and "determinants" where divided into predefined categories. Only "determinants" significant related (at a 5% level, if applicable after correction for potential confounders) are displayed; given odds ratio's represent the odds for receiving (no) treatment in wherein patients with the characteristic concerned were compared to patients without this characteristic unless stated otherwise.

Study	Subject	"Reasons" given for NTD*	"Determinants" associated with NTD*
Antani 1996 [38]	The frequency in which warfarin was prescribed to patients in according to patient and physicians' characteristics. "Reasons" for not prescribing warfarin were recorded.	1. Refusal of anticoagulation 2. Old age; History of bleeding; Intermittent atrial fibrillation 4. Risk of falls 9. Intention to consider warfarin prescription later	2. Age ≥ 75 Y (OR 0.25 [95% CI 0.10 to 0.65)
Lip 1996 [42]	Variations in the management (whether or not to anticoagulate) of patients with newly diagnosed atrial fibrillation.	2. Clinical history of heart failure, valve disease or stroke; Contra-indications	No "determinants" studied
Beyt 1996 [43]	Determines opinions of physicians toward warfarin use in patients with atrial fibrillation, according to patients age, risk of bleeding and -stroke	No "reasons" studied	
McCrory 1995 [40]	Patients' age and physicians' reported likelihood of using anticoagulant therapy or the intensity of anticoagulant therapy for patients with nonvalvular atrial fibrillation.	. Refusal of patient 3. Treatment impairs QOL 4. High costs to patients; Risk of hemorrhage too high; Risk of embolus too low; Inconvenience of blood test monitoring 5. Belief that aspirin is better; Belief that anticoagulant treatment in older patients is more difficult; Doubt effectiveness of anticoagulant therapy	2. Older age
Myocardial infarction			
Chandra 1997 [50]	Age-related differences in the use of thrombolytic therapy in patients with MI.	No "reasons" studied	2. Older age (treatment OR 5.0 [95% CI 3.7 to 6.7], patients aged < 55 Y compared to patients aged ≥75y)
Krumholz 1997 [51]	The effect of age, clinical symptoms and electrocardiographic signs on the use of thromolytic agents in patients hospitalized with acute MI who were eligible for the therapy on presentation.	2. Advanced age ; Absence or resolution of chest pain; History of peptic ulcer or gastrointestinal bleeding , equivocal electrocardiographic criteria 7. Delay in presentation 8. No "reasons" documented	2. Older age (treatment OR 0.92 [95% CI 0.89 to 0.95] for each advancing year); No chest pain at presentation (OR 0.31 [95% CI 0.21 to 0.48]); History of bypass surgery (OR 0.30 [95% CI 0.14-0.65]); confusion 0.34 [95% CI 0.14—0.80]; coma 0.07 [95% CO 0.01 to 0.56]); electrocardiographic characteristics (OR 0.04 [95% CI 0.01 to 0.17] to OR 0.62 [95% CI 041 to 0.98]) 7. Delay in presentation (treatment OR 0.26 [95% CI 0.17 to 0.38] for patients > 6h chest pain versus patients with acute chest pain)

Woods 1998 [45]	"Determinants" influencing the chance for not receiving thrombolytic therapy in patients with acute myocardial infarction (MI) without contraindication	No "reasons" studied	2. Older age (treatment OR 0.27 [95% CI 0.26 to 0.28] for patients aged 75-84Y; OR 0.09 [95% CI 0.08 to 0.10] for patients aged ≥ 85Y 0 with patients aged <55 Y as reference group)
Stone 1996 [46]	influence of sex, rage and age on management (invasive anti-ischemic therapy) of unstable angina pectoris and non-Q-wave MI.	No "reasons" studied	2. Age ≥ 75 Y (undergoing coronary catheterization RR 0.65 [95% CI 0.58 to 0.73]), revascularization therapy RR 0.79 [95% CI 0.69 to 0.92]) 7. Black race and female gender, undergoing coronary catheterization (respectively RR 0.65 [95% CI 0.58 to 0.72] and 0.71 [95%CI 0.65 t 0.78]) and revascularization (respectively RR 0.44 [95% CI 0.37 to 0.52] and 0.66 [95% CI 0.59 to 0.76])
Gurwitz 1996 [47]	age-related differences in the use of thrombolytic therapy in patients with acute MI	No "reasons" studied	2. Older age (treatment OR 0.23 [95% CI 0.22 to 0.24] for patients aged 75-85 Y ; OR 0.08 [95% CI 0.07 to 0.09] for patients aged > 85 Y; reference group patients aged < 55 Y)
Oka 1996 [52]	"Determinants" associated with withholding coronary angiography, revascularization or thrombolytic therapy in patients with MI	No "reasons" studied	2. Older age (with increasing age with 10 years, OR for angiography 0.78 [95% CI 0.71 to 0.85], OR for thrombolytic therapy 0.84 [95% CI 0.74 to 0.95]); Severely diseased patients were less likely to receive for coronary angiography and thrombolysis (respectively OR 0.66 [95% CI 0.61 to 0.72] and OR 0.59 [95% CI 0.48 to 0.72]). 7. Females (treatment OR 1.39 [95% CI 1.12 to 1.22] for angiography in men); Hispanics (OR 0.45 [0.27 to 0.76] for revascularization); Delay time to presentation (OR 0.98 [95% CI 0.98 to 0.99] for trombolytic therapy per 10 minutes delay)
McLaughlin 1996 [49]	The influence of age and gender on pharmacological treatment of patients with MI	No "reasons" studied	2. Older age (treatment OR 0.2 [95% CI 0.1 to 0.4] for receiving trombolysis, OR 0.4 [95% CI 0.3 to 0.6] for receiving Aspirin; OR 0.4 [95% CI 0.2 to 0.8] for receiving β-blockers; OR 0.6 [95% CI 0.5 to 0.8] for receiving lidocaine treatment; for patients aged >74 y versus patients aged < 65 y) 6. Urban no teaching hospital (lidocaine-use OR 0.2[95% CI 0.1 to 0.6]) 7. Female gender (treatment OR 0.7 [95% CI 0.6 to 0.9] for receiving aspirin)
Ketley 1995 [48]	'Determinants" limiting the use of thrombolytic therapy in patients admitted to a hospital with MI.	No "reasons" studied	2. Older age (treatment OR 0.17 [95% CI 0.05 to 0.51]for patients aged > 74Y versus patients aged < 65 Y); Recent trauma or surgery(OR 0.09 [95% CI 0.0-0.64]); ST depression OR 0.22 [9% CI 0.11 to 0.41] or bundle branche block OR 0.18 [95% CI 0.07 to 0.44] compared to patients with ST-elevation on ECG) 4. History of stroke (treatment OR 0.18 [95% CI 0.04-0.53])
Hannaford 1994 [53]	Factors associated with withholding thrombolysis is patients with myocardial infarction.	No "reasons" studied	2. Older age 7. delay in presentation

OR- Odds ratio; LVEF- left ventricular ejection fraction; NHr- Nursing home residen



CHAPTER 8

DECISIONS TO WITHHOLD DIAGNOSTIC INVESTIGATIONS IN NURSING HOME RESIDENTS WITH A CLINICAL SUSPICION OF VENOUS THROMBOEMBOLISM

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ABSTRACT

Background This study aimed to gather insights in physicians' considerations for decisions to either refer for- or to withhold additional diagnostic investigations in nursing home patients with a suspicion of venous thromboembolism.

Methods Our study was nested in an observational study on diagnostic strategies for suspected venous thromboembolism in nursing home patients. Patient characteristics, bleeding-complications and mortality were related to the decision to withhold investigations. For a better understanding of the physicians' decisions, 21 individual face-to-face in-depth interviews were performed and analysed using the grounded theory approach.

Results Referal for additional diagnostic investigations was forgone in 126/322 (39.1%) patients with an indication for diagnostic work-up. 'Blind' anticoagulant treatment was initiated in 95 (75.4%) of these patients. The 3-month mortality rates were higher for patients in whom investigations were withheld than in the referred patients, irrespective of anticoagulant treatment (odds ratio 2.45; 95% confidence interval 1.40 to 4.29) but when adjusted for the probability of being referred (i.e. the propensity score), there was no relation of non-diagnosis decisions to mortality (odds ratio 1.75; 0.98 to 3.11). In their decisions to forgo diagnostic investigations, physicians incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning.

Conclusion Referral for additional diagnostic investigations is withheld in almost 40% of Dutch nursing home patients with suspected venous thromboembolism and an indication for diagnostic work-up. We propose that, given the complexity of these decisions and the uncertainty regarding their indirect effects on patient outcome, more attention should be focused on the decision to either use or withhold additional diagnostic tests.

INTRODUCTION

Both the annual incidence and the mortality rate of venous thromboembolism (VTE, deep vein thrombosis (DVT) or pulmonary embolism(PE)) rise considerably with increasing age.[1,2] Diagnosing VTE is particularly challenging in older patients as symptoms and signs are nonspecific and might be camouflaged by co-morbidity in these patients.[3–6] Moreover, the specificity of D-dimer tests (e.g. the commonly used high sensitive ELISA-assays or latex agglutination assays) decreases with age to only 15% in patients aged 80 years and over.[7,8] As imaging examination is indicated for those with an abnormal D-dimer test or a high probability of VTE obtained by application of a clinical decision rule, many older patients are being referred to a hospital for imaging examination (e.g. compression ultrasonography for DVT or CT pulmonary angiography for PE; procedures not typically available in primary care or in nursing homes). Nevertheless, many of these patients do not have VTE (typically 15 to 20% of older patients who undergo imaging examinations for clinically suspected venous thromboembolism are actually affected).[7,9]

Prior work has shown that frail older patients are vulnerable to distress and complications resulting from transitions to hospital-care.[10–12] Gillick et al found that hospitalisation was associated with psychological and physiological symptoms (e.g. confusion, falling and incontinence) in 40% of hospitalized older patients (> 70 years as compared to 9% in patient < 70 years), irrespective of the medical diagnosis.[13] Yet, the burden and risks of hospital-attendance are of particular concern in these patients. Moreover, contrast enhanced computed tomography of the pulmonary arteries can cause nephropathy.[14] Though additional imaging examinations might prevent the sequelae of a missed diagnosis in a number of patients by directing appropriate treatment decisions, many will be exposed to the potential harms of referral for additional diagnostic work-up. Currently, there is growing concern that VTE might be overdiagnosed and thereby overtreated because of lower thresholds for application of increasingly sensitive imaging tests.[15,16] Yet, little light has been shed on the actual burden and risk of the procedure of diagnostic investigations itself or to physicians' decisions to either refer for- or withhold diagnostic investigations ('non-diagnosis decisions') in older patients with suspected VTE. Therefore, this study aimed to explore physicians' considerations in such decisions.[17,18]

METHODS

A mixed-method study consisting of two parts was performed. In the first part, we quantitatively approached reasons for non-diagnosis decisions and compared the characteristics and patient-outcomes of the referred patients to those of the non-referred patients. Second, for a better understanding of the reasons underlying these decisions, we performed a qualitative study, applying the grounded theory approach and semi-structured in-depth interviews.[19,20]

The quantitative approach

This study was nested in the Venous Thromboembolism in the Elderly-study (VT-elderly study) which aimed to quantify the accuracy of two diagnostic decision rules to diagnose or refute VTE in nursing home patients and community dwelling elderly patients across the Netherlands. The study had an observational and pragmatic design. Between October 2008 and April 2013, consecutive patients with a clinical suspicion of VTE were included by their physician (general practitioners for community dwelling patients, elderly care physicians for patients residing in nursing homes).[21] Patients were not eligible for inclusion if they received anticoagulant treatment (vitamin K antagonists or oral direct thrombin- or factor Xa-inhibitors) at presentation or if they declined providing informed consent. Each patient's medical history, clinical characteristics, signs and symptoms, results on the diagnostic decision rule under study (the Wells score for patients primarily suspected of PE or the Oudega rule for patients primarily suspected of DVT) and on the D-dimer test-result were systematically recorded (Clearview Simplify D-dimer assay®, Inverness Medical Princeton, NJ USA).[22,23] Three months after inclusion it was verified whether the participant was still alive and if thromboembolic or bleeding-complications had occurred. Though referral for imaging examination (that is, compression ultrasonography of the entire proximal deep vein system in case of a suspicion of DVT, or CT-pulmonary angiography of VQ scanning when PE was suspected) was recommended for all patients with a high clinical suspicion of VTE, it was left to the physicians' discretion whether patients were indeed referred. This high clinical suspicion of VTE was based on either an abnormal D-dimer test or on a score >4 points on the Wells-rule for patients primarily suspected of PE; or on a score >3 on the Oudega-rule for patients primarily suspected of DVT.[22,23] The referred patients with confirmed VTE were treated with coumarins and - until a stable INR in the therapeutic range was achieved- with a therapeutic dose of low molecular weight heparin. Patients in whom VTE had been refuted received no anticoagulant treatment. For the non-referred patients with a high clinical suspicion of VTE, it was left to the physicians' discretion whether patients received anticoagulant treatment. Physicians who decided to withhold referral for imaging examination in participants with a high risk of VTE were requested to identify appropriate reasons for this decision. For the current analysis, we included only patients residing in nursing homes with a high clinical suspicion of VTE. Within this group, we tested the differences between patients referred for additional diagnostic testing and non-referred patients, regarding patient characteristics and 3-month bleeding rate and -mortality, according to received treatment. To assess to what extent the differences in the referred and non-referred groups contributed to their outcomes (i.e. potential confounding by indication) we calculated the probability of being referred for further diagnostic investigations based on the patients' characteristics (i.e. propensity score-estimation) and subsequently adjusted for this probability in a multivariable model. We used Statistical Package for Social Sciences (SPSS) version 20 for these analyses.

