

OPTIMIZING D-DIMER THRESHOLD FOR VENOUS THROMBOEMBOLISM

**OPTIMIZING THE D-DIMER THRESHOLD USED TO EXCLUDE VENOUS
THROMBOEMBOLISM**

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ABSTRACT

Background A D-dimer threshold $<500\mu\text{g/L}$ has high negative predictive value (NPV) for venous thromboembolism (VTE), but is non-specific. Two strategies increase the specificity and utility (defined as the proportion of patients with a negative test) of D-dimer testing: 1) using a higher D-dimer threshold with increasing age (IAIT Strategy); and 2) using a high threshold in low clinical pretest probability (CPTP) patients and the standard threshold in moderate CPTP patients (CPTP Strategy). It is unknown whether the gain in specificity of the IAIT Strategy is simply due to using a higher threshold in some patients and whether the CPTP Strategy has better diagnostic accuracy than the IAIT Strategy.

Methods In a retrospective analysis of 1649 outpatients with suspected VTE, I compared the diagnostic accuracy of the IAIT Strategy to 1) its opposite: using a higher D-dimer threshold with decreasing age (DAIT strategy); 2) using a higher D-dimer threshold in all patients (Median Age Strategy); and 3) the CPTP Strategy.

Results The NPV of both the IAIT and DAIT Strategies was 99.6% and the NPV of the Median Age Strategy was 99.7%. The utility was almost identical in the IAIT and DAIT Strategies (50.9% vs. 50.6%) and greater in the Median Age Strategy (53.9%, $p<0.001$). The NPV of the CPTP and IAIT Strategies were 99.6% and 99.7%, respectively. The utility was higher in the CPTP Strategy than the IAIT Strategy (56.1% vs. 50.9%, $p<0.001$).

Conclusions The NPV and utility of using a higher D-dimer threshold in older patients (IAIT Strategy) is the same as using a higher D-dimer threshold in younger patients. The CPTP Strategy had the greatest utility while maintaining a high NPV and therefore appeared to be the optimal strategy of D-dimer interpretation.

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TABLE OF CONTENTS

ABSTRACT	iii
ACKNOWLEDGEMENTS	v
TABLE OF CONTENTS	vi
LIST of FIGURES and TABLES	ix
LIST of COMMON ABBREVIATIONS	x
GLOSSARY	xi
DECLARATION OF ACADEMIC ACHIEVEMENT	xiii
SECTION 1: OBJECTIVES	1
1.1 General Objective	1
1.2 Specific Objectives	1
SECTION 2: STUDY BACKGROUND	3
2.1 Risk Factors for and Natural History of VTE	3
2.1.1 Risk Factors for VTE	3
2.1.2 Natural History of VTE	4
2.1.3 Impact of Anticoagulation on Natural History of VTE	6
2.2 Diagnosis of VTE	6
2.2.1 Study Designs Used to Assess Diagnostic Tests for VTE	7
2.2.2 Diagnostic Accuracy Parameters	9
2.2.3 Testing for VTE in Clinical Practice	13
2.2.4 Diagnostic Tests for DVT and their Accuracy	17
2.2.5 Diagnostic Tests for PE and their Accuracy	20
2.3 Role of D-dimer in the Diagnosis of VTE	24
2.3.1 D-dimer Formation	24
2.3.2 Causes of an Elevated D-dimer Level	25
2.3.3 Determinants of D-dimer Level Among Patients with VTE	25
2.3.4 Measurement of D-dimer Level	26
2.3.5 Categorization of D-dimer Results as Positive or Negative	27
2.3.6 Diagnostic Accuracy of D-dimer Assays	28
2.3.7 Standard Use of D-dimer in Clinical Practice	28

2.3.8 Strategies to Improve Diagnostic Utility of D-dimer Testing.....	30
2.3.9 Comparison of Strategies to Improve Utility of D-dimer Testing	34
SECTION 3: METHODS.....	37
3.1 Study Hypotheses	37
3.2 Classification of Patients as VTE-positive or VTE-negative	37
3.3 D-dimer Assay	38
3.4 Eligibility Criteria	38
3.4.1 Inclusion Criterion	38
3.4.2 Exclusion Criteria	38
3.5 Strategy Definitions	40
3.5.1 Standard Strategy (single threshold)	40
3.5.2 Increasing Age, Increasing Threshold (IAIT) Strategy (variable threshold)	40
3.5.3 Median Age Strategy (single threshold).....	40
3.5.4 Decreasing Age, Increasing Threshold (DAIT) Strategy (variable threshold)	41
3.5.5 CPTP Strategy (variable threshold)	41
3.6 Data Analysis and Statistics	42
3.6.1 Diagnostic Accuracy	42
3.6.2 Predefined Subgroups	44
3.7 Methodological Issues	44
3.7.1 Differential Verification Bias	44
3.7.2 Effect of Prevalence on Estimates of NPV.....	46
3.8 Safety and Ethical Considerations.....	47
SECTION 4: RESULTS.....	48
4.1 Description of the Study Population	48
4.2 Distribution of D-dimer Levels	50
4.3 LR for VTE Associated with D-dimer Levels.....	50
4.4 Evaluation of the IAIT Strategy.....	52
4.4.1 Comparison of IAIT and Standard Strategies	52
4.4.2 Comparison of IAIT and Median Age Strategies.....	54
4.4.3 Comparison of IAIT and DAIT Strategies.....	56
4.5 Evaluation of the CPTP Strategy.....	58
4.5.1 Comparison of CPTP and Standard Strategies	58

4.5.2 Comparison of CPTP and IAIT Strategies	60
4.6 Mean D-dimer Threshold According to Strategy	62
4.7 Patients with Suspected DVT versus PE.....	62
4.8 Differential Verification Bias.....	63
4.9 Effect of Prevalence of VTE on NPV Estimates	64
SECTION 5: DISCUSSION	66
5.1 Validity of the IAIT Strategy	66
5.2 The CPTP Strategy is the Optimal Strategy	67
5.3 IAIT Strategy: Comparison of Current Analysis with Existing Literature.....	69
5.4 CPTP Strategy: Comparison of Current Analysis with Existing Literature..	71
5.5 Strengths and Limitations of the Analysis.....	73
5.6 Conclusions	74
SECTION 6: REFERENCES	75
Appendix A: Description of SELECT and SIMPLE Studies	81
Appendix B: Defining an Acceptable NPV	85

LIST of FIGURES and TABLES

Table 1 *Risk Factors for VTE*

Table 2 *Two by two Contingency Table*

Table 3 *Test Results that Rule In or Rule Out VTE During Follow-up*

Table 4 *Wells' Criteria for DVT*

Table 5 *Wells' Criteria for PE*

Table 6 *Patient Characteristics*

Table 7 *Prevalence of VTE According to CPTP by Population*

Table 8 *Prevalence of VTE according to D-dimer level in Total Population*

Table 9 *Diagnostic Test Accuracy by Strategy for Patients with Low or Moderate CPTP*

Table 10 *Comparison of IAIT Strategy and Standard Strategy: Prevalence of VTE*

Table 11 *Comparison of IAIT Strategy and Median Age Strategy: Prevalence of VTE*

Table 12 *Comparison of IAIT Strategy and DAIT Strategy: Prevalence of VTE*

Table 13 *Comparison of CPTP Strategy and Standard Strategy: Prevalence of VTE*

Table 14 *Comparison of CPTP Strategy and IAIT Strategy: Prevalence of VTE*

Table 15 *Negative Predictive Value and Utility in Patients with Suspected DVT and Suspected PE*

Table 16 *Negative Predictive Value with Increasing Prevalence of VTE among Patients with Low and Moderate CPTP*

Table A1 *Investigations Used during Follow-up in the SELECT and SIMPLE Studies*

Figure 1 *Relationship Between Age and D-dimer Threshold for the IAIT, DAIT and Median Age Strategies*

Figure 2 *Study Flow Diagram*

LIST of COMMON ABBREVIATIONS

CI	confidence interval
CPTP	clinical pre-test probability
CT	computed tomography
CTPA	computed tomographic pulmonary angiogram
CUS	compression ultrasound
DVT	deep vein thrombosis
ELISA	enzyme-linked immunosorbent assay
FEU	fibrinogen equivalent unit
DAIT	decreasing age, increasing threshold
IAIT	increasing age, increasing threshold
LR	likelihood ratio
NNT	number needed to test
NPV	negative predictive value
OR	odds ratio
PE	pulmonary embolism
PPV	positive predictive value
VTE	venous thromboembolism
V/Q	ventilation/perfusion

GLOSSARY

<i>CPTP</i>	Probability of disease based on clinical assessment (history and physical examination) of the patient
<i>CPTP Strategy</i>	Method of selecting a D-dimer threshold where a higher D-dimer threshold (1000ug/L) is used in patients with low CPTP and the standard threshold (500ug/L) is used in patients with moderate CPTP
<i>Criterion standard</i>	Test (or group of tests) accepted as having the highest accuracy for disease against which other tests can be compared
<i>DAIT Strategy</i>	Method of selecting a D-dimer threshold where the D-dimer threshold is highest in young patients and lowest in older patients
<i>Diagnostic accuracy</i>	Ability of a test to correctly identify patients with and without disease
<i>Diagnostic accuracy study</i>	Study of how well a new test distinguishes patients with and without disease compared with the criterion standard among patients with suspected disease
<i>IAIT Strategy</i>	Method of selecting a D-dimer threshold where the threshold is lowest in young patients and highest in older patients
<i>Isolated distal DVT</i>	Deep vein thrombosis of the leg involving the deep or muscular veins of the calf but not involving the popliteal or more proximal deep veins
<i>Management study</i>	Study documenting the long-term clinical outcomes of patients managed according to the results of a new diagnostic test
<i>Median Age Strategy</i>	Method of selecting a D-dimer threshold where the threshold is set equal to the median age of patients over 50 years multiplied by 10
<i>Negative predictive value</i>	Proportion of patients with a negative test result who do not have disease
<i>Positive predictive value</i>	Proportion of patients with a positive test result who have disease
<i>Proximal DVT</i>	Deep vein thrombosis of the leg involving the popliteal or more proximal deep veins

<i>Sensitivity</i>	Proportion of patients with disease who have a positive test result
<i>Serial proximal CUS</i>	Repeated ultrasound examinations of the proximal deep veins of the leg, with the second examination usually done within 6-8 days of the initial examination
<i>Specificity</i>	Proportion of patients without disease who have a negative test result
<i>Strategy</i>	Method of D-dimer interpretation
<i>Threshold</i>	Level above which a test is categorized as positive and below which a test is categorized as negative
<i>Utility</i>	Proportion of patients undergoing a test in whom VTE is ruled in or ruled out without the need for further testing

DECLARATION OF ACADEMIC ACHIEVEMENT

The content of this thesis was completed by Sarah Takach Lapner. It is recognized that Dr. Lori-Ann Linkins, Dr. Shannon Bates, Dr. Clive Kearon, Dr. Alfonso Iorio, Dr. Roman Jaeschke and Jim Julian contributed preliminary data, as well as advice and direction on the research process and on the completed thesis. Their contributions are much appreciated.

SECTION 1: OBJECTIVES

1.1 General Objective

To determine the optimal way of selecting the D-dimer threshold in order to maximize the proportion of patients who can have venous thromboembolism (VTE) safely excluded by D-dimer testing combined with clinical pre-test probability (CPTP).

1.2 Specific Objectives

I will focus on two established strategies of selecting the D-dimer threshold: the Increasing Age, Increasing Threshold (IAIT) Strategy and the CPTP Strategy.

(1) To determine if the IAIT Strategy is a valid approach to categorizing D-dimer results as positive or negative.

The IAIT Strategy is known to increase the specificity of D-dimer testing compared with the Standard Strategy of D-dimer interpretation. I will compare the diagnostic accuracy of the IAIT Strategy with two other strategies of adjusting the D-dimer threshold: the Decreasing Age, Increasing Threshold (DAIT) Strategy and the Median Age Strategy. This comparison will allow us to determine whether the increase in specificity of the IAIT Strategy is due to using a higher D-dimer threshold specifically in the elderly or whether it is simply due to using a higher D-dimer threshold in a proportion of patients.

(2) To determine if the CPTP Strategy is a better approach to categorizing D-dimer results as positive or negative than the IAIT Strategy.

It has been established that the CPTP Strategy also increases the specificity of D-dimer testing. I will compare the CPTP Strategy to the IAIT Strategy to determine whether the CPTP Strategy results in a higher proportion of patients in whom VTE can be ruled out, and whether the CPTP Strategy is safer than the IAIT Strategy.

SECTION 2: STUDY BACKGROUND

VTE is the collective term used for deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT usually starts in the calf and then extends proximally. Pieces of a DVT can break free and travel to the lungs to cause PE. Therefore, DVT and PE can be thought of as different stages of VTE.

The symptoms that arise due to VTE are non-specific and less than one in five patients with suspected VTE will have the diagnosis confirmed by objective testing. The purpose of this thesis is to identify the most efficient way of using a blood test, the D-dimer, to exclude VTE.

2.1 Risk Factors for and Natural History of VTE

2.1.1 Risk Factors for VTE

The combination of hypercoagulability, vessel wall injury and stasis, known as Virchow's triad, results in VTE. Risk factors for VTE are known to result in one or more of these components.¹ Strong risk factors for VTE (5-fold or greater increase in risk; i.e. odds ratio [OR] ≥ 5) include recent surgery, malignancy and trauma, while weaker risk factors (less than 5-fold increase in risk; OR < 5) include immobility, obesity and estrogen hormone therapy (Table 1).^{1, 2} Most VTE (about three quarters) are associated with obvious risk factors. In these cases, the patient is said to have a "provoked" VTE. Often more than one risk factor can be identified in a patient with provoked VTE, for example hospitalization and malignancy.³ The combined effect of multiple risk factors is at least additive in

predisposing to VTE. The remainder of VTE (about one quarter) occur in the absence of an apparent risk factor. These patients are said to have an “unprovoked” VTE.

Table 1
Risk Factors for VTE

Major Risk Factors (OR ≥ 5)	
<i>Intrinsic</i>	Age >70 Previous VTE
<i>Acquired</i>	Surgery: orthopedic or requiring general anesthesia for >30 minutes Major trauma Hospitalization Paralysis Malignancy Cancer chemotherapy Heparin induced thrombocytopenia Antiphospholipid antibody syndrome
Minor Risk Factors (OR < 5)	
<i>Intrinsic</i>	Hereditary thrombophilia
<i>Extrinsic</i>	Prolonged immobility Estrogen therapy Pregnancy and puerperium Obesity

2.1.2 Natural History of VTE

The majority of DVT begin in the veins of the calf, and are known as isolated distal DVT. Some, but not all, isolated distal DVT will propagate to involve the proximal veins (popliteal or more central). In patients with symptomatic distal DVT who do not receive therapeutic anticoagulation, about a third extend to the proximal veins. Extension of distal DVT usually occurs within one week.^{4, 5} The

proportion of distal DVT that extend is even lower for asymptomatic distal DVT.⁶

DVT usually do not cause symptoms (e.g. pain and swelling) unless the thrombosis involves the proximal veins: about two thirds of DVT diagnosed in symptomatic patients involve the proximal veins whereas only a quarter of DVT diagnosed in asymptomatic postoperative patients using sensitive screening tests, such as venography, involve the proximal veins.^{7, 8}

PE usually occurs after a DVT breaks apart, travels with the venous return and lodges in the lung. The risk of PE is higher in patients with proximal DVT than in patients with isolated distal DVT. High probability ventilation perfusion lung scans are found in thirty to fifty percent of patients with documented proximal DVT whereas high probability ventilation perfusion lung scans are found in only about 10% of patients with isolated distal DVT.^{9, 10}

Thirty to 50% of patients with untreated symptomatic VTE will experience recurrent VTE within the subsequent three months.^{11, 12} VTE can cause serious adverse health outcomes. Pulmonary embolism is rapidly fatal in 10% of patients and is the third leading cause of cardiovascular death after heart attack and stroke.^{13, 14} A further 5-10% of PE are associated with hypotension at presentation, which is associated with a short term mortality rate of 50%.¹⁵ The severity of symptoms that occur because of PE depend not only on the size and location of the thrombi but also on the presence of other respiratory comorbidities and the cardiovascular reserve of the patient.^{14, 16}

2.1.3 Impact of Anticoagulation on Natural History of VTE

Treatment with anticoagulation reduces the risk of thrombus extension and recurrent VTE. Barritt and Jordan performed a randomized trial of anticoagulation versus no anticoagulation in patients with PE in 1960. This study showed a dramatic reduction in recurrent PE with anticoagulation (0/16 recurrences) versus no anticoagulation (10/19 recurrences, half of which were fatal).¹¹ Hull et al compared treatment with therapeutic intensity vitamin K antagonists to treatment with low dose subcutaneous heparin therapy and found a similar dramatic reduction in recurrent VTE in patients receiving therapeutic anticoagulation (0/17) compared with patients receiving only low dose therapy (9/19).¹² A low rate of recurrent VTE in patients receiving adequate treatment was also shown in a systematic review of studies in which all patients received therapeutic anticoagulation: the pooled recurrence rate was 4% during the first three months and was similar between patients initially presenting with DVT and patients initially presenting with PE.¹⁷ Therefore, acute anticoagulation is very effective in patients with DVT and PE, reducing the risk of progression by about 80%.

2.2 Diagnosis of VTE

The substantial mortality associated with PE and the understanding that PE is common in patients with proximal DVT underscores the importance of diagnosing and treating patients with proximal DVT and PE. Before outlining the tests used

to diagnose DVT and PE, it is worthwhile to consider the types of studies that are performed to assess diagnostic tests for VTE.

2.2.1 Study Designs Used to Assess Diagnostic Tests for VTE

New diagnostic tests for VTE are required to have an advantage over existing tests, such as being easier to perform or having lower cost. Before a new diagnostic test can be used in practice, however, its diagnostic accuracy and safety must be evaluated. Two types of study designs are commonly used to assess diagnostic tests for DVT and PE: *diagnostic accuracy studies* and *management studies*.

Diagnostic Accuracy Studies

Diagnostic accuracy studies evaluate how well a diagnostic test identifies VTE. In an accuracy study, patients undergo testing with both the new test and the criterion standard. The criterion standard is defined as a test or group of tests that is accepted as having the highest accuracy for detecting disease.¹⁸ The criterion standard test is assumed to correctly identify the presence or absence of disease. Accuracy studies allow calculation of the sensitivity and specificity, positive and negative predictive values and positive and negative likelihood ratios of the new test (see section 2.2.2). Accuracy studies can be prospective: patients with suspected disease undergo the new test and the criterion standard at the same time. Accuracy studies can also be retrospective: the new test is performed on

stored biologic samples and compared with previously collected data on the criterion standard.

Management Studies

Tests for VTE that appear to be accurate for VTE are then evaluated in a management study. Management studies determine if using the new test to make management decisions is associated with safe clinical outcomes. For example: if the diagnostic test indicates that VTE is absent, further diagnostic testing is withheld and patients are followed prospectively to determine if they remain well or if progressive or recurrent VTE occurs. Management studies allow calculation of the negative predictive value (NPV) of the test, which is the proportion of patients with a negative test who do not experience progressive or recurrent disease during follow-up (see section 2.2.2). Management studies are prospective and can be either a cohort study or a randomized trial. With a cohort study, the new diagnostic strategy is evaluated and outcomes are compared with historical controls or expectations. With a randomized trial, both the new and the old diagnostic strategies are evaluated, and outcomes with the two strategies are compared. When performed as a randomized trial, management studies represent the final stage of diagnostic test evaluation, as they allow the comparison of the ultimate health outcomes of individuals managed using the new test to the health outcomes of individuals managed according to the existing standard of care.¹⁹

Management studies also offer the opportunity to measure other aspects of a new diagnostic test, such as cost or frequency of complications related to the diagnostic test; for example, nephrotoxicity with studies that require intravenous contrast dye.

2.2.2 Diagnostic Accuracy Parameters

The ability of a test to correctly identify patients with and without disease is termed diagnostic accuracy. The diagnostic accuracy of a dichotomous test (i.e. one with a positive or negative result) can be summarized in a 2x2 table that divides the test result into four categories: true positives, false positives, true negatives and false negatives (Table 2). From the 2x2 table, several parameters can be calculated that together describe the diagnostic accuracy of the test.

Table 2: 2 x 2 Contingency Table

		Criterion Standard		
		<i>Disease Present</i>	<i>Disease Absent</i>	
New Test	<i>Test Positive</i>	<i>a</i>	<i>b</i>	# Patients with positive test results
	<i>Test Negative</i>	<i>c</i>	<i>d</i>	# Patients with negative test results
		# Patients with disease	# Patients without disease	Size of population <i>n</i>

a = true positives; *b* = false positives; *c* = false negatives; *d* = true negatives

Sensitivity and Specificity

Sensitivity (Se) is the proportion of patients with disease who have a positive test, and specificity (Sp) is the proportion without disease who have a negative test:

$$Se = \frac{a}{a + c} \text{ and } Sp = \frac{d}{b + d}$$

Sensitivity and specificity describe the probability of a test outcome given the presence or absence of disease.

A test with continuous results (e.g. D-dimer) can be transformed into a test with dichotomous results by setting a threshold above which the test is considered positive. Sensitivity and specificity of the test can then be calculated. If the threshold is changed, the sensitivity and specificity of the test will also change.

The relationship between sensitivity and specificity for tests with continuous results can be summarized using a receiver operating characteristic (ROC) curve.

The ROC curve plots sensitivity against one minus specificity. These curves illustrate the trade off in sensitivity and specificity that occurs when the threshold that defines a positive test is altered.²⁰ As the threshold that defines a positive test increases, sensitivity decreases while specificity increases. As the threshold that defines a positive test decreases, sensitivity increases while specificity decreases. While both high sensitivity and specificity are desired characteristics of a diagnostic test, often one parameter is clinically more important depending on whether the test is used to rule in or rule out disease or both. For example, high sensitivity is arguably more important than high specificity for tests that rule out disease where the goal is to minimize the number of false negative results.

Likelihood Ratios

A likelihood ratio (LR) is calculated as the proportion of sick individuals with a particular test result divided by the proportion of well individuals with the same test result. For tests with a dichotomous outcome, LRs are expressions of the sensitivity and specificity of the test.²¹ For example, in the 2x2 configuration of Table 2, a positive LR is calculated as sensitivity divided by one minus specificity²²:

$$LR^+ = \frac{Se}{1-Sp} = \left(\frac{a}{a+c} \right) / \left(\frac{b}{b+d} \right)$$

LRs allow us to calculate the probability of disease associated with a positive or negative test result (i.e. post-test probability) if we know the probability of disease before diagnostic testing (i.e. pre-test probability). This is achieved by 1) converting the pre-test probability to the pre-test odds; then 2) multiplying the pre-test odds by the LR to obtain a post-test odds; and then 3) converting the post-test odds to a post-test probability. The extent to which the post-test probability differs from the pre-test probability depends on how far the LR is from unity. A good diagnostic test will have a LR that is far from one (e.g. a LR for a positive test greater than 10 or a LR for a negative test less than 0.1) as LR in this range result in a large change in post-test probability. In contrast, poor diagnostic tests have LRs that are close to one and therefore only change the probability of disease slightly.²²

The process of diagnosis often involves performing sequential tests. To calculate the combined LR associated with a series of tests, the LRs for the

individual test results can be multiplied together, so long as the tests are independent.¹⁸ Two tests are independent of each other if their individual sensitivities and specificities do not change once the result of the other test is known. Test results that are concordant (i.e. test results which both increase the post-test probability of disease or both decrease the post-test probability of disease) are helpful to rule in or rule out disease.

Positive and Negative Predictive Values

Predictive values are the estimated post-test probability of disease given the test result. The positive predictive value (*PPV*) is the proportion of patients with a positive test result who have the disease, and the *NPV* is the proportion of patients with a negative test result who do not have the disease (Table 2):

$$PPV = \frac{a}{a + b} \text{ and } NPV = \frac{d}{c + d}$$

Predictive values therefore provide the information that is required to make management decisions in clinical practice.²³

Predictive values are dependent on the prevalence of disease (i.e. pre-test probability). For example, the NPV of a test increases as the prevalence of disease decreases. In populations with low disease prevalence, NPV may be high even for tests that have only a moderately low LR for a negative test (e.g. 0.3).

Measuring Clinical Usefulness of a Diagnostic Test

Tests are clinically useful when they allow a disease to be “ruled in” or “ruled out” in a high proportion of patients. There are several ways of quantifying the clinical usefulness of a test. Utility can be calculated as the proportion of patients who do not need further diagnostic testing once the results of the test under study are known. As an example, for a test where patients with a negative result have disease ruled out without the need for further testing and patients with a positive result need further investigation, the utility has been defined as the number of negative test results divided by the total population.^{24, 25} Number needed to test (NNT) to rule in or rule out disease is another way to express clinical usefulness of a test and can allow comparisons between study populations.²⁵ NNT is calculated as the reciprocal of the proportion of patients with negative results.

2.2.3 Testing for VTE in Clinical Practice

The goal of diagnostic testing for VTE is to identify which patients should be treated and which should have anticoagulation withheld. When VTE is suspected, diagnostic testing is performed until the post-test probability is either 1) high enough that there is consensus that patients should be treated, or 2) low enough that there is consensus that patients should not be treated. There is consensus that a post-test probability of greater than 85% justifies treatment for VTE without further testing. In patients with high CPTP and a high probability ventilation perfusion lung scan, 85% have PE; this supports using a post-test probability of

85% to justify treatment.²⁶ There is consensus that a post-test probability of 2% or less for developing progressive or recurrent VTE in the next three months justifies not treating for VTE. This criterion has been used in management studies that have evaluated the safety of various combinations of test results to rule out VTE. It is also supported by the finding that patients with a probability of PE of 2% or less are more likely to be harmed by further testing (i.e. from adverse effects of computed tomographic pulmonary angiography) than benefit from the information obtained from the test.²⁷ If the post-test probability of VTE is less than 85% but greater than 2%, additional diagnostic testing is required, with the goal of obtaining a post-test probability of greater than 85% or less than 2%.

Most tests for DVT and PE are insufficiently powerful to rule in and rule out VTE on their own. Therefore, most patients require more than one diagnostic test to rule in, or rule out, VTE. Table 3 outlines test results that are diagnostic for VTE.