Ethics statement

This study was judged as exempt from review by the local ethics review board of the University Medical Center Utrecht, the Netherlands (08-124/E) and conducted according to the Federation of Medical Scientific Societies' code of conduct for health research.[24]

The qualitative approach

Participants and data collection

Within the VT-elderly study, we qualitatively focussed on physicians' decisions to forgo referral for diagnostic investigations. By applying the "grounded theory" approach we set out to gain a higher level of understanding on the quality, that is the context wherein- and the perspective from which physicians decided to withhold further diagnostic investigations in nursing home residents with suspected venous thromboembolism. This understanding is "grounded" in a close and systematic analysis from in-depth interviews. The "grounded analysis" is based on three key principles: 1) simultaneous cycles of data collection and analysis (iterative analysis), 2) wherein emerging themes are refined and explored in the next interviews with participants who might have different perspectives (purposeful sampling), and 3) by comparison of issues of interest in the data with other examples for similarities and differences (constant comparison). [20,25]

We purposefully sampled elderly care physicians who included one or more patients for whom it was decided to forgo referral for imaging examination despite a high risk of VTE. To diminish recall bias, only inclusions between January 2011 and May 2012 were selected, as the interviews were held between May and July 2012. Of 26 eligible elderly care physicians, 21 physicians (84%) participated, 4 physicians declined participation and one person was no longer employed as an elderly care physician. The five non-participating physicians (3 females, 4 from rural areas and one from an urban area) had all enrolled one patient for whom they withheld further investigations (2 patients primarily suspected of PE and 3 of DVT) and provided the following reasons for their decisions: 'alternative diagnosis more likely' and 'advanced dementia'. These reasons and characteristic were comparable to those of the 21 participating physicians. The participating physicians were on average 52 years old and had an average of 20 years of experience as board certified elderly care physician; a medical specialty in the Netherlands in nursing home and primary care geriatric medicine.[21] None of the participants had affiliations with hospitals or with universities. The majority of the participants was female and most physicians provided care to patients with psychogeriatric disorders as well as to patients with somatic disabilities (table 1). The physicians underwent individual in-depth interviews, approximately 45 minutes in length at their workplaces, at a time chosen by the physicians. All physicians gave oral consent prior to the interview. To increase recall and to find a joint starting point, the interviewers (MK or HJS) introduced each interview with a résumé of the clinical situation of the patient for whom the decision to withhold additional diagnostic testing was made. Afterwards, the physicians were asked to describe the situation of the patient and to discuss their decision in detail. A topic list based on discussion

Table 1 Characteristics of the participants in the qualitative study

Characteristic (n=21)	n
Participants in current study (total included, %)	21 (100)
Age (median, range)	52 (37 to 61)
Work experience as elderly care physician (years, median, range)	20 (4 to 27)
Female (%)	15 (71.4)
Patient population under physician's care*	
Patients with psychogeriatric disorders (%)	20 (95.2)
Patients with somatic disorders (%)	17 (80.1)
Rehabilitation patients (%)	4 (19.0)
Palliative care patients (%)	3 (14.3)
Patients with psychiatric disorders or non-congenital brain injury(%)	2 (9.5)

* 17 physicians had more than one type of patients' populations

and a systematic review of the research group was used at the end of each interview to ensure that all topics were discussed.[17] The interviews were conducted and analysed through constant comparison; after each interview the topic list was reviewed and modified according to the topics emerging from the interviews. After 13 interviews were performed, saturation was reached for the major concepts; this was confirmed with eight subsequent interviews. Consistency among the interviewers was encouraged by giving each other verbal feedback after each interview.

Data analysis

Data collection alternated with data analysis. Interviews were audio-recorded, professionally transcribed verbatim, anonymized and checked for accuracy. Data was analysed according to the steps described in the QUAGOL.[26] Narrative reports were written after each interview and memos were formulated during the analytical phase to enhance a consistent analysis process. After reading and rereading the data, two researchers marked each meaningful text segment separately and developed preliminary codes based on the first six interviews (open coding, MK and HJS).[27] The subsequent seven interviews were also separately coded by the two researchers. During joint meetings, they constantly compared their analysis to identify common themes and worked towards consensus in interpretation of the data (researcher triangulation).[20] The subsequent eight interviews were similarly coded by one investigator (MK) and checked by a second investigator (HJS) (axial coding). A third investigator was consulted (HLK) to resolve discrepancies between the first two investigators. Afterwards, the interpretations of each code were specified and their appropriateness was monitored. Simultaneously constant comparisons within and across the preliminary categories were iteratively made to examine interrelationships between the categories that provided the basis for a theoretical framework. Interdisciplinary sessions were regularly held to review and appraise the emerging patterns (researcher triangulation, HLK, JJvD, MK and HJS),

there was no substantial disagreement between the researchers during these sessions.[20] During all phases of the analyses, alternative explanations of the findings were proposed and discussed to ensure strictly inductive and data-driven formulation of concepts.[26] Data-analysis was supported by NVivo 10 software.

Rigour

After all interviews and analysis were performed, a focus group meeting took place in order to obtain peer review of the results. The participants of this focus group were 7 physicians (not being respondents in the interviews) employed in nursing homes within one organisation in Utrecht, the Netherlands. One investigator (HJS) presented the theoretical framework and invited the group to critically reflect on this concept in a reciprocal dialogue.[20] The presented model was acknowledged by the focus group at large; the meeting gave no cause to collect extra data.

RESULTS

Quantitative approach

A total of 423 nursing home residents with clinically suspected VTE were enrolled in the VT-elderly study (294 patients primarily suspected of DVT and 129 of PE) of whom 322 patients had a high probability of VTE and/or an abnormal D-dimer test. Referral for additional diagnostic investigations was forgone in 126/322 (39.1 %) patients. Anticoagulant treatment was initiated in 95 (75.4%) of these 126 patients in whom an objective diagnosis was lacking. The presence of co-morbidity and 'a limited life-expectancy' were most frequently indicated by physicians as reasons for their decision to withhold additional diagnostic imaging examination (respectively 73.8% and 50.0%; table 2).

The non-referred patients were more often bedridden or chair-bound (respectively 68.5% versus 52.0%, p=<0.01), more often primarily suspected of PE instead of DVT (48.4% versus 20.1%, p<0.01) and had a lower score on the clinical decision rule compared to the referred patients (table 3). Moreover, the 3-month mortality rates were higher in patients in whom investigations were withheld than in the referred patients, irrespective of anticoagulant treatment (31.0% versus 17.1%, odds ratio crude 2.15 (95% confidence interval 1.26 to 3.67) and odds ratio corrected for treatment 2.45 (1.40 to 4.29); table 4 and table 5). However, after adjustment for the probability of referral for additional diagnostic investigation (i.e. propensity scores) there was no significant difference in mortality between the non-referred and the referred patients (odds ratio 1.75 (0.98 to 3.11)). Moreover, there were no significant differences in bleeding rates between the referred and non-referred patients; no bleeding occurred in any patient who was not treated with anticoagulant treatment.

Table 2 Reasons given by physicians (n=84) to withhold additional investigations; ticking of more than one reason was allowed

Reason n=84	Frequency of given reason n (% of physicians ticking the reason)
Co morbidity	62 (73.8)
Limited life-expectancy	42 (50.0)
Limited quality of life	30 (35.7)
Agreed palliative policy	27 (32.1)
Agreed symptomatic policy	22 (26.2)
Contra-indication anticoagulant treatment	6 (7.3)
Unusual in our nursing home	5 (6.0)

Qualitative approach: motivations for non-diagnosis decisions

Further analyses were restricted to the qualitative analysis of the in-depth interviews. In the physicians' reasoning, three key-themes were identified. These key-themes were translated to three key-questions describing the most important reasons in the physicians' consideration of the proportionality (that is the harm-benefit ratio) of the referral for additional diagnostic interventions (table 6): 1) What is the relative impact of the potential disease? 2) Does performing additional diagnostic investigations agree with advance care planning? 3) And, do potential benefits of additional diagnostic investigations outweigh burden and risks for the patient? Furthermore, physicians named several non-patient related factors that influenced their decisions; we called these factors 'modulating factors' (table 7).

Key question 1: What is the relative impact of the potential disease? The impact of the potential VTE-event was estimated (that is, a combination of the severity of symptoms and estimated prognosis) and was considered in the perspective of the patient's chronic condition. For some patients, the impact of the potential VTE-event was overshadowed by their chronic condition; physicians expected that the potential VTE-event would not significantly alter their quality of life or life-expectancy as this was largely determined by their chronic condition. For example, a physician of a patient with paraplegia due to a spinal cord lesion considered the suspected DVT as 'just a detail' for his patient (table 6) which was the main reason to withhold further diagnostic work-up for this patient. However, the presence of more severe symptoms (e.g. severe discomfort due to suspected PE) or severe complication risks inclined physicians to perform additional diagnostic tests.

Key question 2: Does performing of additional diagnostic investigations agree with advance care planning? Physicians stated that it is common practice to discuss advance care planning

with every resident at their admission in Dutch nursing homes. Advance care planning implies a decision concerning the outline of the goals and boundaries for medical interventions based on regularly held discussions with the patient or his/her legal representative. Next to the patient's chronic condition and estimated prognosis, the patients' attitude and his/her (negative) experiences with previous hospital admissions commonly played a role in the goals of medical interventions. Physicians experienced this predefined advance care planning as guiding principles for their medical decisions, next to the wish of the patient and his or her family at the time of the clinical suspicion of VTE. Though referral to a hospital was generally considered inappropriate within a "palliative-" or "symptomatic goal" (i.e. medical treatment aimed at optimal well-being and an acceptable quality of life rather than on cure or extension of life),[28] it was generally believed that anticoagulant treatment would relieve the complaints of the patient and therefore it was considered as an appropriate intervention for patients with such an in-advance planned "palliative-" or "symptomatic goal". However, one physician consciously decided- in consultation with the patients' representatives- to withhold anticoagulant treatment for a patient and hoped that the possible PE would be an opportunity to let the patient pass away (table 6); for this patient, the pre-determined goal of medical care was to optimize well-being rather than on cure or extension of life.

Key question 3: Do the potential benefits of the investigation outweigh its burden and risks? In the light of relative impact of the potential disease, the potential net-benefits of investigations were estimated. Physicians stated that the performance of investigations driven by curiosity or 'just to know the diagnosis' did not fit in their professional standards (table 7). The pursuit of a diagnosis was considered of limited value if this would not lead to an alteration in management.

Several physicians seemed to strongly rely on their diagnostic reasoning: they estimated the probability of VTE (based on clinical signs and symptoms, D-dimer testing) as very high ("there was no alternative explanation for these symptoms") and subsequently immediately started anticoagulant treatment. In their opinion, anticoagulant treatment would have been initiated anyhow, so they considered imaging examination of limited value. In contrast, several physicians would only start anticoagulant treatment if the diagnosis of VTE would be confirmed by imaging examination and considered the complication risks of treatment unacceptable if the diagnosis would not be established (table 6). Others withheld treatment in particular patients as they judged the disadvantages of the treatment - either due to complication risk or burden of the administration and monitoring- of overriding importance.

Physicians felt that the transport to a hospital and undergoing additional investigations would bring on physical and mental burden to their patients. It was felt that hospital care was not sufficiently set up for frail older people. Fear of disturbing the patient's mental equilibrium was another reason cited by physicians to not seek additional diagnostic tests. Physicians considered that a hospital admission would strain their coping and that it could even be detrimental due to

Table 3 Baseline characteristics, patients referred and not referred for additional diagnostic testing

Patients with a high risk of VTE in whom imaging examination was indicated	**Patients referred for investigations**	**Non-referred patients**	**p (X^2)**
n=322	**n=199**	**n=126**	
Demographic characteristics			
Male	56 (28.1)	35 (27.8)	0.94
Age mean (SD)	82.3 (9.0)	82.3 (10.6)	0.45[a]
Symptoms and signs			
Acute onset of symptoms	138 (69.3)	84 (66.7)	0.61
Duration of symptoms in days, median (interquartile range)	2.0 (4.0)	3.0 (6.0)	0.10
Painful leg	91 (45.7)	38 (30.2)	<0.01
Swollen leg	158 (79.4)	67 (53.2)	<0.01
Erythema of leg	78 (39.2)	33 (26.2)	0.02
Clinical probability of VTE			
Physicians' estimation of the probability of VTE (Gestalt) in %, median (interquartile range)	65 (30)	70 (33)	0.62[b]
D-dimer abnormal	195 (98.0)	121 (96.0)	0.30
Medical history and functionality			
Previous DVT	22 (11.1)	10 (7.9)	0.36
Previous pulmonary embolism	14 (7.0)	8 (6.3)	0.81
Active malignancy	26 (13.1)	17 (13.5)	0.91
Bedridden or chairbound (i.e. unable to walk)	103 (52.0)	85 (68.5)	< 0.01
Outcomes within 3 months			
Anticoagulant treatment initiated	-	95 (75.4)	-
VTE confirmed	118 (59.3)	-	-
Clinical significant bleeding	6 (3.0)	9 (7.1)	0.08[e]
3-months mortality	34 (17.1)	39 (31.0)	<0.01[e]
Patients primarily suspected of DVT	**n= 159**	**n=65**	
Difference in calf circumference in cm, mean (SD)[c]	3.8 (2.0)	3.4 (2.2)	0.93
Oudega score for DVT (clinical variables only), mean (SD)[c]	2.6 (1.5)	2.2 (1.7)	0.24[a]
DVT confirmed	22 (55.0)	-	
3-monts mortality	25 (15.7)	14 (21.5)	0.30

Table 3 (continued) Baseline characteristics, patients referred and not referred for additional diagnostic testing

Patients primarily suspected of PE	n= 40	n=61	
Cough[d]	8 (20.0)	11 (18.0)	0.81
Pain at inspiration[d]	17 (42.5)	17 (27.9)	0.13
Dyspnoea[d]	31 (77.5)	52 (85.4)	0.80
Tachycardia (> 100 per minute)[d]	13 (32.5)	28 (45.9)	0.18
Total score on the Wells rule for pulmonary embolism, mean (SD)[d]	4.5 (1.9)	3.6 (2.2)	0.28[a]
Pulmonary embolism most likely diagnosis[d]	30 (75.0)	31 (50.8)	0.02
PE confirmed	46 (70.8)	-	-
3-months mortality	9 (22.5)	25 (41.0)	0.06

a- Independent samples T-test; b- Mann- Witney U-test; c- Data only available for patients primarily suspected of DVT; d- Data only available for patients primarily suspected of pulmonary embolism; e- provided p-values over the total groups of patients. The p-values within the strata 'primarily suspected of PE' or 'primarily suspected of DVT' were >0.05

Table 4 Multivariable association with decisions to withhold additional diagnostic testing; stepwise backward selection of variables

Variable	Odds ratio (95% confidence interval) for physicians' decision to withhold additional investigation
Total score on clinical decision rule	0.86 (0.75 to 0.99)
Chair bound or bedridden (reference= able to walk)	1.96 (1.18 to 3.25)
Initial suspicion DVT (reference= primary suspicion of PE)	0.21 (0.12 to 0.36)

Table 5 The association of decision to withhold diagnostic testing with patient outcomes within 3 months; odds ratios (95% confidence interval)

	3 month mortality	3 month bleeding rate (any clinically significant bleeding)
Non diagnosis decisions (crude)	2.15 (1.26 to 3.67)	2.60 (0.90 to 7.48)
Non diagnosis decisions (treatment added)	2.45 (1.40 to 4.29)	2.24 (0.76 to 6.60)
Non diagnosis decisions (Propensity score added as continuous variable*)	1.75 (0.98 to 3.11)	2.78 (0.90 to 8.60)
Non diagnosis decisions (Propensity score and anticoagulant treatment added*)	1.99 (1.09 to 3.62)	2.38 (0.75 to 7.54)

* Propensity score for the probability of referral for further diagnostic investigations based on the following variables: gender, age, mobility, primary suspicion DVT or PE, duration of symptoms, acute onset, painful leg, swollen leg, previous DVT, previous PE, decubitus, antiplatelet use, estimated probability of VTE by physician, total score on decision rule. There was a moderately to good balances for all variables within the propensityscores.