The first step in diagnostic testing for VTE involves making a clinical assessment of the probability of VTE. What tests follow after the clinical assessment depend on the estimated probability of disease, as well as the comorbid conditions of the patient.²⁸

Table 3

*Test Results that Rule In or Rule Out VTE during Follow-up**

Diagnostic for DVT
Venous Ultrasound: new non-compressible segment of the proximal leg veins on initial or repeat CUS at 6-8 days Venography: intraluminal filling defect
Excludes DVT
CPTP: Low CPTP and negative ELISA (threshold 500ug/L), latex agglutination (threshold 500ug/L) or qualitative D-dimer D-dimer: negative ELISA test (threshold 500ug/L) Venous Ultrasound: (a) fully compressible proximal leg veins on initial <i>and</i> repeat CUS at 6-8 days <i>or</i> (b) fully compressible proximal leg veins on initial CUS <i>and</i> low CPTP for DVT <i>or</i> (c) fully compressible proximal leg veins on initial CUS <i>and</i> negative moderately sensitive D-dimer Venography: All deep veins seen and no intraluminal filling defects
Diagnostic for PE
Ventilation-perfusion Lung Scan: (a) High probability scan <i>and</i> moderate or high CPTP <i>or</i> (b) Non-diagnostic scan <i>and</i> non-compressible segment of the proximal leg veins on initial or repeat CUS at 6-8 days CTPA: (a) Intraluminal filling defect involving a lobar or more central pulmonary artery <i>or</i> (b) Intraluminal filling defect involving a segmental pulmonary artery <i>and</i> moderate or high CPTP <i>or</i> (c) Normal scan <i>and</i> non-compressible segment of the proximal leg veins on initial or repeat CUS at 6-8 days <i>or</i> (d) Non-diagnostic scan <i>and</i> non-compressible segment of the proximal leg veins on initial or repeat CUS at 6-8 days Pulmonary Angiography: intraluminal filling defect
Excludes PE
CPTP: Low CPTP and negative ELISA (threshold 500ug/L), latex agglutination (threshold 500ug/L) or qualitative D-dimer

D-dimer: negative ELISA test (threshold 500ug/L)

Ventilation-perfusion Lung Scan:

- (a) Normal *or*
- (b) Non-diagnostic scan *and* fully compressible proximal veins on CUS *and* low CPTP *or*
- (c) Non-diagnostic scan *and* fully compressible proximal veins on initial *and* repeat CUS at 6-8 days *or*
- (d) Non-diagnostic scan *and* full compressible proximal veins on CUS *and* negative moderately sensitive D-dimer

CTPA:

- (a) Negative good quality study *or*
- (b) Non-diagnostic scan and fully compressible proximal veins on CUS and low CPTP *or*
- (c) Non-diagnostic scan and fully compressible proximal veins on initial and repeat CUS at 6-8 days *or*
- (d) Non-diagnostic scan and full compressible proximal veins on CUS and negative moderately sensitive D-dimer

Pulmonary Angiography: normal

CPTP, clinical pre-test probability; CTPA, computed tomographic pulmonary angiogram; ELISA enzyme linked immunosorbent assay; DVT, deep vein thrombosis; PE, pulmonary embolism

* Adapted from Takach Lapner S, Linkins LA, Kearon C. *Venous Thromboembolism. In Practical Hemostasis and Thrombosis 3rd Edition*, Key N, Makris M, Lillicrap D Eds. Oxford: Wiley. In press

2.2.4 Diagnostic Tests for DVT and their Accuracy

CPTP Assessment

Clinical probability can either be an unstructured (gestalt) or a structured assessment using a validated prediction scoring system, such as the Wells' Score (Table 4). Clinical probability assessment incorporates evaluation of 1) the presence of typical signs and symptoms of DVT; 2) risk factors for VTE; and 3) whether an alternative diagnosis is as likely to account for the patient's symptoms. Clinical probability assessment divides patients into high (prevalence ~50%), moderate (prevalence ~20%) and low clinical probability of DVT (prevalence ~5%).²⁹ A dichotomized version of the Wells score has also been validated, in which patients are categorized as "unlikely" clinical probability of DVT or "likely" clinical probability.³⁰

Table 4: Wells' Criteria for DVT³⁰

Criterion		Points	
Active cancer (ongoing treatment or within previous 6 months or palliative)		1	
Paralysis, paresis or recent plaster immobilization of the lower extremities		1	
Bedridden > 3 days or major surgery within 4 weeks		1	
Localized tenderness along deep veins distribution		1	
Entire leg swollen		1	
Calf swelling 3cm > asymptomatic side (measured 10cm below tibial tuberosity)		1	
Unilateral pitting edema of symptomatic leg		1	
Dilated superficial veins (non-varicose)		1	
Previously documented DVT		1	
Alternative diagnosis as likely or more likely than DVT		-2	
Clinical Post-Test Probability Determined by Different Scoring Methods			
Method 1	Total Points	Method 2	Total Points
Low	≤ 0	Unlikely	≤ 1
Moderate	1 to 2	Likely	≥ 2
High	≥ 3		

D-dimer Blood Testing

D-dimer levels are almost always increased in patients with DVT, therefore, a negative D-dimer test can be used to rule out DVT. However, because a multitude of other conditions also increase D-dimer levels, a positive D-dimer is non-specific and cannot rule in DVT. D-dimer testing and its role in the diagnostic algorithms for DVT are discussed in detail in section 2.3.

Venography

Venography involves injecting radiopaque dye into a vein in the foot or ankle and taking radiographic images of the opacified deep veins. DVT is diagnosed if a constant filling defect is seen in the deep veins. It can detect both proximal and distal DVT. Traditionally, venography has been the criterion standard for the diagnosis of DVT, however, venography is expensive, technically difficult, potentially painful and can cause allergic reactions and nephrotoxicity. For these reasons, venography has been replaced as the criterion standard by non-invasive tests such as clinical assessment, D-dimer testing and single or repeated CUS that, when combined, have a high accuracy for DVT. In select cases where non-invasive testing is not diagnostic for DVT, venography can be still be used.

Venous Ultrasonography

Venous compression ultrasound (CUS) is an imaging technique that uses compression to bring the walls of a deep vein together. If there is thrombus in the lumen of a vein, it prevents the complete compression of the vein.

CUS is highly accurate for proximal DVT with a sensitivity of 97% and specificity of 94%.³¹ However, CUS limited to the proximal veins will not detect DVT that are confined to the calf veins (i.e. isolated distal DVT). Therefore proximal CUS must be combined with other diagnostic tests, such as CPTP assessment, D-dimer, or a repeat proximal CUS done about a week later (i.e. serial proximal CUS) in order to exclude distal DVT that propagates proximally.

CUS performs less well in detecting isolated distal DVT because CUS is more difficult to perform below the knee and is highly operator dependent. The sensitivity of CUS for distal DVT is only 73%, while the specificity remains good at 94%. However, the rate of VTE during follow-up after a negative whole leg ultrasound in patients with suspected DVT is 0.57%.³² Therefore, a single negative whole leg ultrasound has a NPV high enough to exclude VTE as a stand-alone test.²⁸

Combinations of Tests for the Diagnosis of DVT

Clinical Assessment and CUS: The accuracy of proximal CUS depends on how concordant the CUS results are with the clinical probability of disease. The post-test probability of DVT after an abnormal proximal CUS is approximately 100% for patients with high CPTP for DVT but only 63% in patients with low CPTP for DVT.³³ The post-test probability of DVT after a normal proximal CUS is less than 1% for patients with low CPTP for DVT but up to 24% for patients with high CPTP for DVT.^{28, 33} Therefore, the combination of a single negative proximal CUS and a low CPTP assessment can be used to safely exclude DVT.^{33, 34} However,

patients with a combination of a single negative proximal CUS and a moderate or high CPTP have a prevalence of DVT between 5% and 24% and therefore need further testing to rule-in or rule-out DVT.²⁸

D-dimer and Clinical Assessment or CUS: the combination of D-dimer and clinical assessment, or D-dimer and CUS, in the diagnostic algorithm for DVT is discussed in section 2.3.7.

2.2.5 Diagnostic Tests for PE and their Accuracy

CPTP Assessment

As for DVT, CPTP assessment can be unstructured (gestalt) or can follow a structured scoring system, of which the Wells' score and modified Geneva score, have been best validated (Table 5). Components of the clinical prediction rules include 1) the presence of the typical signs and symptoms of PE; 2) presence of risk factors; 3) symptoms of DVT; and 4) whether another diagnosis could account for the patient's symptoms. Using the Wells' scoring system, patients are divided into high (prevalence ~60%), moderate (prevalence ~25%) or low (prevalence ~5%) clinical probability of PE.³⁵ A dichotomized version of the Wells scoring system has also been validated.³⁶ Here patients are divided into unlikely (prevalence 8%) and likely (prevalence 35%) clinical probability of PE.³⁵

Table 5: Wells' Criteria for PE^{37, 38}

Criterion		Points	
Clinically suspected DVT		3	
Alternative diagnosis less likely than PE		3	
Heart rate > 100 beats/minute		1.5	
History of VTE		1.5	
Immobilization or surgery in the previous 4 weeks		1.5	
Malignancy		1	
Hemoptysis		1	
CPTP Determined by Different Scoring Methods			
Method 1	Total Points	Method 2	Total Points
Low	≤ 4	Unlikely	≤ 4
Moderate	4.5 to 6	Likely	≥ 4.5
High	≥ 6.5		

D-dimer Blood Testing

A negative D-dimer can be used to rule out PE but a positive test indicates that further testing is required. The use of D-dimer blood testing in the diagnosis of PE is discussed in section 2.3.7.

Pulmonary Angiography

Pulmonary angiography has been the criterion standard for diagnosis of PE. It is now rarely used because it is invasive and carries the risk of allergic reaction and nephrotoxicity due to radiocontrast dye. Pulmonary angiography has largely been replaced as the criterion standard for PE by non-invasive diagnostic tests, such as computed tomographic pulmonary angiogram, clinical probability assessment, D-dimer testing and CUS that, when combined, have a high accuracy for PE. Pulmonary angiography can still be used in cases where non-invasive testing is non-diagnostic.³⁹

Computed Tomographic Pulmonary Angiogram

Computed tomographic pulmonary angiogram (CTPA) is the most commonly used imaging test for PE. The overall accuracy of CTPA for PE is high with a sensitivity of 83% and specificity of 96%.⁴⁰ In patients with a negative CTPA, the rate of VTE diagnosed during follow-up is less than 2%, therefore the NPV for CTPA is 98%.⁴¹

The accuracy of CTPA is dependent on the location of the filling defect. The PPV of a defect in a main or lobar pulmonary artery is 97%, 68% for a segmental level artery and only 25% for a subsegmental level artery.⁴⁰ Isolated subsegmental defects are generally considered non-diagnostic and further testing is required to rule-in or rule-out VTE.

Ventilation Perfusion Lung Scanning

Ventilation perfusion (V/Q) lung scanning detects PE by identifying areas of lung that have compromised perfusion in the presence of normal ventilation. Scans with a total of 1.5 segmental defects are associated with a prevalence of PE of over 85% and are termed a “high probability” V/Q scan. Only half of patients with PE have a high probability scan.²⁶ A normal V/Q scan excludes PE but is found in only 25% of patients.^{38, 42} Therefore more than half of patients who are assessed with a V/Q scan will have a non-diagnostic scan and will require further diagnostic testing. Non-diagnostic scans are more frequent in older individuals and those with comorbid respiratory disease.

V/Q lung scanning has been largely replaced by CTPA. However, the V/Q scan still has a role in patients with contraindications to CTPA, such as those with renal failure. It delivers less radiation to the chest and it is preferred over CTPA in patients (such as young women) in whom the exposure to chest radiation should be minimized.

Combinations of Tests for the Diagnosis of PE

Clinical assessment and CTPA: The diagnostic accuracy of CTPA is dependent on whether the results of CTPA are concordant with the clinical probability of disease. In an accuracy study, the PPV of CTPA was 96% among patients with high CPTP for PE, but only 60% among those with low CPTP. Conversely, the NPV of CTPA was 96% in patients with low CPTP for PE but only 60% in patients with high CPTP.⁴⁰ However, as mentioned above, subsequent management studies have shown that the rate of VTE in patients with a negative CTPA who did not receive anticoagulation is only 1.3-2%.^{36, 43} Therefore, a negative good quality CTPA can be used to exclude PE in patients with low, moderate or high clinical probability of PE.⁴⁴

Clinical assessment and high probability V/Q lung scan: As for CTPA, the post-test probability of PE in patients undergoing V/Q lung scanning depends on the clinical probability of PE. The post-test probability of PE is greater than 88% for patients with moderate or high CPTP who have a high probability V/Q scan, and therefore this combination is sufficient to rule in PE. Patients with a low

probability of PE and a high probability V/Q scan require further testing as the prevalence of disease in these patients is only 56%²⁶.

Non-diagnostic V/Q lung scan and CUS: A non-diagnostic V/Q lung scan combined with a single negative CUS is insufficient to rule out PE. However, when also combined with a low CPTP assessment for PE, a non-diagnostic lung scan and a negative CUS is associated with a rate of VTE during follow-up of 1.7% to 2%.^{42, 45} Therefore, this combination is associated with a sufficiently low post-test probability to exclude PE. A non-diagnostic V/Q lung scan and negative CUS can also be combined with D-dimer testing and is described in section 2.3.7.

Clinical assessment and D-dimer testing: the combination of D-dimer and CPTP assessment in the diagnostic algorithm of PE is discussed in section 2.3.7.

2.3 Role of D-dimer in the Diagnosis of VTE

2.3.1 D-dimer Formation

D-dimer units are formed when cross-linked fibrin is broken down by plasmin. Each fibrin monomer contains a D domain on either end of the strand. During polymerization and cross-linking of fibrin, fibrin monomers join end to end to form long strands. The end-to-end arrangement of fibrin monomers brings D domains from two separate fibrin monomers into close proximity. The D domains are then covalently linked by activated factor XIII. During fibrinolysis, plasmin cleaves cross-linked fibrin, releasing the cross-linked D domains as a single unit, the D-dimer. The end products of plasmin-mediated digestion include one D-dimer

product for each fibrin monomer. D-dimer is therefore a marker of both clot formation and breakdown, as both processes are required for its formation.

2.3.2 Causes of an Elevated D-dimer Level

D-dimers are detectable in the circulation of healthy individuals, as small amounts of fibrinogen are converted to fibrin physiologically.⁴⁶ D-dimer levels are increased in almost all cases of acute VTE. However, D-dimer levels can also be increased during any process that increases fibrin production or breakdown. Such conditions include surgery, pregnancy, inflammation and cancer.⁴⁷ As a result, increased D-dimer levels are non-specific for acute VTE.