Table 6 The main categories in the physicians' considerations

Key question	Considerations inclining the physician to refer the patient for additional imaging examination	Considerations inclining the physician to withhold referral additional imaging examination	Citations illustrating the consideration
What is the relative impact of the potential disease?	**Potential disease;** risks/threats of the disease for the patient's prognosis; mortality risk; severity and burden of current symptoms; expected burden of potential complications of disease	**Chronic condition of the patient;** low quality of life; high age; worse prognosis/ short life expectancy; cognitive decline; (irreversible) chronic burden of disease	I1: "The spinal cord lesion and the paraplegia determine the rest of her life, irrespective of how long that may be. It is of course already an old lady. And in my experience, it does not make sense to mess up things for a particular detail, such as a complication of thrombosis. This might seem strange, but with all these major miseries, it is just a detail."
Does performing investigations agree with the goals for medical interventions as established in advance care planning?			I13: "Consider a patient (…) who is in a preterminal phase. In such a case we focus on the prognosis and life expectancy. Which complications may occur when we refrain from actions? And how does that affect the quality of life?". I12: "So, here is actually a woman of whom we disrespectfully say "this is someone who has forgotten to die." Perhaps, this may sound bad, but she really is not happy. So, we secretly hoped for that this would be her time to finally die "
Do the potential benefits of the investigation outweigh its burden and risks for the patient?	**Potential benefit of diagnostic investigation**	**The burden and risks of investigation**	I21: "In a nursing home it is not obvious to exhaust all possibilities and resources. Almost all things you do is a consideration of the expectancy and the burden of something, and also the expected course afterwards."
	Alteration in management; the likelihood that further investigations will alter intended management	**Physical burden of investigation;** duration of hospital visit; transport to hospital; physical complication risk	I16: "Sure, you act in good conscience, also in this case. Yeah, you never know for certain, but the clinical picture gives me the impression that there is a high probability the diagnosis is correct." I14:"I consider this as a great burden: in the ambulance, lying there for hours, bearing several examinations, family that has to accompany…. and then returning several hours later reporting; 'the examination has failed'."
	Proportionality of the burden of treatment; establishing the diagnosis makes the burden of treatment more proportional.	**Burden of treatment;** risk of (bleeding) complications; Burden of drug administration and monitoring	I14: "If one frequently falls and there are signs of PE, therefore you should treat, but you also know that one falls and could even get an intracranial haemorrhage, then –with a person who is fine- the priority of the diagnosis takes over the argument."

Added value for the patient's quality of life; through assessment of prognosis or through guidance and care for the patient	**Mental, psychological and emotional burden and coping;** Not understanding what is going on; unable to lie still; offering resistance; risk of mental complications(e.g. delirium)	I12: "What counts as well is that, in many of my years of experience, I have seen so much misery: people going to the hospital and either dying there, tremendously delirious, tied up to the bed, or returning in a condition that makes you say: "Oh my, I wish we had never started this." I9: "Well, in her case it also played a role that the confirmation of the diagnosis did not outweigh the increasing risk of delirium by doing these kind of things "

complications. Particularly for patients with cognitive decline or psychiatric diseases, referral was considered burdensome. For some patients it was felt that it would even be impossible to perform imaging examinations, as they would get restless because they would not understand what was going on, or that they would offer resistance.

Modulating factors

Next to the considerations of the proportionality of investigations for a particular patient, we detected several factors that affected the physicians' decisions more in general (listed in table 7). As a result of their decision to withhold diagnostic investigations physicians felt that they had to accept more uncertainty in their treatment decisions. Physicians with more work experience tended to be less concerned by this uncertainty and placed greater emphasis on their clinical judgement. Moreover, their estimations of the relative benefits of investigations for the patients tended to be less positive. Some physicians expressed the fear that their lead role in decision-making would be lost if patients were referred to the hospital. Others experienced resistance from hospital workers if they intended to hand over a patient to hospital care. In addition, various practical considerations could also persuade the physician to forgo referral; for example the inconvenience of arranging a referral or the absence of someone to accompany the patient.

DISCUSSION

This study explored physicians' decisions to withhold diagnostic investigations in elderly patients, both in a quantitative and qualitative manner. We found that almost four out of ten nursing home patients with a high risk of VTE were not referred for additional diagnostic investigations. Generally, elderly care-physicians considered referral for additional diagnostic testing as a great burden for their frail older patients and aimed to reserve referrals for problematic cases. This was in line with previous studies pointing out the risks and burden of hospital transfers in frail older patients.[11,12,29] Hospital-transitions among nursing home residents are associated with in increased risk of functional decline, development of decubitus ulcers, tube feeding insertion (adjusted odds ratios up to 2) and a 20% risk of adverse drug events due to prescription errors.[10,13,30,31] Compared

Table 7 Modulating factors

Physician related factors	Experience	Duration of work as physician in elderly care
		Feedback on own acting
		Medical training
	Standards and values	Not wanting to do medically pointless interventions
		Though aware of it, costs of medical interventions are no deciding factor
		Starting or continuing interventions is considered easier than stopping or withdrawing interventions
		Physician takes (responsibility for) decision and tries to get the patient ('s family) to go along
		Aim to prevent a conflict with patient('s family)
	Professional standards	In general being reserved to refer to a hospital
		Little available diagnostic technology in the nursing home lead to more often withholding it
		Curiousness or 'wanting to know' of less importance
		Holistic patient approach
		Pursuit of quality of life and comfort
		Being aware of the verges of life
	Fear for losing direction when referring	Risk for more diagnostic interventions than requested
	Experienced resistance proceeding from hospital	
	Diagnostic uncertainty	
Patient('s family) related factors	Patient's wish	Negative experience with previous hospital admissions
	Derived patient's wish	Desire to reduce the duration of the patient's suffering
		Previous statements of the patient which support restraint management
	Family	Negative experience with patient's previous hospital admissions
		Unable to take leave of the patient
		Unable to handle uncertainty
		Having a feeling of guilt
		Considered burden of the patient for the informal caregiver
		Composition of the family and family bonds
	Religion/culture	Religious patients tend to wish to continue medical interventions to the very end

Table 7 (continued)

Circumstances	Distance to hospital
	Availability of diagnostic interventions
	Availability of someone to accompany the patient
	Time of the day/week
	Workload
	Inconvenience to arrange referral
Other factors	Conceived burden of the referral for the caregivers in the hospital
	Characteristics of the nursing home hardly influences the decision making
	Not knowing the patient inclines the physician to referral

to the patients who were referred for additional diagnostic investigations, the non-referred patients had a higher crude 3-month mortality rate; almost one out of three of these patients died within three months. Due to the non-randomized design of the study we cannot firmly interpret these findings. Though it is possible that the lack of an adequate diagnosis and subsequently under- or overtreatment partly contributed to the higher mortality-rates in the non-referred patients,[32] it is much more likely that the worse outcomes of the non-referred patients can be explained by a worse prognosis of these patients non-referred beforehand; compared to the referred patients, the non-referred patients were more often primarily suspected of PE (instead of DVT) and more often severely impaired in their mobility. Moreover, though univariable analysis revealed a higher 3-month mortality-rate for the non-referred patients, there was no longer an association between non-diagnosis decisions and mortality when the probability of being referred (i.e. the propensity score) was added to the multivariable model. Yet, the differences in 3-month mortality largely derives from differences in patient characteristics rather than by the effect of the decision to withhold diagnostic investigations and subsequently guided therapy. Therefore, our results raise the important management question whether the potential (but unknown) benefit of definite diagnosis versus empirical treatment outweighs the known harms of hospital transfer in nursing home residents with a clinical suspicion of venous thromboembolism in whom an objective diagnosis is lacking.

Strikingly, anticoagulant treatment was initiated in most (75%) of the patients for whom was decided to withhold investigations. Though there was a general belief among physicians that anticoagulation treatment would relieve the complaints of their patients, there appeared to be a large variation in the physicians' notions on the risks and benefits of anticoagulant treatment in older patients and in the subsequent effects of these notions on their decisions. Several physicians considered the complication risks of anticoagulant treatment insignificant and were inclined to initiate treatment without confirmation of the diagnosis, whilst others considered the bleeding risk as substantial and were only willing to initiate treatment if the diagnosis was objectively con-

firmed, whereas others decided to withhold further diagnostic testing as they intended to withhold anticoagulant treatment irrespective of the diagnosis. Previous studies showed that in older patients with multi-morbidities, anticoagulation treatment is associated with a more than twofold increased bleeding risk.[33–35] However, despite this risk, anticoagulant treatment is highly effective in prevention of (fatal) recurrences of VTE (absolute risk reduction of 52.6% of fatal and non-fatal recurrences), and therefore, even high age, multiple comorbidities and/or cognitive impairment are not necessarily contra-indications for anticoagulant treatment.[33,36,37]

The strengths of our study derive from the combined quantitative and qualitative methods to gain understanding of the physicians' diagnostic decision making and the context of- and important reasons in this diagnostic decision making. Furthermore, there was good concordance in the analysis of the researchers who separately and subsequently jointly reviewed transcripts. Also, validation of the results by means of the focus group meeting did not show serious disagreement with the analysis.

Yet, for full appreciation of our results, some aspects of our study warrant comment. First, our study was a post-hoc analysis on data of a prospective study which aimed to validate clinical decision rules in combined with normal D-dimer testing to rule out VTE in older nursing home patients. Consequently, not all variables identified in our qualitative study to potentially correlate with the physicians' decision to withhold additional diagnostic investigations were systematically collected in the quantitative study. Specifically, we did not determine a frailty index score, the presence of 'do not resuscitate' orders, or the presence of either cognitive or renal function impairment. Moreover, our study was not primarily powered to detect differences between referred and non-referred patients. A larger sample size would possibly have resulted in more significant differences between these two groups.

Second, the single-country of the study might hamper generalization of our findings to other countries, as the organization and healthcare ethics in the Dutch nursing home care may be different from other countries.[21,38] Medical care for nursing home residents in the Netherlands is delivered by so called 'elderly care physicians'; a medical specialty in the Netherlands in nursing home geriatric medicine. These physicians have completed a medical specialisation training of three years and - in general- exclusively deliver care to geriatric nursing home patients (i.e. not in hospital settings). In a qualitative study comparing decisions of Dutch and American physicians (from North Carolina) to treat or withhold treatment in nursing home residents with pneumonia, Helton and colleagues found that American physicians were more deferential to family preferences and were inclined to treat more aggressively, even in cases when they considered families' wishes for care as inappropriate.[38] Therefore, more studies - particularly in other settings and countries- are needed to further explore physicians' diagnostic reasoning and also to quantify the impact of additional diagnostic testing on patients' quality of life in clinically relevant subgroups.

Third, the semi structured face-to-face interview method offered a context for the physicians to speak honestly about difficult clinical situations and their considerations in their decision-making

and the interviewers made every effort to stimulate the physicians' frankness. Nevertheless, the possibility of socially acceptable answers by the participants could not fully be excluded.
Last, though the pragmatic and observational study-design of the VT-elderly study did not force physicians to refer patients with high scores on the clinical decision rule, it is possible that physicians were less prone to include the frailest patients or patients in whom they deviated from the rule in the VT-elderly study (gatekeeping).[39] This might have introduced selection bias which might have led to an underestimation of the frequency of non-diagnosis decisions for patients residing in Dutch nursing homes. Nevertheless, we do not expect that this hampered the completeness in the variety of our presented categories in the qualitative analysis of non-diagnosis decisions.[20,25]

In conclusion, our results suggest that elderly care physicians are frequently faced with the difficult task to decide whether referral for additional diagnostic investigations is of benefit to their individual patient with suspected VTE. For almost four out of ten nursing home patients with a high clinical suspicion of VTE, additional diagnostic investigations were withheld. 'Blind' anticoagulant treatment was initiated in three out of four of the non-referred patients. The 3-month mortality rates were higher for patients in whom investigations were withheld than in the referred patients, irrespective of anticoagulant treatment. However, when adjusted for the propensity score, there was no relation of non-diagnosis decisions to mortality. We unravelled the physicians' complex decisions to forgo additional diagnostic investigations. Our analysis revealed that the physicians' decision to forgo additional diagnostic investigation was a complex one that appeared to be primarily based on their judgment of the benefit balanced against potential harms likely to come from such testing. Given the complexity of these decisions, more attention for this formerly undiscussed topic is needed. This may open debate among physicians and contribute to well-considered decision making.