D-dimer levels have been shown to increase with age.^{48, 49} In a population cohort of healthy 1047 individuals, the upper 95th percentile of D-dimer level increased from 920ug/L in patients less than 50 years old to 2309ug/L in patients 70 years or older.⁵⁰

2.3.3 Determinants of D-dimer Level Among Patients with VTE

Among patients with VTE, D-dimer levels are higher among patients with a larger clot burden. In 107 patients diagnosed with DVT by venography, the median D-dimer in patients with popliteal or more proximal DVT was about three times higher than that in patients with isolated distal DVT.⁵¹ Similar results were obtained among 393 patients undergoing whole leg CUS for DVT.⁵² In the case of PE, the extent of vascular obstruction as detected by V/Q scanning or CTPA also

correlates with D-dimer levels. Patients with larger defects, such as those involving at least 50% of lung volume or a main pulmonary artery, had D-dimer levels that were about three times higher than patients with smaller defects, such as those involving less than 30% of total lung volume or only a segmental or subsegmental level artery.^{53 54} These studies highlight that the sensitivity of D-dimer testing is higher among patients with larger clot burden, in whom the need for treatment is most compelling, and poorer for patients with distal DVT or subsegmental PE where the need for treatment is less clear.

D-dimer levels fall with increasing duration of symptoms. In a cohort of 107 patients diagnosed with DVT, the D-dimer concentration was lower in patients with DVT who had symptoms for more than seven days compared with patients with a shorter duration of symptoms.⁵¹ D-dimer levels also fall rapidly after initiation of treatment. After 24 hours of heparin therapy, D-dimer levels were observed to fall by 25%.⁵⁵ Therefore, D-dimer testing is most accurate in patients who have symptoms for less than a week and who have D-dimer testing performed before initiation of therapy.

2.3.4 Measurement of D-dimer Level

The process of measuring D-dimer levels can be conceptually divided into two steps: 1) D-dimer fragments must be captured by monoclonal antibodies; and 2) the D-dimer/monoclonal antibody complexes must be detected and quantified. There are multiple types of D-dimer assays available, which differ in both the

target antigen of the monoclonal antibodies used to capture D-dimer, and the detection system used to quantify the presence of complexes.

D-dimer assays are either 1) quantitative, where the D-dimer level is reported as a continuous result or 2) qualitative, where the D-dimer result is reported as positive or negative. My thesis focuses on the use of quantitative assays in the diagnosis of VTE.

D-dimer assays report their results as a unit of mass per volume, such as micrograms per litre (ug/L). However, there are two different units used to describe D-dimer mass: 1) purified D-dimer units; or 2) fibrinogen equivalent units (FEU). FEU express the mass of D-dimer as the equivalent mass of fibrinogen that would be needed to produce the D-dimer in the sample; 1ug/L in D-dimer units is about equal to 2ug/L in FEU.⁵⁶

2.3.5 Categorization of D-dimer Results as Positive or Negative

D-dimer is measured as a continuous variable, the results of which are dichotomized into positive and negative results using a “threshold”. The threshold that defines a positive D-dimer test is not based on the distribution of D-dimer levels in the healthy population. Rather, the threshold that defines a positive D-dimer test is derived by comparing the distribution of D-dimer levels in patients with proven VTE to the distribution in patients in whom the diagnosis was suspected but excluded, and is selected to optimize use of the test to diagnose patients. Traditionally, a low threshold has been chosen in order to maximize the

sensitivity of the test. However, because D-dimer is a non-specific test, use of a low threshold results in a high frequency of false-positive results. D-dimer testing using a low threshold, therefore, is associated with a high NPV, but only a small proportion of patients with suspected VTE have a negative test.

2.3.6 Diagnostic Accuracy of D-dimer Assays

The diagnostic accuracy of D-dimer testing is determined by 1) the type of assay that is used; and 2) the threshold chosen to define a positive test. D-dimer assay types that are commonly used today include quantitative enzyme linked immunosorbent assays (ELISA), quantitative latex agglutination assays, and qualitative whole blood agglutination assays.

2.3.7 Standard Use of D-dimer in Clinical Practice

The value of D-dimer is based on its ability to help rule out VTE. D-dimer tests can be used to: 1) to rule out VTE as a stand-alone test; or 2) to rule out VTE in combination with other tests that do not have high enough NPV to exclude VTE on their own.²⁸

D-dimer as Stand-alone Test to Rule Out VTE

In a management study of 918 patients with suspected DVT or PE, a D-dimer less than 500ug/L using an ELISA was associated with a NPV of 99.3% (95% confidence interval [CI], 97.5 to 99.9%).⁵⁷ However, the D-dimer was negative in only 31% of patients. Therefore, D-dimer using an ELISA test with a threshold of

500ug/L can be used as a stand-alone test to rule out DVT and PE; however, a small proportion of patients will have a negative test.²⁸

Although this study used D-dimer to exclude VTE in patients of all CPTP categories, D-dimer is not routinely used to exclude VTE in patients with high CPTP for the following reasons: 1) a negative D-dimer has a lower NPV in high CPTP patients due to a higher prevalence of VTE; 2) the estimates of NPV for D-dimer are less precise in high CPTP patients as they were fewer in number compared with patients with low or moderate CPTP; and 3) D-dimer results are only rarely less than 500ug/L in patients with high CPTP because a large proportion of patients have thrombosis.

D-dimer in Combination with Other Assessment Modalities

A D-dimer less than 500ug/L using a latex agglutination assay or an ELISA combined with a low CPTP assessment is associated with a NPV of 99% for DVT and PE.^{29, 58,59} In patients with suspected DVT, a D-dimer < 500ug/L using an ELISA combined with a negative CUS has been shown to have a NPV of 99%.⁶⁰ In patients with suspected PE, a negative D-dimer test using a qualitative whole blood agglutination assay with a non-diagnostic lung scan and negative CUS is associated with a similarly high NPV.^{38, 42}

Scenarios where D-dimer Testing is Unlikely to be Useful

The specificity of D-dimer testing for VTE is particularly poor in patients with comorbidities that are known to increase D-dimer levels, such as after surgery, or

in patients with malignancy. Therefore, there is little use to performing D-dimer testing if a patient is likely to have a high D-dimer level in the absence of VTE.

2.3.8 Strategies to Improve Diagnostic Utility of D-dimer Testing

Increasing the D-dimer Threshold to Increase the Utility of D-dimer Testing

Increasing the D-dimer threshold will increase the proportion of patients with suspected VTE who will have a negative test. Strategies to improve the utility of D-dimer testing include increasing the threshold in 1) all patients; or 2) selectively in subgroups of patients. Each strategy of increasing the D-dimer threshold is associated with a gain in specificity at a cost of loss in sensitivity; however, it is unknown which strategy has the greatest gain in utility and specificity for the least cost in NPV.

Increasing the D-dimer Threshold in Some Patients Based on Age

The specificity of D-dimer testing decreases with increasing patient age. In 1029 patients with suspected PE who were evaluated with an ELISA assay (VIDAS DD with a threshold of 500ug/L), the specificity of D-dimer decreased from 67% in patients less than 40 years old to 30% in patients 70-79 years old and 10% in patients over 80.⁶¹ The clinical utility of measuring D-dimer levels in the elderly has therefore been questioned.

It has been proposed that a higher threshold should be applied to elderly patients in order to increase the specificity and clinical utility of D-dimer testing. Increasing the D-dimer threshold from 500ug/L to 700ug/L in patients over 70

years old increased the specificity of D-dimer testing from 20% to 30%. However, increasing the D-dimer threshold with age results in a loss in sensitivity: in patients aged 60 or more evaluated with an ELISA test, increasing the D-dimer threshold resulted in a decrease in sensitivity of 1% for every increase of 100ug/L above the standard 500ug/L threshold.⁶² When the D-dimer threshold was increased from 500ug/L to 800ug/L for patients 60-69 years old and 900ug/L for patients 70 years old or older, the NPV of D-dimer testing fell to from 99% to 93%.

Therefore, D-dimer testing using a higher threshold in older patients has insufficient sensitivity and NPV to exclude VTE as a stand-alone test.

The combination of using a higher D-dimer threshold in elderly patients with a low or moderate CPTP assessment appears to have high enough NPV to safely exclude VTE. In a retrospective analysis of 4 cohort studies of patients with suspected PE and low or moderate CPTP, Douma et al multiplied the individual patient's age by 10 to calculate the D-dimer threshold for patients 50 years old or older. A standard threshold of 500ug/L was used in patients younger than 50 years. I call this the *Increasing Age, Increasing Threshold (IAIT) Strategy*. The NPV of the strategy was 99.5%.²⁴

Data from 13 retrospective studies that used the IAIT Strategy of D-dimer interpretation combined with low or moderate CPTP assessment have been pooled in a meta-analysis. The pooled sensitivity of the IAIT Strategy was 97.8% (95% CI, 95.9 to 98.8%), only slightly lower than the sensitivity of using the standard threshold of 500ug/L in all patients (99.3%; 95% CI, 98.4 to 99.7%).⁶³

There was no significant decrease in sensitivity with increasing age. The specificity of the IAIT Strategy in patients over 50 years old was 48.8% (95% CI, 42.9 to 54.7%), higher than the specificity with the standard threshold of 36.1% (95% CI, 30.8 to 41.7%).

The IAIT Strategy was subsequently assessed in a prospective management study of 3324 patients with suspected PE, of whom 2898 had low or moderate CPTP of PE. The NPV of the IAIT Strategy was 99.7%.⁶⁴ PE was ruled out in an additional 337 (11.3%) patients using the IAIT Strategy compared with using the standard threshold of 500ug/L in all patients.

I, however, am sceptical of the logic of the IAIT Strategy. First, it is not known whether the increase in specificity of the IAIT Strategy compared with the use of the standard threshold is due to selectively using a higher threshold in the elderly or due to simply using a higher threshold in some patients (i.e. a higher average threshold). In addition, the prevalence of VTE tends to be higher in older patients, both in the general population and among patients investigated for VTE.^{61, 63} It is irrational to use a higher (and therefore less sensitive) threshold in patients with a higher prevalence of VTE because this should compromise the NPV.

Increasing the D-dimer Threshold in Some Patients Based on CPTP

The NPV of D-dimer testing using the standard threshold of 500ug/L is highest in patients with low CPTP because the prevalence of VTE is lowest in this subgroup of patients.⁶⁵ It has been shown that the NPV of D-dimer testing remains high in patients with low CPTP even when a higher and therefore less sensitive

threshold is used. Retrospective analyses have shown that the NPV of D-dimer testing is 98% or greater in patients with low CPTP even when the D-dimer threshold is doubled to 1000ug/L.^{25, 66-68} These studies have also demonstrated that in patients with low CPTP, using a higher D-dimer threshold was associated with an increase in specificity (50% to 75%) and the proportion of patients in whom VTE could be ruled out by D-dimer testing (40% to 55%).

Selectively using a D-dimer threshold of 1000ug/L to rule out DVT in patients with low CPTP while keeping the threshold at the standard level in patients with moderate CPTP (the *CPTP Strategy*) has been shown to be equally safe as using the standard threshold of 500ug/L in all patients. A randomized controlled trial of 1723 patients with suspected DVT compared the safety of a diagnostic management plan where the D-dimer threshold was adjusted according to the clinical probability of VTE (1000ug/L in low CPTP patients, 500ug/L in moderate CPTP patients and not used in high CPTP patients) to the use of the standard threshold of 500ug/L in all patients.⁶⁹ In patients in whom DVT was ruled out by CPTP assessment and D-dimer testing, there was no difference in the rate of VTE diagnosed during three months of follow-up between the two arms. Twenty-two percent more patients in the low CPTP group had DVT excluded by D-dimer testing using a D-dimer threshold of 1000ug/L (80%) compared with the standard threshold of 500ug/L (58%).

2.3.9 Comparison of Strategies to Improve Utility of D-dimer Testing

Both the IAIT and the CPTP Strategies of D-dimer interpretation have been shown to improve specificity and utility of D-dimer testing while maintaining a high NPV in patients with low or moderate CPTP. However, there are no analyses that have compared these strategies with each other or with other strategies of D-dimer interpretation, such as using a higher single threshold in all patients with low or moderate clinical probability. Therefore, it is unknown which strategy results in the greatest gain in specificity and utility while maintaining a high NPV. In section 3 and 4 of this work, I will describe the methods and results of an analysis designed to identify the optimal strategy of D-dimer interpretation. This analysis will answer the following two questions:

(1) Is the improvement in utility of D-dimer testing associated with the IAIT Strategy compared with the Standard Strategy simply due to using a higher threshold in some of the patients?

To address this question, I will compare the diagnostic accuracy of D-dimer testing using the IAIT Strategy in patients with two other strategies for increasing the D-dimer threshold. The first will use a single D-dimer threshold that is equal to the median age of patients over 50 years old multiplied by 10. This strategy will be called the *Median Age Strategy*. The second will vary the D-dimer threshold according to age, but in a manner opposite to the IAIT Strategy. Instead of using a low threshold in young patients and a higher threshold as patients get older, this strategy will use a high threshold in young patients and a lower threshold as

patients get older. This strategy will be called the *Decreasing Age, Increasing Threshold (DAIT) Strategy*. I am not proposing that the DAIT Strategy has the potential to be used in clinical practice. The only purpose of evaluating this strategy is to test the rationale of the IAIT Strategy. If the IAIT Strategy is valid, it should have much better specificity and utility than the DAIT Strategy (its opposite). If the IAIT Strategy is not valid, I expect that the accuracy and utility of the IAIT Strategy and the DAIT Strategy will be similar. Also, if the better specificity and utility of the IAIT Strategy compared with the Standard Strategy is just due to using a higher average D-dimer threshold, I expect that the specificity and utility of the IAIT Strategy and the Median Age Strategy will be similar.