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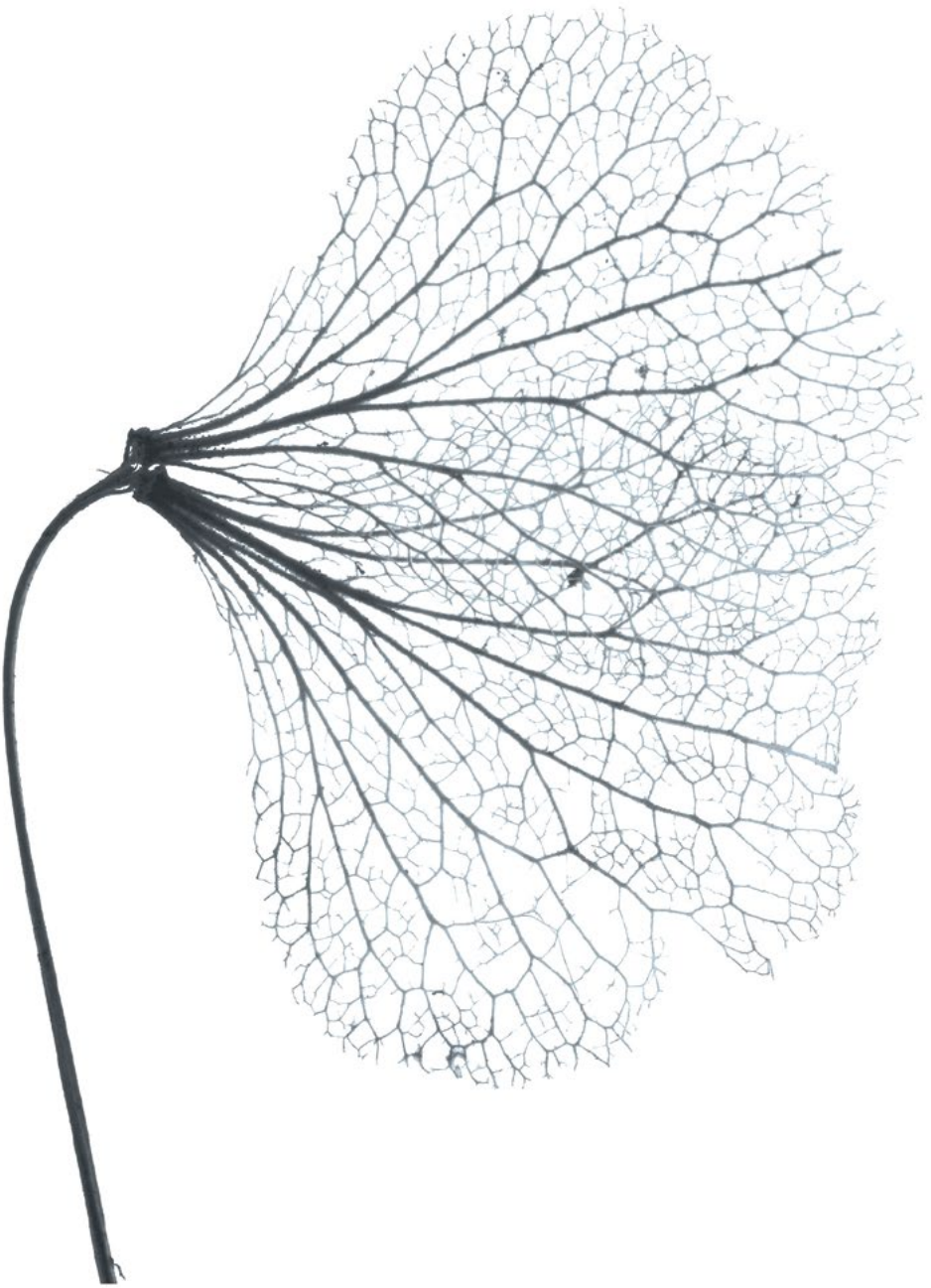


CHAPTER 9

SUMMARY AND GENERAL DISCUSSION
NEDERLANDSE SAMENVATTING

The main difficulty in the diagnostic work up of patients with suspected venous thromboembolism (pulmonary embolism and deep vein thrombosis) is to adequately and timely distinguish the minority of patients in whom venous thromboembolism is indeed present and who require anticoagulant treatment from those who do not have the disease and in whom treatment can be safely withheld.[2;3] This diagnostic work-up is a process in which the physicians' estimation of the probability of the presence of venous thromboembolism based on information obtained from history taking and physical examination is implicitly updated with additional diagnostic tests (such as a clinical decision rule, D-dimer testing or imaging examination) in order to change this probability towards a probability above or below a threshold of which the physician is confident enough to make treatment decisions (figure 1).[4;5] Ideally, the more burdensome and costly modalities (CT pulmonary angiography or compression ultrasonography) are avoided which would also reduce exposure to nephrotoxic contrast and carcinogenic radiation. Appropriate treatment decisions are important as anticoagulant therapy may prevent the potential fatal sequelae of venous thromboembolism whereas unnecessary use in those without the disease is inconvenient, costly and carries risk of (major) bleeding.[6-9]

For patients, the impact of the accuracy of the diagnostic strategy thus results from their physicians' decisions to either (correctly of wrongly) initiate or to withhold anticoagulant treatment as guided by the final diagnosis (figure 2).[1;10] An appropriate diagnostic workup of venous thromboembolism is particularly important for older patients as both their short term mortality-risk of venous thromboembolism and their complication-risks resulting from anticoagulant treatment and further diagnostic testing are high.[11-14]

In this thesis, we aimed to answer three questions. The first two questions focused on the accuracy of commonly used diagnostic tests in older patients with suspected venous thromboembolism:

1. What is the accuracy of existing clinical decision rules in older patients with suspected venous thromboembolism?
2. What is the diagnostic value of the D-dimer test using either conventional or age-adjusted cut-off values in older patients with suspected venous thromboembolism?

With the third question, we focused on physicians' decision-making in the diagnostic work-up of older patients with suspected venous thromboembolism.

3. What are physicians' considerations in their decisions to either refer for- or withhold additional diagnostic investigations in older frail patients with suspected venous thromboembolism?

In this chapter, the studies presented in this thesis will be summarized and discussed in a broader perspective.

SUMMARY OF THE FINDINGS

What is the accuracy of existing clinical decision rules in older patients with suspected venous thromboembolism?

To correctly exclude the presence of venous thromboembolism without the need for further diagnostic work-up, so-called diagnostic decision rules - based on a weighed combination of signs and symptoms and the result of the D-dimer test - have been developed.[15] These strategies have been derived and validated in both primary and secondary care patients suspected of venous thromboembolism. Notably frail older patients might benefit from such a strategy provided that it can safely rule-out venous thromboembolism in a substantial proportion of them without needing to be referred for imaging examination. Yet, the accuracy of these existing clinical decision rules to rule-out venous thromboembolism has never been tested in elderly populations. We discussed in **chapter 2** how diagnosing venous thromboembolism in older patients might differ from diagnosing venous thromboembolism in younger adult patients. The predictive performance

Figure 1 Physicians' implicit decision-process in diagnostic work up of patients with suspected venous thromboembolism (based on the work of Grobbee and Hoes)[4]

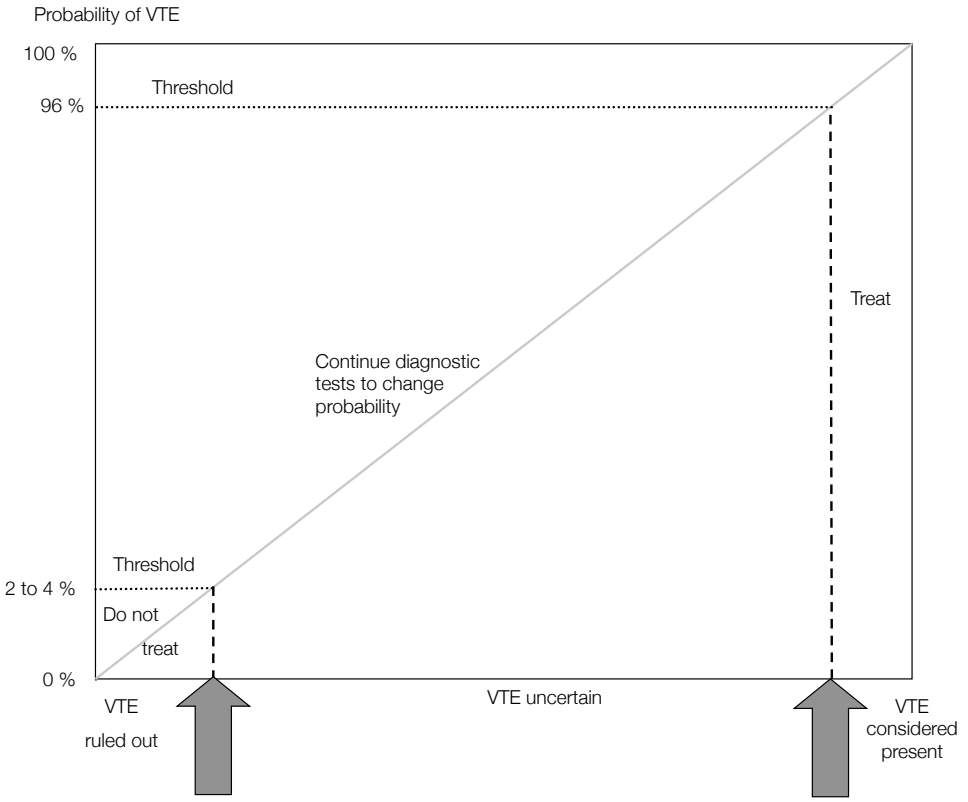
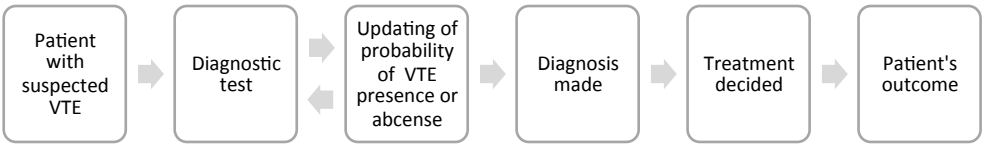


Figure 2 The ultimate goal of diagnostic testing is to alter physicians' decision making in patients' treatment, and thereby to improve patients' outcomes. VTE= venous thromboembolism, based on di Ferrante et al[1].



of clinical decision rules is susceptible to changes in patient populations and these rules might therefore perform worse in older patients in whom the prevalence of both venous thromboembolism and co-morbidity are higher and the presentation of venous thromboembolism might be more obscure.[16-21] In addition, current available diagnostic strategies recommend referral for further imaging examination for more than half of the patients, whereas diagnostic decision strategies that would spare higher proportions of older patients the possible hazardous referral for imaging examination might better serve their needs (see **chapters 7 and 8**). Yet, before existing clinical decision rules can be extrapolated to an elderly care setting, their accuracy should first be formally tested in an elderly population and (if needed) be adapted for this particular setting as was done in **chapter 3** for clinical decision rules for deep vein thrombosis and in **chapter 4** for clinical decision rules for pulmonary embolism.[16]

The accuracy of clinical decision rules to exclude deep vein thrombosis in older out-of-hospital patients was assessed in **chapter 3**. We performed a prospective validation study in frail older nursing home patients and primary care patients (mean age 81 years) with clinically suspected deep vein thrombosis. Venous thromboembolism occurred in 47% of the study participants. This prevalence was much higher than in previous studies in populations of younger adult patients (reporting a prevalence between 7% and 20%)[3;22-24] which resulted in a higher probability of venous thromboembolism within the patients with a 'very low risk': the failure rate in patients who had a low score on the clinical decision rule and a normal D-dimer test was 6% in our study versus below 2% in previous studies. In our population of frail older patients, the probability of venous thromboembolism was 70% in patients who had a 'likely' Wells-score and an abnormal D-dimer test. This approach has the potency to rule-in venous thromboembolism in one in two older out-of-hospital patients if referral for further diagnostic work-up is considered too burdensome.

In **chapter 4**, we assessed the validity of the Wells-strategy combined with a point-of-care D-dimer test to rule-out pulmonary embolism in older out-of-hospital patients (mean age 76 years).[25] The prevalence of pulmonary embolism was 30%, which was also higher than in previous studies on the same strategy in younger adult patients (prevalence ranging from 9.5% to 23%).[2;15;26-31] This higher prevalence in our study resulted in a higher prior-probability for pulmonary embolism which in turn led to a higher proportion of patients with confirmed pulmonary embolism (failure

rate 6%) despite an 'unlikely' score on the Wells-rule (total score ≤4) and a normal D-dimer test. A revised Wells-strategy resulted in a lower failure rate (3%) and - based on the high prevalence in this elderly population for whom further diagnostic workup may bring along considerable burden - the rule has also the potency to rule-in venous thromboembolism in 18% of patients having a 74% probability of pulmonary embolism, in whom treatment may be directly initiated if referral for further diagnostic work-up is considered non desirable. This combined rule-out and rule-in approach would enable clinicians' decision-making for 42% of patients without the need for further diagnostic work-up.

What is the diagnostic value of the D-dimer test using either conventional or age-adjusted cut-off values in older patients with suspected venous thromboembolism?

A normal D-dimer test can rule out venous thromboembolism in patients with a non-high clinical probability according to a clinical decision rule. Since D-dimer levels increase with age, D-dimer testing is less useful to exclude venous thromboembolism in older patients if the conventional cut-off value (500 µg/L) above which the test is considered abnormal is applied.[19;32;33] As potential solution of this problem, researchers proposed to use an age-adjusted cut-off value (age*10 µg/L) in patients >50 years for the D-dimer test.[33] **Chapter 5** describes a study on the safety and accuracy of this age-adjusted D-dimer cut-off value in older primary care patients with suspected deep vein thrombosis. Use of the age-adjusted cut-off value instead of the conventional cut-off value resulted in a higher proportion of patients in whom deep vein thrombosis could be excluded (48% with the age-adjusted versus 42% with the conventional cut-off value) whilst the false negative rate remained low (0.5% versus 0.3% respectively). This increase in diagnostic efficiency was largest in patients older than 80 years (35% versus 21% respectively).

The accuracy of age-adjusted D-dimer levels was further examined with a systematic review and bivariate random effects meta-analysis described in **chapter 6**. We searched the Medline and Embase databases for studies published before 21 June 2012. We included 13 cohorts that enrolled older patients suspected of venous thromboembolism in whom D-dimer testing (using both conventional and age-adjusted cut-off values) and reference testing were performed. Based on published data we reconstructed 2x2 tables, stratified by predefined age-categories and applied D-dimer cut-off value. If complete reconstruction of 2x2 tables using the desired age categories was not possible based on the data as presented in the papers, we contacted the authors and requested to reanalyze their data according to the predefined age class categories and to complete the cross tables for all age categories and for both the conventional and age adjusted D-dimer cut-off level. We found that the proportion of patients with a non-high clinical probability in whom D-dimer testing could exclude venous thromboembolism was only 12.4% in those aged more than 80 years. Yet, D-dimer testing has limited utility in older patients when the conventional cut-off value is applied. Application of age-adjusted cut-off values increased the specificity with-

out modifying the sensitivity which remained above 97% in all age categories and would result in correctly avoided imaging examinations in 30 to 42% of patients over 60 years with a non-high probability as compared to 12 to 33% when the conventional cut-off value would be applied.