(2) Is the diagnostic accuracy of the CPTP Strategy superior to the IAIT Strategy?

To test whether the diagnostic accuracy of the CPTP Strategy is superior to the IAIT Strategy, I will compare their accuracy and utility. I suspect that the NPV and utility of the CPTP Strategy will be better than the IAIT Strategy for the following reasons:

- a) The NPV of the CPTP Strategy is expected to be better because it uses a less sensitive threshold in a subset of patients who have a lower prevalence of VTE (low CPTP); by comparison, the IAIT Strategy uses a less sensitive threshold in patients who may have a higher prevalence of VTE.
- b) The utility of the CPTP Strategy is expected to be better because it uses a more specific D-dimer threshold in a greater proportion of patients than the IAIT

Strategy. Low CPTP patients (CPTP Strategy threshold 1000ug/L) usually comprise about two-thirds of patients; by comparison, only 25% of patients are over 75 years old (IAIT Strategy threshold 750ug/L) and usually no patients are over 100 years old (IAIT Strategy threshold 1000ug/L).

SECTION 3: METHODS

This thesis was a retrospective analysis of data from two studies. First, the SELECT study, a randomized trial, compared two diagnostic management strategies in patients with suspected DVT.⁶⁹ Second, the SIMPLE study, a prospective cohort study, evaluated a diagnostic management strategy in patients with suspected PE.⁷⁰ The data and banked blood samples from these two studies will be used to evaluate and compare the accuracy of different D-dimer-based diagnostic strategies for suspected VTE.

3.1 Study Hypotheses

- 1) The IAIT Strategy will not be associated with a higher NPV or utility compared with the DAIT Strategy and the Median Age Strategy. This would be evidence against using the IAIT Strategy.
- 2) The CPTP Strategy will be associated with as high a NPV, and a higher utility, compared with the Standard Strategy and the IAIT Strategy. This would be evidence in favour of using the CPTP Strategy.

3.2 Classification of Patients as VTE-positive or VTE-negative

All patients were categorized as VTE-positive or VTE-negative, according to a criterion standard which was a predefined composite of CPTP, D-dimer testing, diagnostic imaging and prospective follow-up and is described in Appendix A. VTE-positive patients were defined as those with VTE diagnosed by imaging

studies either a) on the day of presentation or b) during follow-up. VTE-negative patients were defined as those who had VTE excluded on the day of presentation^{*}, were not treated for VTE and did not have VTE during 3 months of follow-up.

3.3 D-dimer Assay

Using a commercial laboratory, quantitative D-dimer levels were measured on banked blood samples taken from patients at the time of enrolment in the SELECT and SIMPLE studies. D-dimer was measured using the STA-Liatest assay, a quantitative rapid latex agglutination immunoassay (Diagnostica Stago, Asnières, France). D-dimer levels using this assay range from 210 ug/L (lower limit of detection) to over 50,000ug/L.

3.4 Eligibility Criteria

3.4.1 Inclusion Criterion

Patients were enrolled in the SELECT or SIMPLE studies.

3.4.2 Exclusion Criteria

Patients were excluded if they had any of the following:

1. Inpatient at time of enrolment;

^{*} VTE excluded on day of presentation by one of the following combinations: 1) low or moderate CPTP and negative D-dimer; or 2) positive D-dimer and negative imaging

2. Insufficient data recorded to determine the Wells score for DVT (SELECT study) or the Wells score for PE (SIMPLE study) at enrolment;
3. Age at enrolment not recorded;
4. No banked blood sample available or unable to measure STA-Liatest D-dimer level;
5. Patient not diagnosed with VTE at enrolment, no VTE diagnosed during follow-up, and follow-up was not completed (i.e. lost to follow-up).

Rationale for Excluding Inpatients from the Current Analysis

The specificity of D-dimer has been shown to be poor among inpatients because of comorbidities that increase D-dimer levels, such as infection or surgery.⁷¹ For this reason, D-dimer is generally not used to diagnose VTE in inpatients. In addition, inpatients accounted for only 10% of patients in the SELECT study and 14% of patients in the SIMPLE study. For these two reasons, I felt it was appropriate to exclude inpatients from the current analysis. I made this decision before doing any analysis.

Rationale for Excluding Patients Lost to Follow-up from the Current

Analysis

I excluded patients who were lost to follow-up because I was uncertain if they were VTE-positive or VTE-negative (i.e. they were not evaluated with the criterion standard for diagnosis of VTE). Only 19 of 1723 patients from the SELECT study and none of 808 in the SIMPLE study were lost to follow-up.

3.5 Strategy Definitions

Five different strategies were used to classify D-dimer levels as positive or negative among patients with low or moderate CPTP. Patients with high CPTP were not included in the strategies for the reasons outlined in section 2.3.7.

3.5.1 Standard Strategy (single threshold)

In the Standard Strategy, all patients with a D-dimer of less than 500ug/L were classified as D-dimer negative and all patients with a D-dimer of 500ug/L or more were classified as D-dimer positive.

3.5.2 Increasing Age, Increasing Threshold (IAIT) Strategy (variable threshold)

In the IAIT Strategy, a threshold of less than 500ug/L was used to define a negative test for patients 50 years old or less, and threshold of less than the patient's age multiplied by 10 was used for patients over 50 years. For example, for a patient who is 78 years old, the threshold was less than 780ug/L (i.e. 78 x10).

3.5.3 Median Age Strategy (single threshold)

In the Median Age Strategy, I used the same threshold in all patients: the median age of patients older than 50 years (i.e. 68 years in the current analysis) multiplied by 10 (i.e. 680ug/L).

3.5.4 Decreasing Age, Increasing Threshold (DAIT) Strategy (variable threshold)

In the DAIT Strategy, the relationship between age and D-dimer threshold was the opposite of that used in the IAIT Strategy. This was accomplished in two parts:

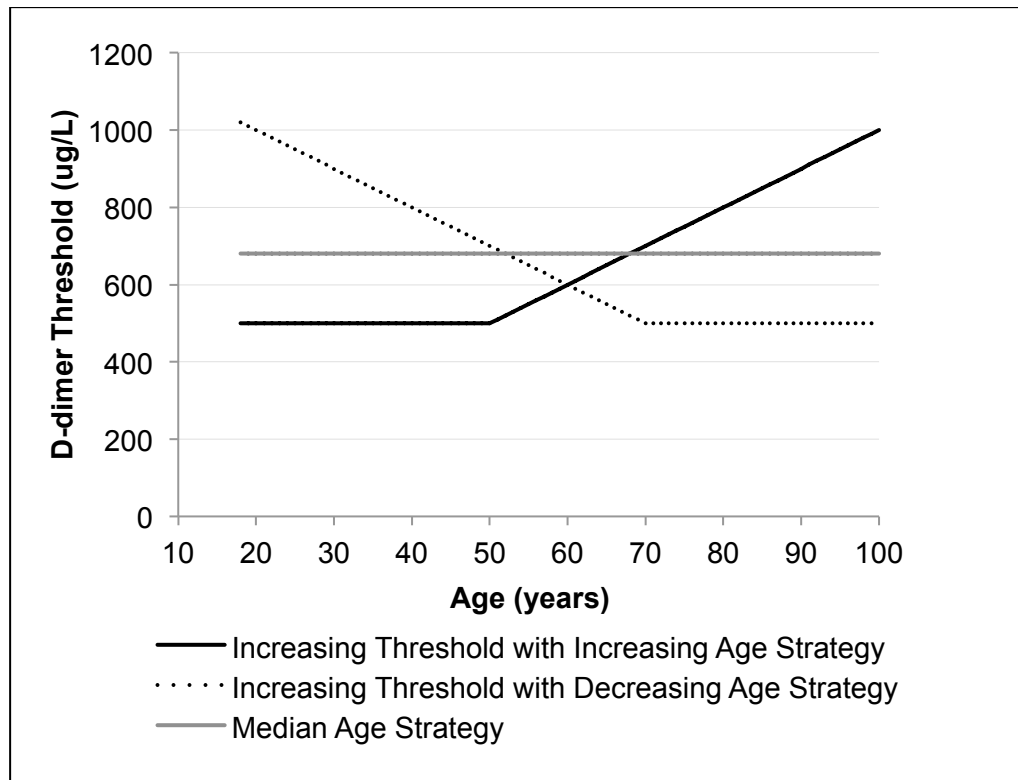
1. With the IAIT Strategy, a threshold of 500ug/L was used for all patients 50 years old or younger, who were 33% of patients. As the opposite, the DAIT Strategy used a threshold of 500ug/L for the oldest 33% of patients. This corresponded to using a threshold of 500ug/L in patients 70 years old or older.
2. For patients less than 70, a progressively higher threshold was used as patient age decreased according to the following: $Threshold = 500 + [(70 - patient\ age) \times 10]$. For example, the D-dimer threshold for a 40-year-old patient is $500 + [(70 - 40) \times 10]$, or 800ug/L. The slope of the relationship between age and D-dimer threshold is the opposite of that used in the IAIT Strategy.

The IAIT, DAIT and Median Age strategies are shown graphically in Figure 1.

3.5.5 CPTP Strategy (variable threshold)

In the CPTP Strategy, the D-dimer threshold was 1000ug/L for patients with low CPTP, and 500ug/L for patients with moderate CPTP.

Figure 1
Relationship between Age and D-dimer Threshold for the IAIT, DAIT and Median Age Strategies



Note: The CPTP Strategy cannot be depicted on this graph because the threshold does not vary with age.

3.6 Data Analysis and Statistics

3.6.1 Diagnostic Accuracy

A 2x2 table was assembled for each strategy according to whether the D-dimer was positive or negative, and whether the patient had VTE or not. Estimates of sensitivity, specificity, NPV and negative LR were calculated for each strategy table. Utility was calculated as the proportion of patients with a negative D-dimer. In addition, the number needed to test (NNT) to exclude one episode of VTE was calculated as the reciprocal of the utility (e.g. with a utility of 33%, the NNT to

exclude one VTE is 3).²⁵ The mean D-dimer threshold used in each strategy was calculated from the thresholds that were used for each patient with that strategy.

Exact confidence intervals for estimates expressed as proportions were calculated using the Wilson Score method.⁷² Sensitivity, specificity and utility were compared between strategies using a McNemar's test for correlated proportions. I compared the NPVs between strategies using Kosinski's weighted generalized score statistic.⁷³ While I was primarily focused on the comparison of NPV between strategies, I also judged whether the NPV of the individual strategies was acceptable. I considered the NPV of the individual strategies to be acceptable if the lower 95% CI around the point estimate was not lower than 98% (the rationale for this value is presented in Appendix B). Comparisons between the mean D-dimer thresholds for the strategies was performed using a paired two-sample t-test. Comparisons were considered statistically significant if the two-sided p-value was less than 0.05. No adjustments were made for multiple testing. All analyses were performed using SPSS version 20 (IBM Armonk, New York) and OpenEPI version 3.0.1. The most important comparisons were the following:

1) IAIT Strategy versus DAIT Strategy:

- a) NPV: I anticipated no difference between the two strategies;
- b) Utility: I anticipated no difference between the two strategies.

2) CPTP Strategy versus IAIT Strategy:

- a) NPV: I anticipated no difference or better NPV with the CPTP Strategy;

- b) Utility: I anticipated better utility with the CPTP Strategy.

3.6.2 Predefined Subgroups

Patients with Suspected DVT versus PE

In current practice, the same D-dimer threshold is used to exclude DVT and PE. This is consistent with sensitivity and specificity of D-dimer assays having been shown to be similar in patients with PE and DVT.^{74, 75} Therefore, the primary analysis was performed on the combined populations of patients with suspected DVT (SELECT study) and suspected PE (SIMPLE study). However, I also determined the accuracy indices separately for patients with suspected DVT and patients with suspected PE. For each strategy, I compared the NPV and utility between subgroups to test the appropriateness of combining the two groups of patients as a single population.

3.7 Methodological Issues

3.7.1 Differential Verification Bias

Bias in diagnostic studies results in an artificial increase or decrease in diagnostic accuracy of the test under investigation. Differential verification bias may occur when different reference tests are used to decide if patients are VTE-positive or VTE-negative. Some reference tests are more likely to classify patients as VTE-positive (or VTE-negative) than other reference tests. For example, in patients with suspected PE, CTPA at initial presentation is expected to detect almost all patients with a PE. However, if PE is considered excluded without doing a CTPA

at initial presentation (e.g. based on a low CPTP assessment and a negative D-dimer) patients will only be considered as VTE-positive if, having had anticoagulation withheld, they are diagnosed with VTE during follow-up. In this example, patients with symptomatic PE that do not have a CPTA done at presentation and who do not progress or recur during follow-up will be categorized as VTE-negative. As only 30 to 50% of PE are expected to progress without anticoagulation,^{11, 12, 76} not having performed CTPA at presentation is expected to artificially (and systematically) inflate the NPV of the new diagnostic test that is being evaluated.

In the current analysis, patients with a negative D-dimer according to the strategies were evaluated with one of two reference standards: 1) diagnostic imaging plus follow-up or 2) follow-up alone. The diagnostic accuracy of diagnostic imaging plus follow-up is likely better than follow-up alone. Bias in the comparison of the strategies may have occurred if the proportion of patients with a negative D-dimer evaluated with each reference standard was different between strategies.