What are physicians' considerations in their decisions to either refer for or withhold additional diagnostic investigations in older frail patients with suspected venous thromboembolism?

Clinical decision rules for venous thromboembolism combined with D-dimer testing allocate patients either in a low- or a high-risk category.[2;25;34] Patients who are in the low-risk category and have a normal D-dimer test-result have a very low probability of venous thromboembolism and do not require further work-up or treatment whilst those within the high-risk category (including patients with an abnormal D-dimer test) require appropriate imaging examination for venous thromboembolism to confirm or refute the diagnosis.[35;36] These imaging modalities are mostly not available in primary care and nursing home settings, necessitating patients in the high-risk category to be referred to a hospital. Prior work has shown that frail older patients are vulnerable for distress and complications resulting from transitions to hospital-care.[11;12;37] Hence, physicians might feel reluctant to refer frail elderly patients for additional investigations. Contrary to decisions to withhold treatment, decisions to withhold diagnostic investigations in older frail patients have hardly been studied.

Chapter 7 sets out the results of a systematic review on physicians' decisions to withhold diagnostic or therapeutic interventions in older patients with (suspected) cardiovascular diseases. A total of 45 articles on decisions to either withhold treatment (non-treatment decisions) or diagnostic interventions (non-diagnosis decisions) were included and compared with each other. Several similarities between the two types of decision-making were found: the patient's condition before the intervention (including age and comorbidity) and the expected quality of life after the intervention were associated with both types of decisions. However, in articles on non-treatment decisions we found that the proportionality of an intervention (i.e., the risk or burden of an intervention opposed to that of no intervention) was associated with the decision-making whilst this was not found in articles on non-diagnosis decisions. On the other hand, physician- and care institution related characteristics, such the physicians' age or the employment of physician assistants, were more frequently associated with non-diagnosis decisions than with non-treatment decisions. Moreover we found a relation between decision-making and the presence of no-resuscitate directives in articles on non-diagnosis decisions, but not in articles on non-treatment decisions.

In **chapter 8**, we further focussed on physicians' considerations in their decision-making to either refer for or to withhold additional diagnostic investigations in nursing home patients with suspected venous thromboembolism. We applied both quantitative and qualitative methods in this study.

In the quantitative part, patient outcomes were related to the decision to withhold diagnostic investigations. Referral for additional diagnostic investigations was withheld in four out of ten nursing home patients for whom imaging examination for suspected venous thromboembolism was indicated (i.e. high-risk patients based on clinical decision rule or D-dimer test). Patients in whom diagnostic investigations were withheld had a higher mortality rate than referred patients. For a better understanding of the elderly care physicians' decisions, in-depth interviews were performed and analysed using the grounded theory approach. In their decisions to forgo diagnostic investigations, physicians incorporated the estimated relative impact of the potential disease (that is the severity of symptoms and the estimated prognosis of the disease in the light of the patients' chronic condition); the potential benefits of diagnostic investigations and whether performing investigations agreed with pre-established management goals in advance care planning (e.g. the patients' living will).

IMPLICATIONS FOR CLINICAL CARE IN OLDER PATIENTS WITH SUSPECTED VENOUS THROMBOEMBOLISM AND FOR FUTURE RESEARCH

Below, we discuss the implications of the main findings of this thesis for clinical practice and for future research.

The value of clinical decision rules in older patients with suspected venous thromboembolism

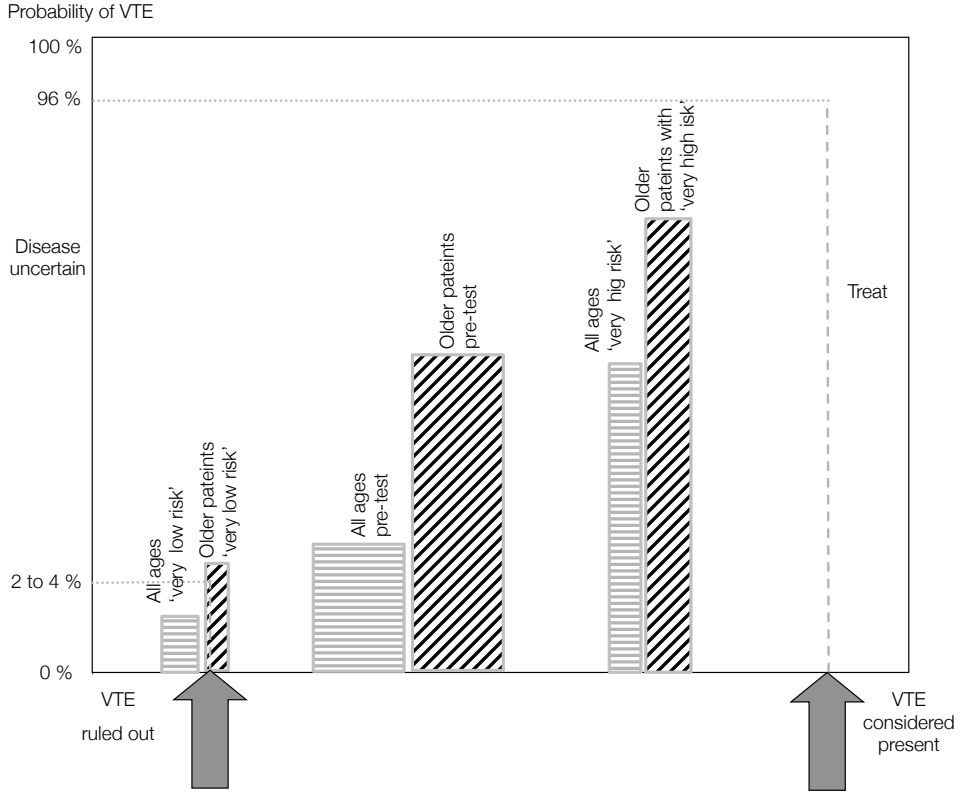
The clinical decision rules for deep vein thrombosis and pulmonary embolism as validated in the **chapters 3 and 4** are both based on readily available clinical signs, symptoms and the D-dimer test. Both studies showed that the use of these clinical decision rules in combination with D-dimer testing in older patients with suspected venous thromboembolism discriminated well and resulted in a substantial change from the pre- to post-test probability of venous thromboembolism. Yet, the prior probability (that is the prevalence) of venous thromboembolism in our older study-population was much higher than in previous studies in younger adult patients. This has important implications for the clinical value of these strategies when applied in older patients. First, physicians should be aware that the probability of venous thromboembolism in patients who have a very low risk according to these strategies (based on a low score on the rule in combination with a normal D-dimer test) is higher when applied in older patients than in younger patients. Second, for those patients with a very high probability according to these strategies, the higher pre-test probability also implies a much higher post-test probability for older patients as compared to younger adult patients with suspected venous thromboembolism in whom the diagnosis might also be ruled in based on this strategy (figure 3).

Before these strategies can be implemented in daily care for elderly patients, we recommend the medical profession to discuss whether these post-test probabilities in older patients as based on the clinical decision rules are considered respectively low or high enough (to respectively rule-out and rule-in of the diagnosis) to guide therapeutic decisions and to withhold further diagnostic testing.

The clinical value of D-dimer testing in older patients with suspected venous thromboembolism

Quantitative D-dimer testing has limited utility in older patients when the conventional cut-off value is applied. Using D-dimer levels below the age adjusted cut-off value will result in correctly

Figure 3 Schematic overview of the effect of prior-probability on the changes from pre-to post-test probability in patients with suspected venous thromboembolism, width of the bars represent proportions of patients in risk-categories.



Pre-test: represents pre-test probability based on the prevalence of venous thromboembolism of all patients before any tests (clinical decision rule or D-dimer test) is performed. 'very low risk'= patients with a low/ unlikely risk according to the clinical decision rule in combination with a normal D-dimer test result, 'very high risk'= patients with a likely/high score on the clinical decision rule in combination with an abnormal D-dimer test result.

avoided imaging examinations in 30% to 54% of older patients with a non-high probability (see **chapters 5 and 6**).

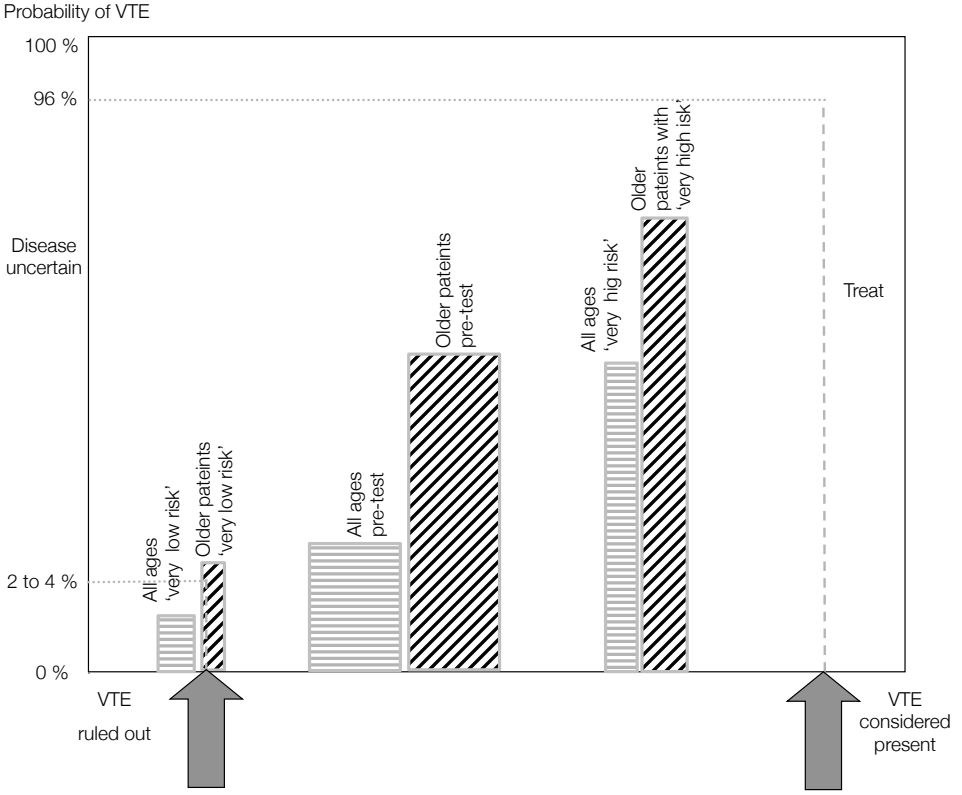
What about the value of the qualitative D-dimer assays as were applied in the studies described in the **chapters 3 and 4**? These tests can easily be performed at the patients' bedside and results are available in 10 minutes and showed to have added diagnostic value to rule out venous thromboembolism as compared to the clinical decision rules alone. However, in the large meta-analysis described in **chapter 6** we examined the accuracy of high-sensitive quantitative (not point-of-care) D-dimer testing using age-adjusted cut-off values (age*10 µg/L for patients aged over 50 years) for non-high risk patients (including patients with a moderate risk according to clinical decision rules). In this study, we found that - even in case of a high prevalence of venous thromboembolism - approximately 33% of patients aged over 60 years would have a normal D-dimer test of whom approximately 2.4% would have venous thromboembolism (failure rate). In contrast, in the studies in **chapter 3 in 4** wherein qualitative point-of-care D-dimer tests were applied, we found proportions of missed cases that were more than twice as high (5.8% in both studies), even in the more selected subgroups of 'low risk' patients according to the clinical decisions rules. In addition we found in chapter 4 that in four of the five cases with pulmonary embolism in the low-risk category (based on a normal qualitative point-of-care D-dimer test and a total Wells-score ≤4), the D-dimer test result would have been classified abnormal according to a (non point-of-care) quantitative D-dimer test (with either age-adjusted or conventional cut-off values). Yet, though we were not able to make a head-to-head comparison of the different D-dimer assays within any of our studies and the differences might be partly explained by differences in case mix between studies, these findings may suggest a somewhat better ability to discriminate older patients who have a truly low risk when high-sensitive quantitative D-dimer assays with age-adjusted cut-off values are used than with qualitative point-of-care tests.[38] Though we cannot make firm recommendations and further research on this topic is needed, we suggest the use of quantitative D-dimer assays in combination with age-adjusted cut-off values to exclude venous thromboembolism in older patients. Physicians who prefer to apply a qualitative point-of-care test should be aware of the slightly higher probability to miss the diagnosis in patients with a normal test result.

Implications for research

The findings in the studies in this thesis highlighted in various ways that frail older patients with suspected venous thromboembolism represent a distinct population and that further research in this population is needed. First, the **chapters 3 and 4** demonstrated how a higher pre-test probability of venous thromboembolism affected the failure rates and thereby the generalizability of existing clinical decision rules (in combination with D-dimer testing) to this population, whilst their discriminatory power was maintained. This underlines that we cannot assume that prediction models can simply be generalized from patients of younger ages to frail older patients, and the need for validation studies of any prediction model in this setting.[16] Second, the **chapters 5 and 6**

underlined the need to validate and adapt the way of application of a commonly used biomarker, the D-dimer test, in this population. These studies illustrated the need to further validate - and probably to adapt - the use of biomarkers in this population. Third, the implicit thresholds in the physicians' estimated probability of venous thromboembolism below or above which treatment decisions are made (and thus further diagnostic work-up is withheld) may vary in older patients. This was highlighted in the **chapters 7 and 8** on non-diagnosis-decisions. These non-diagnosis decisions result in lower patient-burden proceeding from diagnostic testing, but are at the expense of more uncertainty in the appropriateness of the treatment decision (figure 4). Given the complexity of the decisions and as it is unclear how they may indirectly affect patients' outcomes (figure 2), more research on decisions concerning withholding diagnostic investigations in older patients is needed.

Figure 4 Non-diagnosis decisions- Physicians trade off in diagnostic certainty to avoid burdensome diagnostic tests in elderly patients



BEYOND DIAGNOSTIC ACCURACY; A CONCEPT FOR TARGETS IN FUTURE RESEARCH IN OLDER PATIENTS

The ultimate goal of diagnostic testing is to improve patients' outcomes via modification of physicians' treatment decisions (figure 2).[1;39-42] Many studies on diagnostic strategies in venous thromboembolism –including the studies presented in this thesis- have considered accurate and timely diagnosing venous thromboembolism at utmost importance to prevent potential fatal thromboembolic complications or unnecessary exposure to the risks of anticoagulant therapy.[2;3;6;20;33;43] Researchers and physicians have approached venous thromboembolism as a binary entity which is (1) either present or absent and roughly assume that (2) all patients with present venous thromboembolism will benefit from anticoagulant treatment.[44] Recently, this approach was challenged by researchers arguing that categorizing patients as either venous thromboembolism present or not, depends on arbitrary categories and on the extent to which test results truly reflect the presence of venous thromboembolism.[10] The sharp rise in the incidence rates of venous thromboembolism without concordant decrease in absolute mortality rates since the introduction of very sensitive diagnostic tests - notably CT-pulmonary angiography - that are able to detect smaller thrombi, point towards a broadening of the category 'venous thromboembolism present'.[45-47] Rather, venous thromboembolism may be seen a continuous entity with its heterogeneous clinical manifestations representing a range of severities: from small and distal cloths such as superficial vein thrombosis or subsegmental pulmonary embolism of which the prognostic value is still controversial,[48-50] to massive proximal thrombi like phlegmasia dolens or saddle pulmonary embolism.[45-47]

Next to variation in disease severity, patients' bleeding risks varies widely with age, co-morbidity and co-medication.[51-53] For example, imagine patient A with a large proximal pulmonary embolism and without co-morbidity. This patient will probably experience more benefits than harms from treatment as these benefits are likely outweighed by its harms.[8] Yet, in patient B, who has had previous gastrointestinal bleeding and isolated subsegmental pulmonary embolism, treatment effects may be smaller than the possible harms that might be induced by anticoagulant treatment.[49] These two patients, both classified as 'venous thromboembolism present', are thus likely to experience different consequences of the same anticoagulant treatment. As a result, the danger of misdiagnosing and of a subsequent wrong treatment decision (withholding treatment when pulmonary embolism is present) is probably more serious for patient A as compared to patient B.[54]

Unintended effects of diagnostic tests on patients outcomes

If patient B also suffers from renal impairment or cognitive impairment, contrast enhanced CT-scanning might even pose this patient to risk of more than 15% on contrast induced nephropathy or to the risk of acute delirium as result of hospitalization.[14] Yet, performance of diagnostic test might also result in unintended negative effects on patients' outcomes, notably in frail older

patients. This negative effect might result from inconvenience, psychological distress or burden for the patient to undergo the test or due to complications, such as nephropathy induced by contrast enhanced computed tomography.[14] Moreover, there is a risk of misclassification for each test and a risk for unexpected findings, which may occur in more than 55% of older patients undergoing CT scanning of the chest.[55;56] This may un turn induce a cascade of subsequent further diagnostic and therapeutic actions and thereby induce even more patient-burden. Unnecessary additional diagnostic testing will therefore not result in neutral effects on patients' quality of life.

The intended effects of diagnostic tests on patients outcomes

As discussed above, diagnostic tests or strategies for venous thromboembolism can only indirectly benefit patients if it leads to changes in treatment decisions (figure 2).[1;39-42] In other words, the value of a diagnostic test for a patients' outcome depends on the influence of the test on the physicians' decision to either initiate or withhold treatment and the subsequent direction (either more benefit than harm, or more harm than benefit) and magnitude of treatment-effect. This added value of a diagnostic test, that is the tests' potency to change the physician's decision, is conditional on information that is already available such as information obtained from patient characteristics, physical examination and previous tests predicting the patient's outcome.[54;57] Yet, both the severity of disease and potential treatment benefits and harms may differ amongst patients classified as 'venous thromboembolism present'. Therefore, these patients do not represent a homogeneous group in whom benefits of anticoagulation are equally likely to outweigh the harms and thus, the diagnostic test is not at the same value for all these patients.[44] It might therefore be of more relevance to target patients' outcomes (that is, the patients' prognosis) instead of the potency of a diagnostic strategy or test to diagnose venous thromboembolism (i.e. diagnostic accuracy) in future studies on clinical decision making.[1] We propose therefore, in line with previous authors, that clinical decision making in patients suspected of venous thromboembolism should not be approached in terms of pursuing a dichotomous diagnosis (presence of absence of venous thromboembolism), but rather by considering venous thromboembolism as a continuous predictor of the patients' prognosis (for example of quality of life) which is conditional of the disease severity and patient characteristics like comorbidity.[41;44;58] For example, for patient C with severe cardiac failure, even a subsegmental pulmonary embolism might perhaps be life-threatening whilst patient D, a sportsman with a comparable tiny isolated subsegmental pulmonary embolus is likely to have a favorable outcome.[49] This predicted patients' outcome can also interfere with treatment decisions which can either favor this prognosis or induce further harm to the patient. Hence, targeting the potency of a diagnostic test to guide the right treatment decision based on the resulting predicted prognosis of a particular patient might be of more relevance than solely focusing on the diagnostic accuracy of the diagnostic test. To estimate this potency of a diagnostic test to guide the right treatment decision, two (composite) parameters have to be integrated:

1. The tests' accuracy to detect presence and severity of disease; in other words, the magnitude to which the test is able to change the estimation of the continuous prediction for the patients' outcome conditional on the severity of venous thromboembolism and on readily available predictors for the patients' outcome, such as clinical signs, symptoms and comorbidity.
2. Potential treatment harms and benefits conditional on patients' characteristics that interact with these potential treatment benefits or harms. The input for this parameter can be based on (a combination of) existing prediction models for treatment benefit (for example the Vienna or DASH prediction model)[59] and treatment harm (for example the Bleeding Risk Index or RIETE bleeding risk-score).[60]

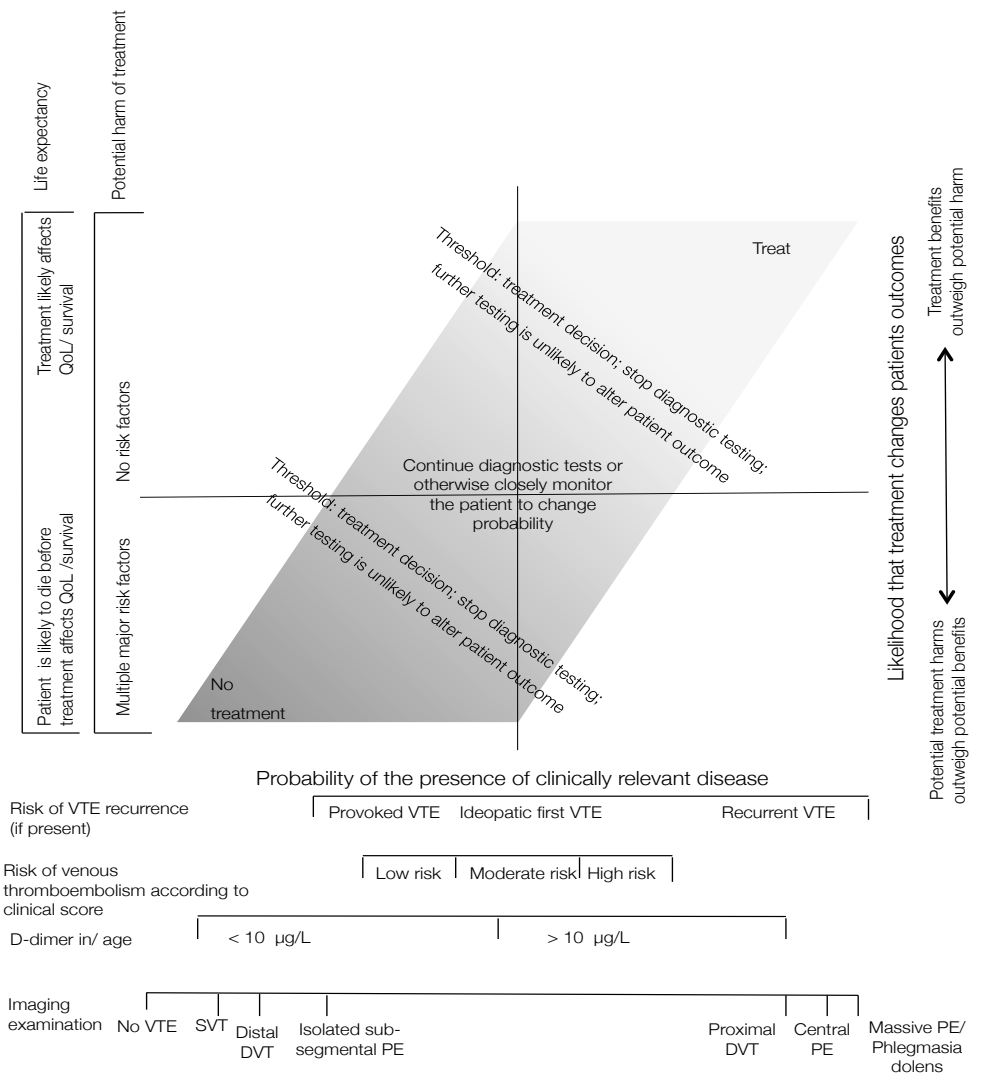
How will this work in future research?

The estimation of the potency of a diagnostic test to increase the probability for the right treatment decision results from the above mentioned two parameters. When we assume that patients with the most severe disease are –conditionally on their other characteristics such as co-morbidity- most likely to benefit from treatment, those two parameters are mutually dependent.[61;62] The both parameters can be plotted in a model with two axes; 1) available test-information - that is information on the probability of disease presence and its severity based on available diagnostic information - is plugged into the model to estimate the value on the x-axes; and 2) patients characteristics that predict potential treatment benefits or harms enter the model via the y-axes. Furthermore, the potential detrimental effect of testing (e.g. the risk for contrast induced nephropathy) and information about the range of probabilities and severities in which a next test can discriminate in disease presence and severity should be incorporated in such a model.[39]

In line with previous studies, suggest that the current design of diagnostic studies should be replaced for a design which resembles the design of a prognostic study.[39;41;44] The patients' outcome, for example in quality adjusted life years, should be the outcome of such a study, instead of diagnostic accuracy measures as sensitivity or specificity. Together with patients characteristics, diagnostic tests and treatments should be the (continuous rather than dichotomous) determinants in this study design. Moreover, the time-axes of such a study should be longitudinal instead of cross-sectional.[4] Such a model can be composed based on available literature on venous thromboembolism; estimations of treatment effect, information on test-characteristics, clinical decision models, estimations of treatment effect and prediction models for harm from treatment. Figure 5 depicts a hypothetical draft of such a model for venous thromboembolism, with potential input for the parameters on both axes.

The output of such a model is twofold: 1) an estimation of the likelihood that treatment benefits outweighs the risk, plus an estimation of the uncertainty in this decision (that is the inverse of the probability of the right treatment decision) as based on readily available information, and 2) the likelihood that the estimated treatment effect would be different if the next test is performed and

Figure 5 Hypothetical management model for patients with suspected venous thromboembolism with potential parameter input. The output can be read from the vertical axes on the right hand side; the width in the estimated probability box reflects the uncertainty in the probability that the treatment choice is best for this patient



more diagnostic information would be added to the model, in combination with an estimation of the detrimental effect of further testing on the patients' quality of life. For example, if patient B, who had renal impairment and previous gastrointestinal bleeding, was suspected of having pulmonary embolism and would have a combination of a unlikely Wells' score (≤4) and abnormal D-dimer tests, his probability of pulmonary embolism would be estimated at approximately 12%.[25] The harms of the performance of a contrast enhanced CT-pulmonary angiography to diagnose pulmonary embolism and eventual subsequent treatment for this patient (given his risk for both contrast-induced nephropathy and bleeding) probably outweigh the potential harms of a missed diagnosis for this patient. Thus, the estimated likelihood that treatment benefits outweighs the risk for this patient (1) might be negative, and the likelihood that the estimated treatment effect would be different if the next test (CT pulmonary angiography) is performed (2) is thus small.

How can this become useful in clinical practice? A global concept.

If it is possible to derive such a multidimensional model which can reliably estimate an individual patient's outcome, such a model can to be translated to clinical practice. One can think of an application on a mobile device, or - even better - in electronically patient charts in which all available relevant patient data (like medical history, comorbidity, co-medication, life expectancy and test results) automatically enters the model. The model can support clinicians' decision making by providing an estimation of the patients' outcome given different management strategies (either to start or withhold treatment, and - if applicable - directions for the dose and duration of treatment), plus the estimated probability that further testing will alter this decision.

Based on this information, physicians can either make a treatment decision (start or withhold treatment) or decide to perform additional diagnostic tests to increase the probability of the right treatment decision. If further tests are performed, the information in the model can be updated with the test information. Ultimately, the treatment decision and outcomes for individual patients are registered and incorporated in the prior of the next patient's estimation.

Ethical considerations

To determine the threshold to stop further testing, the physician can incorporate the patient's preferences and the burden, risk and costs for further testing (**chapter 8** of this thesis). Though the physician's estimation of the patient's prognosis and treatment effects can be guided by the model, the physician's final management decision will thus be multifactorial and depends on many other contextual factors and ethical considerations.