To assess for the potential of differential verification bias in the current analysis, I determined the proportion of patients with a negative D-dimer with each strategy who had VTE excluded by initial imaging (i.e. CPTA or CUS) and the proportion who had VTE excluded by follow-up without initial imaging, and compared these proportions. If the proportions were similar across the strategies,

I concluded that it was unlikely that differential verification would have biased the comparisons of NPV between the strategies.

To account for the possibility that lack of initial imaging may have underestimated the presence of VTE-positive patients, I also performed a sensitivity analysis where the rate of VTE as detected by follow-up alone was adjusted. It is plausible that the rate of initial VTE among those investigated with follow-up alone was two to three times higher than the rate of VTE observed during the course of follow-up. To account for this, the number of events detected by follow-up alone was tripled to see if this changed the conclusions about the comparative accuracy of the strategies.

3.7.2 Effect of Prevalence on Estimates of NPV

As discussed in section 2.2.2, the NPV of a strategy is dependent on the prevalence of VTE. I explored the effect of prevalence on the NPV for the strategies by simulating two populations of patients, one with a prevalence of VTE of 15% and one with a prevalence of 20%. I generated a new 2x2 table for each strategy in the two simulated populations using the sensitivity and specificity calculated from the study population. The NPV of each strategy in the simulated populations was then calculated.

3.8 Safety and Ethical Considerations

The ethical considerations for this study include confidentiality and autonomy.

The data that was analyzed for the current analysis was collected for the SELECT and SIMPLE studies. No new patient data was collected from the patients themselves or their medical charts. Research Ethics Board approval was obtained for both the SELECT and SIMPLE studies. To ensure confidentiality, all identifying patient data was removed before I had access to the data and patients were identified by study number only. Access to the database was also password protected. Patient autonomy was preserved during the original studies by ensuring all patients provided informed consent before enrolling in the original studies. Furthermore, patients provided consent for the storage of blood samples taken during the course of the original study and for further analysis of these samples with their clinical data in future studies.

SECTION 4: RESULTS

4.1 Description of the Study Population

A total of 1774 outpatients with suspected VTE were included in the study population, 1095 from the SELECT study and 679 from the SIMPLE study (Figure 2). The mean age was 58 years, and 68% of the cohort was 50 years old or older (Table 6). The prevalence of VTE was 5.4% in the SELECT study cohort, 12.0% in the SIMPLE study cohort, and 8.0% overall. The prevalence of VTE was 4.4% in patients with low CPTP, 10.2% in patients with moderate CPTP and 25.6% in patients with high CPTP. The prevalence of VTE by CPTP category was lower in the SELECT study cohort than the SIMPLE study cohort, however the likelihood ratios for VTE associated with each CPTP category were consistent between the two studies (Table 7).

Figure 2: Study Flow Diagram

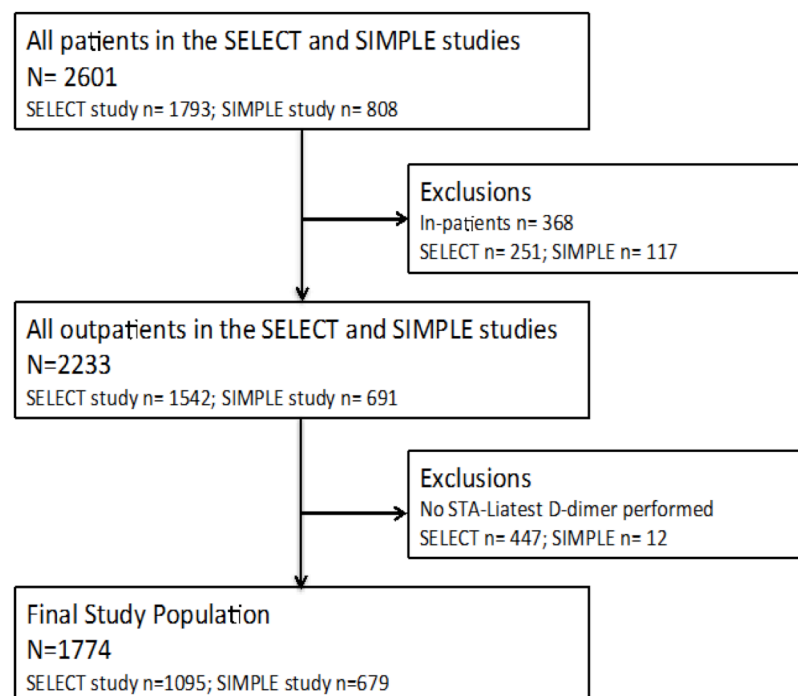


Table 6: Patient Characteristics by Population

Characteristic	SELECT (n= 1095)	SIMPLE (n= 679)	Total (n= 1774)
Age, mean (SD), years	61 (16)	54 (19)	58 (18)
Male, n (%)	417 (38)	205 (30)	622 (35)
Clinical pre-test probability: n (%)			
Low	535 (49)	499 (74)	1034 (58)
Moderate	476 (43)	139 (20)	615 (35)
High	84 (7.7)	41 (6.0)	125 (7.1)
Classified as VTE-positive: n (%)	59 (5.4)	82 (12)	141 (8.0)
VTE diagnosed at initial assessment	55 (5.0)	78 (11)	133 (7.5)
VTE diagnosed during follow-up*	4 (0.4)	4 (0.6)	8 (0.5)

*Includes only VTE diagnosed during follow-up among patients classified as VTE negative at initial assessment; SD, standard deviation; VTE, venous thromboembolism

Table 7: Prevalence of VTE According to CPTP by Population

CPTP	Low	Moderate	High
Total Population			
Frequency (%)	1034 (58.3)	615 (34.7)	125 (7.1)
Prevalence* (%)	46/1034 (4.4)	63/615 (10.2)	32/125 (25.6)
Likelihood Ratio	0.54	1.32	3.99
SELECT Population (Suspected DVT) [†]			
Frequency (%)	535 (48.9)	476 (43.5)	84 (7.7)
Prevalence* (%)	15/535 (2.8)	27/476 (5.7)	17/84 (20.2)
Likelihood Ratio	0.51	1.06	4.46
SIMPLE Population (Suspected PE) [§]			
Frequency (%)	499 (73.5)	139 (20.5)	41 (6.0)
Prevalence* (%)	31/499 (6.2)	36/139 (25.9)	15/41 (36.6)
Likelihood Ratio	0.48	2.54	4.20

CPTP, clinical pre-test probability; VTE, venous thromboembolism

* VTE diagnosed at initial assessment or during follow-up

[†] Low CPTP: Wells Score ≤ 0 ; Moderate CPTP: Wells Score 1-2; High CPTP: Wells Score ≥ 3

[§] Low CPTP: Wells Score ≤ 4 ; Moderate CPTP: Wells Score 4.5-6; High CPTP: Wells Score ≥ 6.5

4.2 Distribution of D-dimer Levels

In the total population, 41.9% had a D-dimer level less than 500ug/L, 12.8% had a D-dimer between 500ug/L and 749ug/L, 8.7% had a D-dimer between 750ug/L and 999ug/L, 5.4% had a D-dimer between 1000ug/L and 1250ug/L, and 31.2% had a D-dimer greater than 1250ug/L (Table 8). D-dimer levels increased with CPTP: D-dimer levels were less than 500ug/L in 50.5% of patients with low CPTP, 32.7% of patients with moderate CPTP and 16.8% of patients with high CPTP ($p<0.01$, *chi-squared test*). D-dimer levels were greater than 1250ug/L in 25.2% of patients with low CPTP, 35.8% in patients with moderate CPTP and 57.6% in patients with high CPTP ($p<0.01$, *chi-squared test*).

4.3 LR for VTE Associated with D-dimer Levels

The LR for VTE increased according to D-dimer level, from 0.03 for patients with D-dimer levels of less than 500ug/L to 3.5 for patients with D-dimer levels above 1250ug/L (Table 8). This pattern was also seen within CPTP categories. The LR for D-dimer was less than 0.1 for D-dimer levels less than 1000ug/L, including in all three CPTP subgroups.

A total of 1649 patients had low or moderate CPTP and were included in the comparison of the diagnostic strategies. The diagnostic accuracy parameters for each of the strategies are presented in Table 9.

Table 8
Prevalence of VTE According to D-dimer Levels in the Total Population

<i>D-dimer Level (ug/L)</i>	< 500	500-749	749-999	1000-1249	> 1250
Frequency (%)	744 (41.9)	227 (12.8)	155 (8.7)	95 (5.4)	553 (31.2)
VTE Prevalence (%)	2/744 (0.3)	2/227 (0.9)	4/155 (2.3)	5/95 (5.3)	128/553 (23.1)
Likelihood Ratio	0.031	0.10	0.31	0.64	3.49
<i>D-dimer Threshold (ug/L)</i>	< 500	< 750	< 1000	< 1250	> 1250
Frequency (%)	744 (41.9)	971 (54.7)	1126 (63.5)	1221 (68.8)	553 (31.2)
VTE Prevalence (%)	2/744 (0.3)	4/971 (0.4)	8/1126 (0.7)	13/1221 (1.1)	128/553 (23.1)
Likelihood Ratio	0.031	0.048	0.083	0.12	3.49

Table 9
*Diagnostic Accuracy Parameters by Strategy
for Patients with Low or Moderate CPTP of VTE*

	Standard Strategy	IAIT Strategy	Median Age Strategy	DAIT Strategy	CPTP Strategy
Sensitivity % (95% CI)	98.2 (93.6-99.5)	97.3 (92.2-99.1)	97.3 (92.2-99.1)	97.3 (92.2-99.1)	97.3 (92.2-99.1)
Specificity % (95% CI)	46.8 (44.3-49.3)	54.4 (51.9-56.8)	57.5 (55.1-60.0)	54.0 (51.5-56.5)	59.9 (57.4-62.3)
NPV % (95% CI)	99.7 (99.0-99.9)	99.6 (99.0-99.9)	99.7 (99.0-99.9)	99.6 (99.0-99.9)	99.7 (99.1-99.9)
False Negative % (95% CI)	0.28 (0.08-1.00)	0.36 (0.12-1.05)	0.34 (0.11-0.99)	0.36 (0.12-1.05)	0.32 (0.11-0.95)
Negative LR (95% CI)	0.04 (0.01-0.15)	0.05 (0.02-0.15)	0.05 (0.02-0.15)	0.05 (0.02-0.16)	0.05 (0.02-0.14)
Utility % (95% CI)	43.8 (41.5-46.3)	50.9 (48.5-53.4)	53.9 (51.5-56.3)	50.6 (48.2-53.1)	56.1 (53.7-58.5)
NNT (95% CI)	2.28 (2.17-2.42)	1.96 (1.88-2.07)	1.85 (1.78-1.95)	1.97 (1.89-2.08)	1.78 (1.72-1.87)

CPTP, clinical pre-test probability; DAIT, increasing age, decreasing threshold; IAIT, increasing age, increasing threshold; LR, likelihood ratio; NNT, number needed to test; NPV, negative predictive value; CI, confidence interval

4.4 Evaluation of the IAIT Strategy

4.4.1 Comparison of IAIT and Standard Strategies

The sensitivity of the IAIT Strategy was not lower than the Standard Strategy (97.3% vs. 98.2%; $p=1.0$). The NPVs of D-dimer testing using the IAIT and the Standard Strategy were 99.6% and 99.7% respectively ($p=0.99$; difference=-0.1%; 95% CI, -0.7 to 0.8%).

The specificity of the IAIT Strategy was greater than the Standard Strategy (54.4% vs. 46.8% respectively, $p<0.001$). As a result, utility of the IAIT Strategy was greater than for the Standard Strategy (50.9% vs. 43.8%; $p=0.003$).

Compared with the Standard Strategy, VTE would be excluded with the IAIT Strategy in an additional 7.1% (95% CI, 5.9 to 8.3%) of patients (Table 10). The prevalence of VTE among the additional 117 patients who had VTE excluded by the IAIT Strategy (D-dimer negative) and not by the Standard Strategy (D-dimer positive) was 0.9% (95% CI, 0.2 to 4.7%). **The IAIT Strategy maintained a high NPV, and was associated with an increase in utility over the Standard Strategy.**

Table 10
*Comparison of the IAIT Strategy and the Standard Strategy
 Prevalence of VTE According to Categorization of D-dimer as Positive or
 Negative*

		Standard Strategy		
		D-dimer Negative (<500ug/L)	D-dimer Positive (>500ug/L)	Total
IAIT Strategy	D-dimer Negative	2/723 (0.28%)	1/117 (0.85%)	3/840 (0.36%)
	D-dimer Positive	0/0 (0%)	106/809 (13.1%)	106/809 (13.1%)
	Total	2/723 (0.28%)	107/926 (11.6%)	109/1649 (6.6%)

IAIT, increasing age, increasing threshold

4.4.2 Comparison of IAIT and Median Age Strategies

The median age of patients older than 50 years was 68 years. The Median Age Strategy therefore used a D-dimer threshold of 680ug/L for all patients. For both of the IAIT and the Median Age strategies, sensitivity was 97.3% ($p=1.0$, Table 9). The NPV of D-dimer testing was 99.6% in both strategies ($p=1.0$; difference=0%; 95% CI, -0.7 to 0.7%).