This decision is a trade-off between certainty in management decisions and patient burden induced by further testing. Though additional imagining examinations might prevent the sequelae of a wrong treatment decisions in some patients with suspected venous thromboembolism, it also exposes many patients to the potential unintended harms of additional diagnostic work-up.[45]

Physicians should be aware that diagnostic testing rarely leads to complete certainty of the disease status of a patient.[54]

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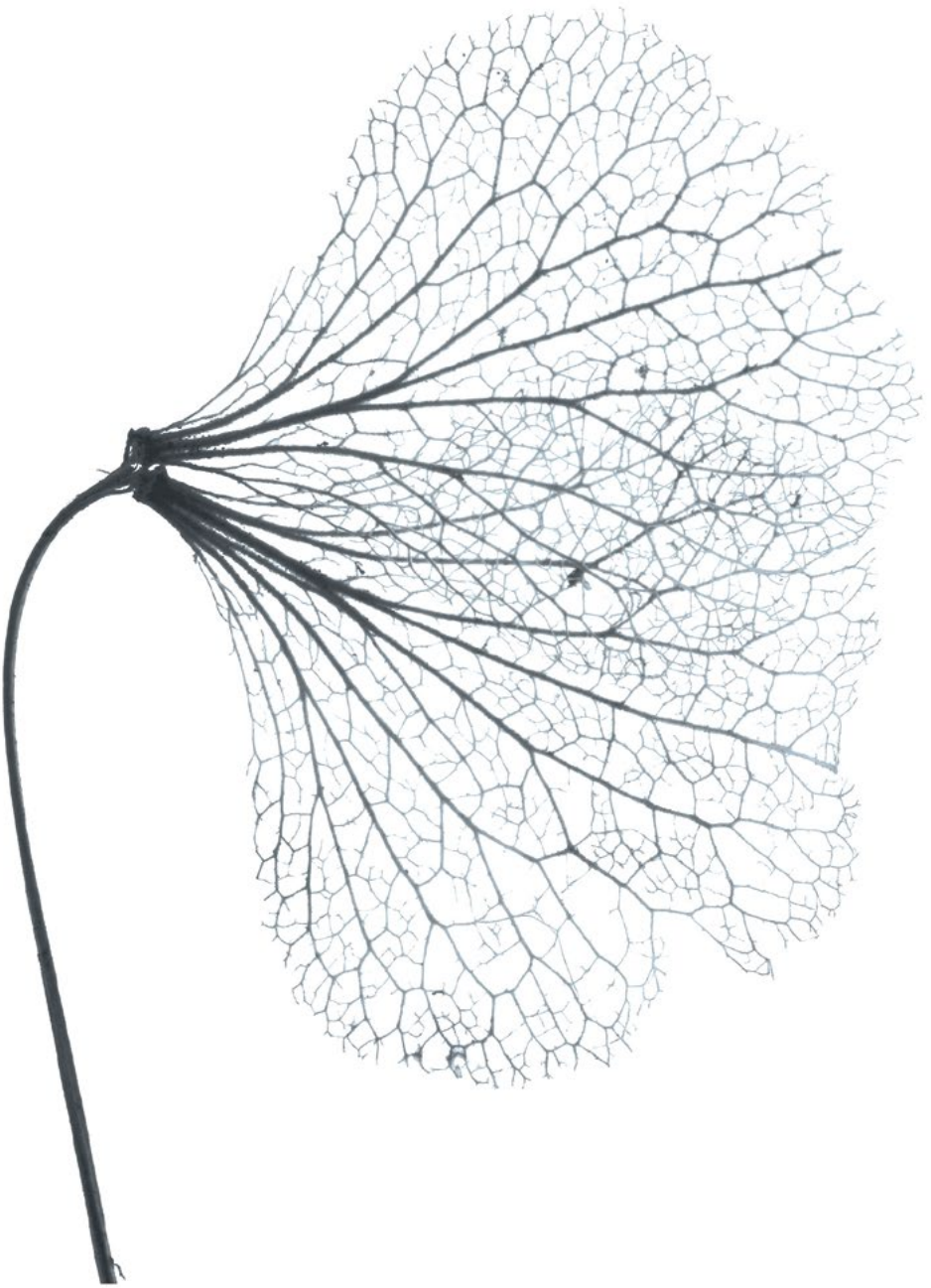


CHAPTER 9

SUMMARY AND GENERAL DISCUSSION
NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift was het optimaliseren van diagnostische strategieën voor oudere patiënten met klinische verschijnselen van diep veneuze trombose of longembolieën. Diep veneuze trombose ontstaat als er een stolsel (trombus) in een beenvat vormt waardoor het vat (de vene) afsluit. Als dit stolsel vervolgens wordt meegevoerd met de bloedstroom en vastloopt in een (kleinere) slagader van de longen spreekt men van een longembolie. Omdat deze ziektebeelden dezelfde ontstaanswijze hebben worden zij vaak samen onder één naam gevat: veneuze trombo-embolieën. In dit hoofdstuk worden de studies die beschreven zijn in dit proefschift samengevat.

Door weinig specifieke symptomen blijkt ongeveer 80% van de patiënten die verdacht worden van veneuze trombo-embolie geen veneuze trombo-embolie te hebben. Daarom start het diagnostisch traject met uitsluiten van de diagnose bij een groot deel van de patiënten. Zowel voor diep veneuze trombose als longembolie kan middels een gewogen combinatie van klinische kenmerken (diagnostische beslisregel) en een laboratoriumtest (D-dimeer test) een risico-inschatting worden gemaakt. Is de kans op trombose hoog? Dan is verwijzing naar het ziekenhuis nodig voor beeldvormend onderzoek. Bij een lage kans is dat niet nodig. Vooral voor kwetsbare oudere patiënten kan het gebruik van een dergelijke strategie - waarmee de ziekte veilig kan worden uitgesloten zonder dat verwijzing voor beeldvormend onderzoek nodig is - voordeel bieden. Er is echter nooit onderzocht of de diagnostische beslisregels betrouwbaar kunnen worden toegepast bij ouderen. In **hoofdstuk 2** bespreken we hoe diagnostiek van veneuze trombo-embolieën bij ouderen kan verschillen van de diagnostiek bij jongere volwassen patiënten. Doordat zowel veneuze trombo-embolieën als andere ziekten met vergelijkbare verschijnselen vaker vóórkomen bij ouderen is het denkbaar dat de regels minder goed voorspellen bij ouderen. Het is daarom van belang om dit te onderzoeken voordat de regels bij ouderen in de dagelijkse praktijk worden toegepast.

In **hoofdstuk 3** onderzochten we of de beslisregel voor diep veneuze trombose veilig en efficiënt kan worden gebruikt om diep veneuze trombose bij ouderen uit te sluiten. Verpleeghuisbewoners en oudere patiënten uit de huisartspraktijk (gemiddelde leeftijd 81 jaar) met een klinische verdenking op diep veneuze trombose werden ingesloten. In vergelijking met voorgaande studies bij jongere volwassen patiënten vielen de volgende bevindingen op: Bij 47% van de deelnemers werd een veneuze trombo-embolie vastgesteld, dit percentage (ofwel de prevalentie) is relatief hoog. Door dit hogere percentage waren er relatief minder patiënten in de 'laagrisico' categorie; dat is de categorie waarbij geen verder onderzoek nodig is (ofwel de efficiëntie was lager). Er waren echter meer patiënten in de 'laagrisico' categorie die toch trombose bleken te hebben (lagere veiligheid van 6%). De regel is dus minder efficiënt en minder veilig bij ouderen. Uit het onderzoek bleek verder dat de regel bij ouderen kon worden gebruikt om patiënten met een heel hoge kans op trombose te onderscheiden.

In **hoofdstuk 4** onderzochten we of met behulp van de Wells regel longembolieën veilig en efficiënt kunnen worden uitgesloten bij oudere patiënten buiten het ziekenhuis (gemiddeld 76 jaar

oud). Ook in deze studie bleek het percentage patiënten bij wie de ziekte werd vastgesteld (de prevalentie) relatief hoog in vergelijking met voorgaande studies bij jongere volwassenen (30% in onze studie, vergeleken met 9.5% tot 23%). Hierdoor was het percentage met patiënten in de 'laag-risico' categorie bij wie toch een longembolie werd geconstateerd relatief hoog (veiligheid 6%). Door aanpassing van de regel verbeterde de veiligheid en kon tevens een groep patiënten met een zeer hoge kans op een longembolie worden onderscheiden.

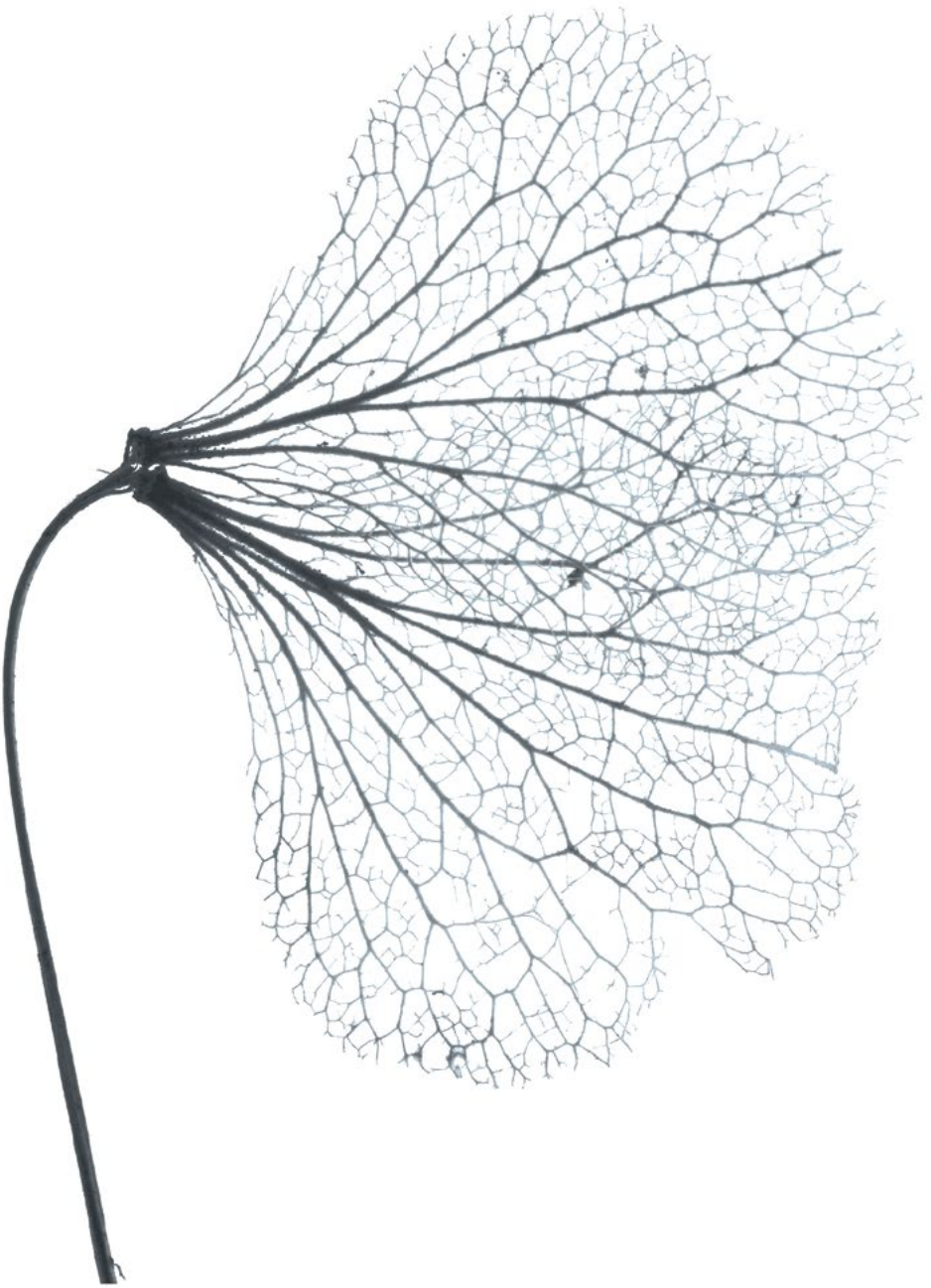
Een normale D-dimeer concentratie wordt gebruikt om veneuze trombo-embolieën uit te sluiten bij patiënten met een niet-verhoogde score op de diagnostische beslisregels. Omdat de D-dimeer concentratie stijgt met de leeftijd is de test bij ouderen vaak vals-positief als de gebruikelijke afkapwaarde waarboven de test als abnormaal wordt beschouwd (500 µg/L) wordt gehanteerd. Om dit probleem op te lossen werd door onderzoekers voorgesteld om een leeftijds-aangepaste afkapwaarde (namelijk leeftijd*10 µg/L) voor patiënten >50 jaar te gebruiken. In **hoofdstuk 5** toonden we aan dat de toepassing van een leeftijds-aangepaste afkapwaarde voor de D-dimeer test leidde tot een aanzienlijke verhoging van het aantal oudere patiënten in de huisartsenpraktijk, bij wie diep veneuze trombose veilig kon worden uitgesloten zonder dat een verwijzing naar het ziekenhuis voor aanvullend onderzoek nodig was (bij 48% met de leeftijds-aangepaste versus bij 42% met de conventionele afkapwaarde). Hierbij bleef het aantal patiënten bij wie de diagnose werd gemist laag (respectievelijk 0.5% versus 0.3%). Bij patiënten van 80 jaar en ouder was het aantal extra patiënten bij wie de diagnose door gebruik van de leefijdsaangepaste afkapwaarde veilig kon worden uitgesloten het grootst (respectievelijk 35% versus 21%).
De waarde van de D-dimeer test bij ouderen - met of zonder leeftijdsaangepaste afkapwaarde - werd verder onderzocht in een meta-analyse die beschreven wordt in **hoofdstuk 6**. Voor deze studie doorzochten we de internationale literatuur op studies bij ouderen die verdacht werden van een veneuze trombo-embolie en bij wie de D-dimeer test was verricht met zowel een conventioneel als leeftijds-aangepast afkappunt. De uitkomsten van de 13 studies die aan deze criteria voldeden werden tezamen geanalyseerd (bivariate random-effects meta-analyse). Hieruit bleek dat bij de patiënten die 80 jaar en ouder waren en een niet-verhoogde klinische verdenking hadden, de D-dimeer test slechts bij 12.4% van de patiënten kon worden gebruikt om veneuze trombo-embolieën uit te sluiten. De D-dimeer test heeft dus weinig nut bij oudere patiënten als de conventionele afkapwaarde wordt gebruikt. Toepassing van de leeftijdsaangepaste afkapwaarde verhoogde het aantal patiënten (>60 jaar) bij wie veneuze trombo-embolieën konden worden naar 30 tot 42% vergeleken met 12 tot 33% bij toepassing van de conventionele afkapwaarde, terwijl het fout-negatief percentage laag bleef (sensitiviteit > 97%).

Naast het onderzoek naar de waarde van de diagnostische beslisregels en D-dimeer test bij ouderen, richtte ons onderzoek zich ook op besluitvorming van artsen. Diagnostische procedures kunnen door artsen worden ingezet om een bepaalde diagnose met meer zekerheid te kunnen

stellen of te kunnen verwerpen. Aan de inzet van diagnostische interventies kunnen echter ook bezwaren kleven. De weging van deze bezwaren kan bij oudere (verpleeghuis)patiënten anders zijn dan bij jongere patiënten. Een arts in de ouderenzorg zal hierdoor soms kiezen om bij specifieke patiënten af te wijken van diagnostische richtlijnen. In de **hoofdstukken 7 en 8** onderzochten wij welke medisch-ethische overwegingen aan deze beslissingen ten grondslag liggen.