The specificity of the IAIT Strategy was lower than the specificity of the Median Age Strategy (54.4% vs. 57.5%; $p<0.001$). The utility of the IAIT Strategy was also lower than the Median Age Strategy (50.9% vs. 53.9%; $p<0.001$; difference=-3.0%; 95% CI, -1.9 to -5.8%). Twenty-three patients were categorized as D-dimer negative according to the IAIT Strategy and positive according to the Median Age Strategy, whereas 72 patients were categorized as D-dimer negative according to the Median Age Strategy and positive according to the IAIT Strategy (Table 11). There were no VTE diagnosed in patients who were D-dimer negative according to one strategy and positive according to the other (i.e. discordant findings). **The Median Age Strategy was associated with a NPV that was equal to the IAIT Strategy but an increased utility to a greater extent.**

Table 11
*Comparison of the IAIT Strategy and Median Age Strategy
 Prevalence of VTE According to Categorization of D-dimer as Positive or
 Negative*

		Median Age Strategy		
		D-dimer Negative ($< 680\mu\text{g/L}$)	D-dimer Positive ($> 680\mu\text{g/L}$)	Total
IAIT Strategy	D-dimer Negative	3/817 (0.37%)	0/23 (0%)	3/840 (0.36%)
	D-dimer Positive	0/72 (0%)	106/737 (14.4%)	106/809 (13.1%)
	Total	3/889 (0.34%)	106/760 (13.9%)	109/1649 (6.6%)

IAIT, increasing age, increasing threshold

4.4.3 Comparison of IAIT and DAIT Strategies

The sensitivity for both of the IAIT and DAIT strategies was 97.3% ($p=1.0$, Table 9). The NPVs of the IAIT and DAIT strategies were also identical (99.6%; $p=1.0$; difference=0%; 95% CI, -0.7 to 0.7%).

There was no difference between the specificities of the IAIT and DAIT strategies (53.4% vs. 53.0%; $p=0.8$). The utility of the IAIT Strategy was also no different than the DAIT Strategy (50.9% vs. 50.6%; $p=0.8$; difference=0.3; 95% CI, -1.3 to 1.9%). Overall, 91 patients were categorized as D-dimer negative (IAIT Strategy) and D-dimer positive (DAIT Strategy), while 86 patients were categorized as D-dimer negative (DAIT Strategy) and D-dimer positive (IAIT Strategy); see Table 12. There were no VTE diagnosed in any patient who had discordant results between the IAIT and DAIT strategies (0 of 91, 95% CI, 0 to 4.1%; 0 of 86, 95% CI, 0 to 4.3%). **The DAIT Strategy was associated with a NPV and utility that was equal to the IAIT Strategy.**

Table 12
Comparison of the IAIT Strategy and DAIT Strategy
Prevalence of VTE According to Categorization of D-dimer as Positive or Negative

		DAIT Strategy		
		D-dimer Negative	D-dimer Positive	Total
IAIT Strategy	D-dimer Negative	3/749 (0.4%)	0/91 (0%)	3/840 (0.36%)
	D-dimer Positive	0/86 (0%)	106/723 (14.7%)	106/809 (13.1%)
Total		3/835 (0.4%)	106/814 (13.0%)	109/1649 (6.6%)

DAIT, decreasing age, increasing threshold; IAIT, increasing age, increasing threshold; VTE venous thromboembolism

4.5 Evaluation of the CPTP Strategy

4.5.1 Comparison of CPTP and Standard Strategies

The sensitivity of the CPTP and the Standard Strategy was 97.3% and 98.2% respectively ($p=1.0$, Table 9). The NPVs of both the CPTP and Standard strategy was 99.7% ($p=1.0$; difference=0.1%; 95% CI, -0.7 to 0.7%). The specificity of the CPTP Strategy was significantly higher than the Standard Strategy (59.9% vs. 46.8%, $p<0.001$). The clinical utility of D-dimer testing using the CPTP Strategy was also significantly higher than the Standard Strategy (56.1% vs. 43.8%; $p<0.001$).

An additional 202 patients (12.3%; 95% CI, 7.5 to 16.5%) were classified as D-dimer negative according to the CPTP Strategy compared with the Standard Strategy (Table 13). There was one VTE diagnosed among those patients categorized as D-dimer negative according to the CPTP Strategy and positive according to the Standard Strategy (0.5%; 95% CI, 0.1 to 2.8%). **The CPTP Strategy maintained a high NPV, and was associated with an increase in utility over the Standard Strategy.**

Table 13
*Comparison of the CPTP Strategy and Standard Strategy
 Prevalence of VTE According to Categorization of D-dimer as Positive or
 Negative*

		Standard Strategy		
		D-dimer Negative ($<500\mu\text{g/L}$)	D-dimer Positive ($>500\mu\text{g/L}$)	Total
CPTP Strategy	D-dimer Negative (<1000 if Low; < 500 if Mod)	2/723 (0.28%)	1/202 (0.50%)	3/925 (0.32%)
	D-dimer Positive (≥ 1000 if Low; ≥ 500 if Mod)	0/0 (0%)	106/724 (14.6%)	106/724 (14.6%)
Total		2/723 (0.28%)	107/926 (11.6%)	109/1649 (6.6%)

CPTP, clinical pre-test probability

4.5.2 Comparison of CPTP and IAIT Strategies

The sensitivity of both the CPTP and IAIT strategies was 97.3% ($p=1.0$, Table 9).

The NPV of the CPTP Strategy and the IAIT Strategy was 99.7% and 99.6% respectively ($p=1.0$; difference=0.1%; 95%CI, -0.6 to 0.8%).

The specificity of the CPTP Strategy was significantly higher than the specificity of the IAIT Strategy (59.9% vs. 54.4%; $p<0.001$). Similarly, the CPTP clinical utility was significantly higher than the IAIT Strategy (56.1% vs. 50.9%; $p<0.001$). Overall 139 patients were categorized as D-dimer negative (CPTP Strategy) and D-dimer positive (IAIT Strategy), and 54 patients were categorized as D-dimer negative (IAIT Strategy) and D-dimer positive (CPTP Strategy); see Table 14. The CPTP resulted in a net gain of 85 additional patients (5.2%; 95% CI, 3.6 to 6.8%) who would be categorized as D-dimer negative compared with the IAIT Strategy. There were no VTE diagnosed among those patients with discordant results between the IAIT and CPTP strategies (0 of 139, 95% CI, 0 to 2.7%; 0 of 54, 95% CI, 0 to 6.6%).

Of the 1649 patients, 329 were over the age of 75; among these older patients, 129 had a negative D-dimer according to the IAIT Strategy, yielding a utility of 39% in this age group. Among the same 329 patients, 122 had a negative D-dimer according to the CPTP Strategy, yielding a utility of 37% in this age group. None of the patients categorized as D-dimer negative by either the IAIT or the CPTP Strategy were found to have VTE in this age group. **The CPTP**

Strategy was associated with a NPV that was as least as high as the IAIT

Strategy but increased the overall utility to a greater extent.

Table 14
Comparison of the CPTP Strategy and IAIT Strategy
Prevalence of VTE According to Categorization of D-dimer as Positive or
Negative

		IAIT Strategy		
		D-dimer Negative	D-dimer Positive	Total
CPTP Strategy	D-dimer Negative (<1000 if Low; < 500 if Mod)	3/786 (0.38%)	0/139 (0%)	3/925 (0.32%)
	D-dimer Positive (≥ 1000 if Low; ≥ 500 if Mod)	0/54 (0%)	106/670 (15.8%)	106/724 (14.6%)
	Total	3/840 (0.36%)	106/809 (13.1%)	109/1649 (6.6%)

CPTP, clinical pre-test probability; IAIT, increasing age, increasing threshold

4.6 Mean D-dimer Threshold According to Strategy

The D-dimer thresholds applied to individual patients varied across the Standard, IAIT, Median Age, DAIT and CPTP Strategies. Of the experimental strategies, the mean D-dimer threshold was 620ug/L (Standard Deviation [SD] = 123ug/L) in the IAIT Strategy, 680ug/L (SD = 0ug/L) in the Median Age Strategy, 644ug/L (SD = 146ug/L) in the DAIT Strategy and 814ug/L (SD = 242ug/L) in the CPTP Strategy. The mean D-dimer level was significantly higher in the CPTP Strategy compared with the IAIT Strategy ($p < 0.001$).

4.7 Patients with Suspected DVT versus PE

The NPV of each strategy was the same in patients with suspected DVT compared with patients with suspected PE ($p > 0.9$ for all comparisons, Table 15). The utility was similar in patients with suspected DVT compared with patients with suspected PE in the Standard Strategy ($p = 0.9$), DAIT Strategy ($p = 0.9$) and the CPTP Strategy ($p = 0.7$). In the IAIT and Median Age strategies, the utility was higher in patients with suspected DVT compared with patients with suspected PE ($p = 0.009$ and $p = 0.05$ respectively). However, when comparing the utility across strategies, the same pattern was seen in patients with suspected DVT compared with patients with suspected PE: the utility was lowest in the Standard Strategy, the utility of the IAIT Strategy was not higher than the Median Age Strategy or DAIT Strategy, and the utility was highest in the CPTP Strategy.

The similarity in the NPV and utility between patients with suspected DVT and suspected PE supported the decision to pool the two populations in the primary analysis.

Table 15
NPV and Utility in Patients with Suspected DVT and Suspected PE

	Standard Strategy	IAIT Strategy	Median Age Strategy	DAIT Strategy	CPTP Strategy
NPV % (95% CI)					
Suspected DVT	99.8 (98.7-100)	99.8 (99.0-100)	99.8 (99.0-100)	99.8 (98.9-100)	99.8 (99.0-100)
Suspected PE	99.6 (98.1-99.9)	99.3 (97.6-99.8)	99.4 (97.8-99.8)	99.4 (97.8-99.8)	99.4 (98.0-99.8)
Utility % (95% CI)					
Suspected DVT	43.8 (40.8-46.9)	51.3 (50.4-56.6)	55.9 (52.8-58.9)	50.5 (47.5-53.6)	56.5 (53.4-59.5)
Suspected PE	43.8 (40.1-47.8)	46.9 (43.0-50.7)	50.8 (46.9-54.7)	50.8 (46.9-54.7)	55.5 (51.6-59.3)

DAIT, decreasing age, decreasing threshold; CPTP, clinical pre-test probability; IAIT, increasing age, increasing threshold; NPV, negative predictive value; DVT, deep vein thrombosis; PE, pulmonary embolism

4.8 Differential Verification Bias

The proportion of patients with a negative D-dimer who were evaluated with follow-up alone was 96.7% in the Standard Strategy, 91.7% for the IAIT Strategy, 89.9% in the Median Age Strategy, 91.6% in the DAIT Strategy and 90.7% in the CPTP Strategy ($p < 0.001$, chi-squared test for 5-way comparison). After excluding the Standard Strategy, the proportion of patients with a negative D-dimer who were evaluated with follow-up alone was similar between the remaining strategies ($p = 0.4$).

In each of the IAIT, Median Age, DAIT and CPTP strategies, there were three patients with false negative D-dimer results. The D-dimer levels of these patients were 240ug/L, 270ug/L and 530ug/L; one was diagnosed with VTE during baseline evaluation and the other two were diagnosed with VTE during follow-up.

Sensitivity Analysis

A sensitivity analysis was carried out in which the NPV of each strategy was re-estimated under the assumption that the rate of recurrent VTE after a first untreated event is 30%. I multiplied the number of patients who were D-dimer negative and diagnosed with VTE during follow-up by 3. This increased the number of false negative D-dimer tests from 3 to 7 for each strategy (1 VTE diagnosed by imaging at baseline plus 2 diagnosed during follow-up times 3).

In the simulation, the NPV was 99.5% for the Standard Strategy, and 99.2% for the IAIT, Median Age, DAIT, and CPTP Strategies. The consistency in NPV across the strategies in the sensitivity analysis suggests that differential verification did not bias the comparisons of NPV in the primary analysis.

4.9 Effect of Prevalence of VTE on NPV Estimates

The NPV of each strategy was estimated in two simulated populations in which the prevalence of VTE was increased to 15% and 20% (Table 16). The NPV of each strategy remained high in both simulated populations. The lower bound of

the 95% CI for the NPV for all the strategies, including the Standard Strategy, fell just below 98.0% in simulations where the prevalence of VTE was 20% or higher.

Table 16
*Negative Predictive Values with Increasing Prevalence of VTE
Among Patients with Low and Moderate CPTP*

Table Values are NPV% (95% CI)

Strategy	Prevalence = 7% (Study Cohort)	Prevalence = 15%	Prevalence = 20%
Standard	99.7 (99.0-99.9)	99.3 (98.2-99.7)	99.0 (97.9-99.6)
IAIT	99.6 (99.0-99.9)	99.1 (98.1-99.6)	98.8 (97.7-99.3)
Median Age	99.7 (99.0-99.9)	99.2 (98.4-99.7)	98.8 (97.8-99.4)
DAIT	99.6 (99.0-99.9)	99.1 (98.1-99.6)	98.7 (97.7-99.3)
CPTP	99.7 (99.1-99.9)	99.2 (98.3-99.6)	98.9 (97.9-99.4)

CPTP, clinical pre-test probability; DAIT, increasing age, decreasing threshold; IAIT, increasing age, increasing threshold; NPV, negative predictive value; CI, confidence interval

SECTION 5: DISCUSSION

The objective of this analysis was to identify the optimal strategy for selecting the D-dimer threshold to exclude VTE, where the optimal strategy is defined as that which excludes VTE in the greatest proportion of patients (highest utility) while maintaining a high NPV (i.e. greater than 98%). My findings suggest that the IAIT Strategy does not maximize the utility of D-dimer testing and therefore do not support increasing the D-dimer threshold with advancing age. Of the strategies I evaluated, the CPTP Strategy maintained a high NPV and had the highest utility. Therefore the CPTP Strategy appears to be the optimal strategy of D-dimer interpretation.

5.1 Validity of the IAIT Strategy

Multiple studies have shown that the IAIT Strategy safely increases the utility of D-dimer testing in patients with low or moderate CPTP. My analysis supports this finding: the utility of the IAIT Strategy was 50.9% and the NPV of the IAIT Strategy was 99.6%. However, I found no difference between the utility and NPV of the IAIT Strategy and the utility and NPV of a strategy that I designed to have the opposite relationship between age and D-dimer threshold (the DAIT Strategy). This is strong evidence against increasing the D-dimer threshold with advancing age.