Hoofdstuk 7 beschrijft het resultaat van een systematisch literatuuronderzoek waarin we beslissingen van artsen om af te zien van behandeling vergeleken met beslissingen van artsen om af te zien van verdere diagnostiek. Er werden 45 geschikte artikelen gevonden waaruit bleek dat er veel overeenkomsten zijn in het besluitvormingsproces van de arts wanneer er wordt afgezien van behandeling of van diagnostiek: voor beide typen beslissingen bleek zowel de toestand van de patiënt voor de interventie (bijvoorbeeld leeftijd en co-morbiditeit) als de verwachting over de kwaliteit van leven na de interventie in belangrijke mate mee te wegen. De belasting van de ingreep bleek vooral van invloed op niet-behandelbeslissingen, terwijl arts-gebonden kenmerken - zoals de leeftijd van de arts en de aanwezigheid van arts-ondersteunende disciplines - juist vaker samen gingen met beslissingen om af te zien van verdere diagnostiek. Verder bleek dat bij mensen met een niet-reanimeer verklaring vaker beslissingen werden genomen om af te zien van diagnostiek.

In **hoofdstuk 8** gingen we dieper in op de beslissingen van artsen om verpleeghuispatiënten die verdacht werden van veneuze trombo-embolieën al dan niet te verwijzen naar een ziekenhuis voor aanvullend diagnostisch onderzoek. Voor dit onderzoek maakten we gebruik van zowel kwantitatieve- als kwalitatieve technieken. In het kwantitatieve deel relateerden we de uitkomst van de patiënt aan de beslissing om af te zien van verdere diagnostiek. Bij vier op de tien patiënten bij wie beeldvormend onderzoek was geïndiceerd werd hiervan afgezien. Onder de niet-verwezen patiënten was een hogere sterfte na drie maanden, maar dit bleek grotendeels verklaard te kunnen worden door de slechtere uitgangspositie van deze patiënten. Om meer inzicht te verkrijgen in de besluitvorming van de artsen werden er diepte-interviews verricht en geanalyseerd volgens de ‘grounded theory’ benadering. In de overwegingen van de artsen kwamen drie belangrijke principes naar voren: ten eerste werd de mate waarin de potentiële ziekte de kwaliteit van leven van de patiënt zou veranderen ingeschat (gegeven de ernst van de symptomen en de chronische toestand van de patiënt); ten tweede werd ingeschat hoe de eventuele winst van het verrichten van aanvullend onderzoek en eventuele therapie zich verhield tot de belasting en risico’s hiervan; als laatste werd beoordeeld of het verrichten van verder onderzoek in lijn was met eerder vastgelegde wensen en afspraken met de patiënt.



CHAPTER 10

CO-AUTHORS
DANKWOORD
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LIST OF PUBLICATIONS

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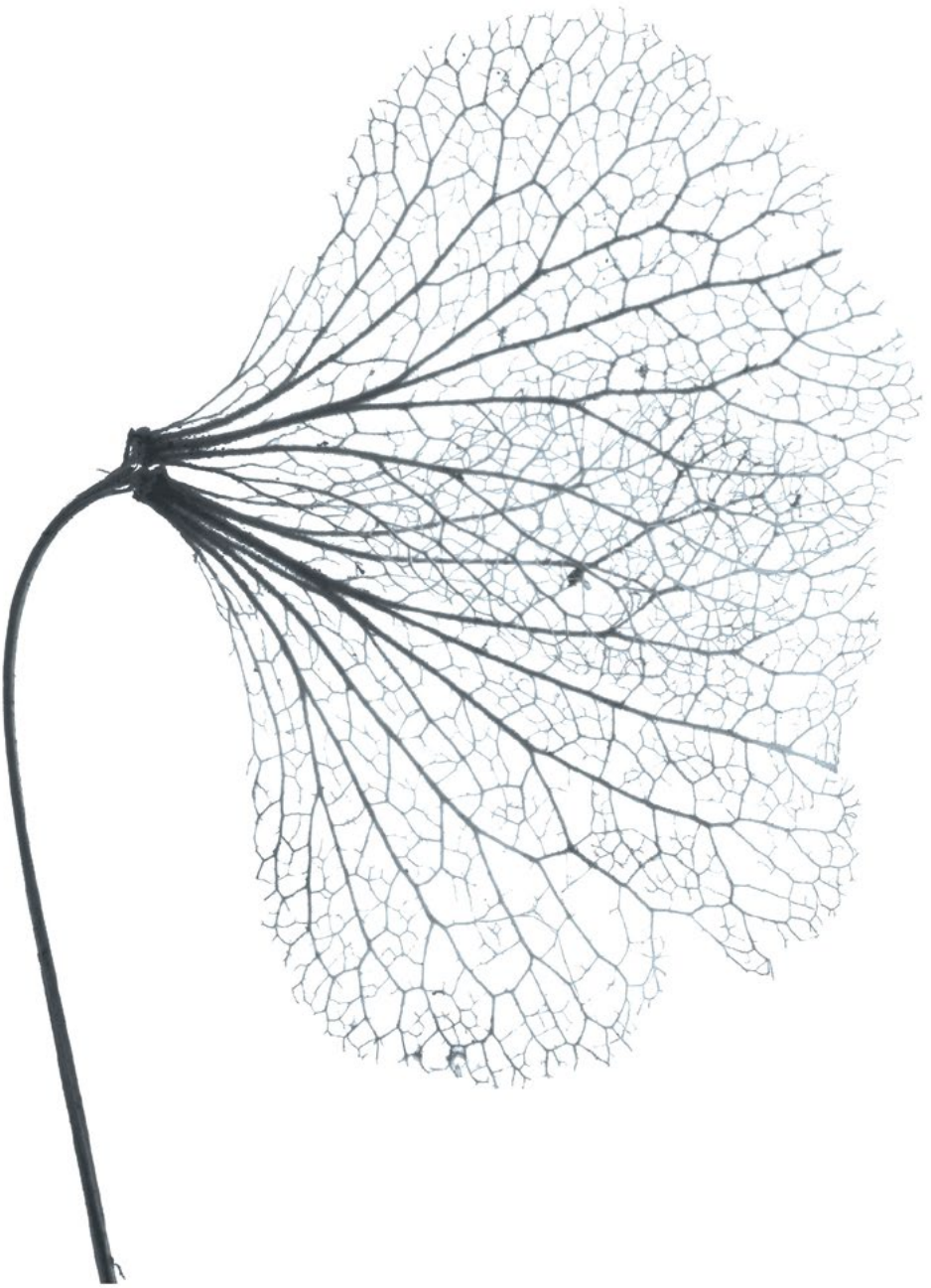

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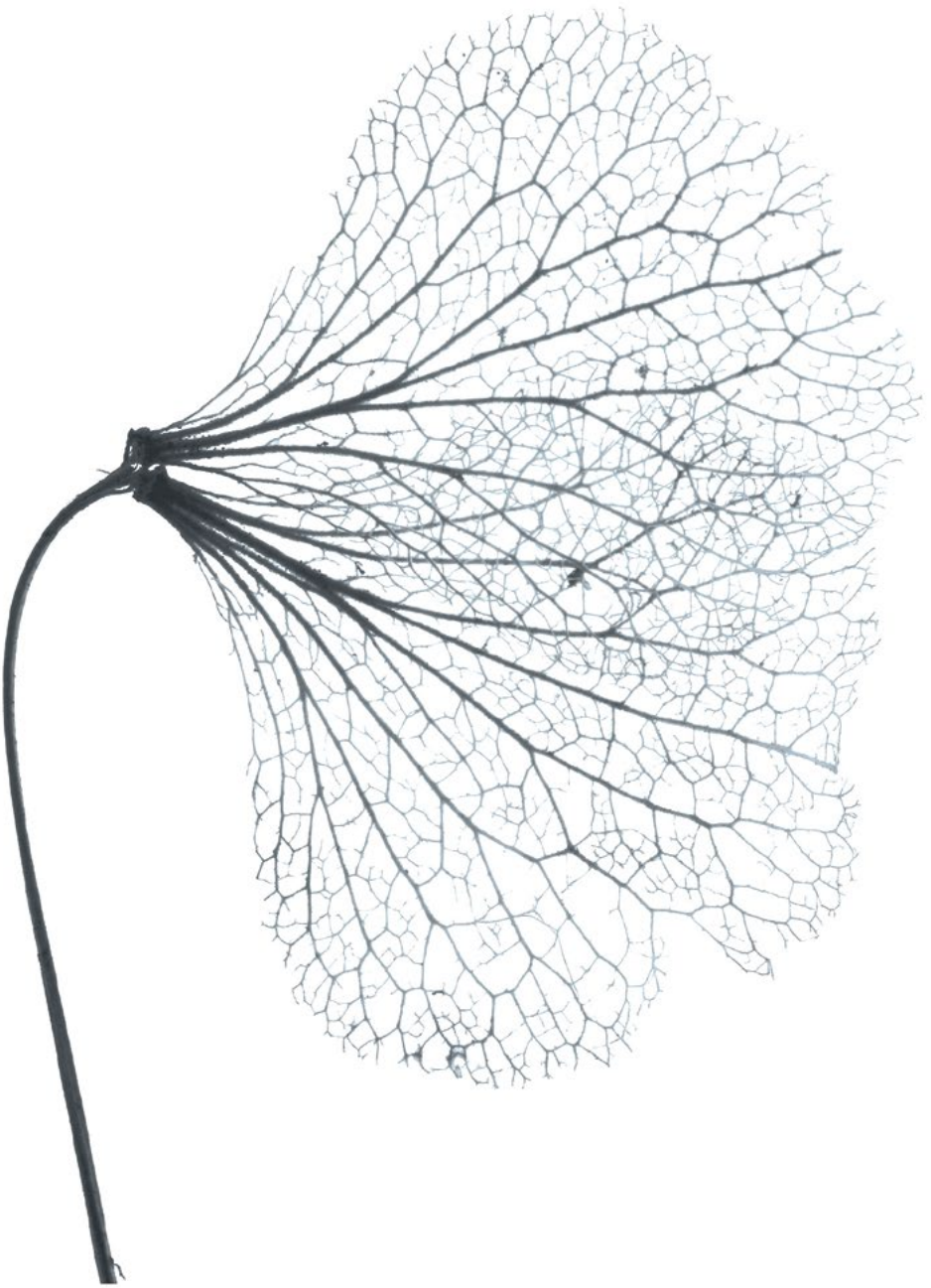
CURRICULUM VITAE

Hendrika Jacoba Schouten was born on Augustus 9, 1985 in Rhenen, the Netherlands. After graduating from secondary school 'het Ichthuscollege' in Veenendaal in 2002, she studied Nursing at the 'Christelijke Hogeschool Ede', the Netherlands. In 2004 she started to study medicine at the Utrecht University. As part of this study, she was involved in a research project at the department of Geriatric Medicine of the University Medical Centre Utrecht. This research focused on the impact of side effects of antipsychotic drugs on patients' quality of life. In October 2010 she obtained her medical degree and subsequently started her residency in geriatric medicine at the University Medical Centre Utrecht (supervisors dr. P.A.F. Jansen and later dr. H.J. Verhaar).
In 2011 she started working as a PhD student on the studies described in this thesis at the Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht (supervised by Prof. dr. K.G.M. Moons, Prof. dr. J.J.M. van Delden, dr. G.J. Geersing and dr. H.L. Koek). She combined her PhD research project with the program of the Postgraduate Master of Clinical Epidemiology at the Utrecht University for which she obtained her degree in 2013.
Henrike resumed her residency in geriatric medicine in October 2013 and she currently works at the Diakonessenhuis in Utrecht (supervisor dr. A.F. Muller). She aims to register as geriatrician in 2017. Henrike is happily married to Maarten Donswijk.



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Manuscripts based on the studies presented in this thesis

Schouten HJ, Koek HL, Moons KGM, van Delden JJM, Oudega R, Geersing GJ. Need for tailored strategies to diagnose venous thrombo-embolism in older primary care patients. Extension of a keynote presentation at the 2012 Wonca Europe conference. *Eur J Gen Pract. 2013 Jan 22.*

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Schouten HJ, Koek HL, Oudega R, van Delden JJM, Moons KGM, Geersing GJ. Accuracy of decision strategies in diagnosing deep vein thrombosis in frail older out-of-hospital patients – a validation study. *Submitted*

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Maessen M, Veldink JH, van den Berg LH, **Schouten HJ**, van der Wal G, Onwuteaka-Philipsen BD. Requests for euthanasia: origin of suffering in ALS, heart failure and cancer patients. *J Neurol. 2010 Jul;257(7):1192-8*

Winckels S, **Schouten HJ**, Beekman H, Atteveld N, Vos MA. Incomplete reversibility of electrical remodelling in chronic AV block dogs is unmasked by anaesthesia and dofetilide. *Chapter in: Ventricular electrical remodelling and arrythmogenesis. 2007:3: 29-44*

Venous thromboembolism is the result of a blood clot occluding a blood vessel in the leg or in the lung. Given the exponential rise of the incidence of venous thromboembolism with increasing age, the majority of venous thromboembolic events occur in older patients. The aim of this thesis was to optimize diagnostic strategies for older patients with clinical signs and symptoms of venous thromboembolism. Due to nonspecific symptoms, the majority of patients with suspected venous thromboembolism turn out not to have the disease. Therefore, the diagnostic approach of venous thromboembolism starts with exclusion of this diagnosis in many patients, based on a weighed combination of clinical characteristics (diagnostic decision rule) and a laboratory test (D-dimer test).

This thesis presents a series of studies on diagnostic decision making for older patients with suspected venous thromboembolism. First, we assessed the accuracy of existing diagnostic decision rules to exclude venous thromboembolism in older patients. The second part of this thesis focusses on the diagnostic value of D-dimer testing for excluding suspected venous thromboembolism in older patients, with a particular interest in whether increasing the threshold for test positivity is a safe and more efficient strategy than using the conventional cut-off. The last part of this thesis describes physicians' considerations in their decision-making to either refer for or to withhold additional diagnostic investigations in nursing home patients with suspected venous thromboembolism.

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