The Median Age Strategy used a D-dimer threshold that was based on the median age of patients who were older than 50 years. This threshold was then

applied to all patients with low or moderate CPTP. There was no difference between the NPV of the IAIT Strategy and the Median Age Strategy. The utility of the Median Age Strategy was greater than the IAIT Strategy which suggests that using a higher D-dimer threshold in patients less than 50 years old as well as those older than 50 years has the potential to improve the utility of D-dimer testing to a greater extent than a strategy that only uses a higher threshold in older patients.

Taken together, these findings suggest that the greater utility of the IAIT compared with the Standard Strategy is simply due to increasing the D-dimer threshold in some patients, or alternatively stated, increasing the mean D-dimer threshold.

5.2 The CPTP Strategy is the Optimal Strategy

The CPTP Strategy was associated with a high NPV. The 95% CI for the NPV of the CPTP Strategy were higher than the predefined acceptable NPV of 98% and there was no detectable difference between the NPV of the CPTP Strategy and the NPV of the Standard Strategy or the IAIT Strategy. The false negative rate of the CPTP Strategy was only 0.5% (one event) among the 202 patients who were categorized as D-dimer negative according to the CPTP Strategy and positive according to the Standard Strategy. This trade-off is considered very acceptable.

The CPTP Strategy improved the specificity and utility of D-dimer testing compared with the Standard Strategy. Twelve percent of patients with low or

moderate clinical pre-test probability were categorized as D-dimer negative according to the CPTP Strategy when compared with the Standard Strategy. All of this benefit is due to increasing the threshold from 500ug/L to 1000ug/L in patients with low CPTP. Therefore, the CPTP Strategy increased the proportion of low CPTP who had VTE excluded by D-dimer by 20% (522/1034 vs. 724/1034).

More interestingly, my analysis showed that the CPTP Strategy significantly improved the specificity and utility of D-dimer testing compared with the IAIT Strategy as well. An additional 5% of patients with low or moderate CPTP would be categorized as D-dimer negative using the CPTP Strategy instead of the IAIT Strategy. This is evidence that the CPTP Strategy is better than the IAIT Strategy.

The utility of D-dimer testing was better in the CPTP Strategy than the IAIT Strategy because a greater proportion of patients were evaluated with a high D-dimer threshold in the CPTP Strategy. A large proportion of the patients (63%) had low CPTP; these patients were evaluated with a high D-dimer threshold (1000ug/L) in the CPTP Strategy. The large proportion of patients evaluated with a high D-dimer threshold in the CPTP Strategy contributed to a high mean D-dimer threshold. In contrast, only patients older than 75 (20%) were evaluated with a high D-dimer threshold (i.e. 750ug/L or higher) with the IAIT Strategy and no patients were evaluated with a threshold of 1000ug/L. The small proportion of patients evaluated with a high D-dimer threshold led to a lower mean D-dimer threshold in the IAIT Strategy.

The IAIT Strategy was designed to increase the utility of D-dimer testing in older patients, as only a small proportion of patients over 75 are found to have a negative D-dimer using the standard threshold of 500ug/L. I found that the utility of D-dimer testing in patients over 75 was comparable between the IAIT Strategy and the CPTP Strategy. Therefore, among the elderly, a similar gain in utility can be achieved by only using a higher D-dimer among those with low CPTP compared with using an age adjusted increase in threshold.

Overall, my findings suggest that the CPTP Strategy safely excludes VTE in patients with low or moderate CPTP while increasing the utility of D-dimer testing to a greater extent than the IAIT Strategy. Therefore, it appears of the strategies I assessed, the CPTP Strategy is the optimal way to interpret of D-dimer levels.

5.3 IAIT Strategy: Comparison of Current Analysis with Existing Literature

The NPV of the IAIT Strategy in this study was very similar to the accuracy seen in other studies.^{63, 64, 77} The NPV of 99.6% for the IAIT Strategy in the current analysis is consistent with the NPV of 99.8%-99.6% published by Douma et al in their derivation and validation cohorts.²⁴ Schouten et al, using pooled estimates of sensitivity and specificity from their meta-analysis, estimated that the IAIT Strategy had a NPV of 99.2%.⁶³ The very recently published study by Righini et al confirmed that the IAIT Strategy is associated with a very high NPV: 2 of 1141 patients with non-high CPTP and a negative D-dimer according to the IAIT Strategy who were managed without anticoagulation had VTE during follow-up,

corresponding to a NPV of 99.8%. Again, this value is similar to the NPV in the current analysis. However, none of these studies evaluated if the IAIT Strategy was better than simply increasing the D-dimer threshold in all patients, or selectively increasing the D-dimer threshold in the low CPTP subgroup.

The gain in utility with the IAIT Strategy in the current study is also consistent with the findings of other groups. In the original article by Douma et al that defined the IAIT Strategy used in this analysis, an additional 5-9% of patients with non-high clinical probability were defined as D-dimer negative with the IAIT Strategy compared with the Standard Strategy.²⁴ In a meta-analysis using pooled estimates of sensitivity and specificity of the IAIT Strategy, Schouten et al estimated that an additional 9% of patients would be categorized as D-dimer negative according to the IAIT Strategy compared with the Standard Strategy.⁶³ These values are similar to my finding of a 7% increase in patients with low or moderate CPTP who would be defined as D-dimer negative according to the IAIT Strategy. To date, there has been only one prospective study of the diagnostic performance of the IAIT Strategy in patients with suspected VTE. Righini et al showed that an additional 11% of patients with non-high clinical probability would be classified as D-dimer negative using the IAIT Strategy compared with using a standard threshold of 500ug/L.⁶⁴ The difference between the gain in utility between the study by Righini et al and the current analysis may be due to the age distribution of patients in the study cohort. The median age in the prospective cohort of patients studied by Righini et al was older (median age 63) than the

population in previous analyses of the IAIT Strategy and well as the current study. The study by Righini et al was a prospective management study, where the investigators were not blinded to the intervention, that is, the use of a higher D-dimer threshold in the elderly. This may have led to the selective enrolment of older patients in this study.

5.4 CPTP Strategy: Comparison of Current Analysis with Existing Literature

The high NPV associated with the CPTP Strategy in my analysis is consistent with the findings of other groups who have examined the use of a higher D-dimer threshold in patients with low CPTP. Among five studies that examined the selective use of a higher D-dimer threshold in patients with low CPTP, the NPV of D-dimer testing was estimated to be greater than 98% in three^{66, 68, 78} and greater than 97% in the remaining two^{25, 67}. An additional study reported that the combination of a Wells score for PE of less than 4.5 and a D-dimer of less than 1000ug/L was associated with a slightly lower NPV of 95%. However, over 80% of the patients with false negative D-dimer results in this study were diagnosed with isolated subsegmental PE, the clinical significance of which is less clear.²⁷

The increase in utility using the CPTP Strategy observed in the current analysis is consistent with the findings of several other groups. In an exploratory analysis, Linkins et al showed that increasing the D-dimer threshold to 2000ug/L in patients with low CPTP increased the utility of D-dimer testing from 41% to

58% in patients with low or moderate CPTP.⁶⁸ Yamaki et al and Kabhrel et al increased the D-dimer threshold in patients with low CPTP by doubling the manufacturer's recommended threshold and used the usual recommended threshold in patients with moderate CPTP.^{66, 78} In both studies, there was a 20% increase in the utility of D-dimer testing among patients with low or moderate clinical probability. Data presented by Righini et al suggest that increasing the D-dimer threshold to 1000ug/L in low CPTP patients while maintaining a threshold of 500ug/L in moderate CPTP patients is associated with an increase in utility from 33% to 47%.²⁵ However, other groups have suggested that the gain in utility using a CPTP Strategy is more modest. In a retrospective analysis of patients with suspected PE, Van der Hulle et al showed that increasing the D-dimer threshold to 1000ug/L in patients with low CPTP and maintaining a threshold of 500ug/L in patients with moderate CPTP resulted in an increase in utility from 31% to only 38%.⁶⁷ However, twice as many patients were classified as moderate CPTP than low CPTP in this study, as the cut-off used to define a patient as low CPTP was less than 2.

The variability in utility of the CPTP Strategy presented above can be partially attributed to differences in the D-dimer threshold chosen for the low CPTP group, which ranged from 1000ug/L to 2000ug/L. There were also differences in the definition of low CPTP for patients with suspected PE, with some studies using a Wells score of less than 2 and others a Wells score of less than 4.5. This choice of cut-off can affect the proportion of patients in the low

CPTP and moderate CPTP categories, which in turn can impact the utility of a CPTP guided strategy.

5.5 Strengths and Limitations of the Analysis

Strengths of the analysis include: 1) using data from two separate prospective cohorts in which patients were evaluated for VTE using standardized protocols, events during follow-up were adjudicated and few enrolled patients were lost to follow-up; 2) there were over 100 VTE positive patients with low or moderate CPTP of VTE; and 3) I defined the D-dimer interpretation strategies before completing the analysis. These strengths, respectively: 1) reduce the potential for misclassification of patients as VTE-positive or VTE-negative; 2) increase precision of my findings and 3) reduce the potential for over emphasis of “chance findings.”

There were several limitations of the analysis. First, the prevalence of VTE was somewhat lower in the study population than in other published cohorts of patients with suspected VTE. While the results of the simulations in which the prevalence of VTE was increased did not show a substantial decrease in NPV, I plan to repeat the analysis in independent cohorts in which the prevalence of VTE was higher. However, it should be recognized that the prevalence of disease among patients tested for VTE has decreased in recent years and, therefore, there is an increasing need to efficiently exclude VTE.⁷⁹ Second, there was the potential for “differential verification bias” in the current analysis as patients with a

negative D-dimer according to the strategies were evaluated using two different reference standards that are expected to have different sensitivities for VTE. The proportion of patients with negative D-dimer results who were evaluated with each reference standard was similar in all four experimental diagnostic strategies. Therefore, I concluded that it is unlikely that the estimates of NPV for any one of the strategies was favoured due to differential verification bias. The estimate of utility was not subject to differential verification bias, as it reflects the proportion of patients who have a negative D-dimer test at initial assessment rather than how patients were categorized as VTE-positive or VTE-negative. Third, because I analyzed only one D-dimer assay, the results may not be generalizable to other D-dimer assays. This is more of a concern for the absolute NPVs and utilities that were calculated, and less of a concern for the comparison of NPV and utility between D-dimer strategies.

5.6 Conclusions

My analysis does not support increasing the D-dimer threshold with increasing age because similar gains in specificity and utility were achieved by doing the opposite: using a high threshold in younger patients and a progressively lower threshold as the patient ages. The CPTP Strategy had better accuracy than the other strategies I evaluated and therefore appears to be the optimal strategy for D-dimer interpretation.

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Appendix A: Description of SELECT and SIMPLE Studies

Selective D-dimer Testing for Diagnosis of a First Suspected Episode of Deep Venous Thrombosis: SELECT study⁶⁹

The SELECT study was a randomized trial that compared the safety of two management strategies for patients with suspected DVT, the Standard Strategy and the CPTP Strategy. It enrolled consecutive inpatients and outpatients who presented with a suspected first DVT. D-dimer testing was performed using quantitative latex agglutination assays: the MDA D-dimer (Biomérieux, Durham, NC) or the STA-Liatest D-dimer (Diagnostica Stago, Asnières, France).

In the Standard Strategy arm, D-dimer level was measured in all patients. If the D-dimer result was less than 500ug/L, D-dimer results were categorized as negative and DVT was excluded without performing a compression ultrasound (CUS). If the D-dimer was 500ug/L or greater, D-dimer results were categorized as positive and a CUS was performed of the proximal leg veins in the symptomatic leg. DVT was excluded if the initial compression ultrasound was normal in patients with low clinical probability, or if initial *and* a repeat CUS performed 6 to 8 days later were normal in patients with moderate or high clinical probability. DVT was diagnosed if there was evidence of a non-compressible segment within the proximal veins during initial or serial compression ultrasound.

In the CPTP Strategy arm, only outpatients with low or moderate clinical probability had a D-dimer performed. DVT was categorized as negative if it was

less than 1000ug/L in patients with low clinical probability or less than 500ug/L in patients with moderate clinical probability. Patients with a negative D-dimer had DVT excluded without additional testing. Outpatients with low or moderate clinical probability and a positive D-dimer underwent compression ultrasonography. Outpatients with high clinical probability and inpatients did not have D-dimer measured (i.e. selective D-dimer testing). Instead these patients had a CUS performed. DVT was excluded if the initial compression ultrasound was normal in patients with low clinical probability, or if initial *and* a repeat compression ultrasound performed 6 to 8 days later were normal in patients with moderate or high clinical probability. DVT was diagnosed if there was a non-compressible segment of the proximal veins during initial or serial compression ultrasound.

All patients were followed for 3 months for recurrent VTE to assess the safety of this diagnostic approach. Patients who reported symptoms of DVT or PE were evaluated with objective testing (see Table A1). A central committee that was unaware of the patient's allocation adjudicated all thrombotic outcomes during follow-up.

Strategy Involving MDA D-dimer in Pulmonary Embolism: SIMPLE Study⁷⁰

The SIMPLE study was a prospective cohort study of patients with suspected first PE. All patients in the cohort had a D-dimer performed using a latex agglutination immunoassay (MDA D-dimer, Biomérieux, Durham, NC). If the D-dimer level was less than 750ug/L, D-dimer was categorized as negative and PE was excluded without further diagnostic testing. If the D-dimer was greater than 750ug/L, D-

dimer was categorized as positive. Patients with a positive D-dimer underwent V/Q lung scanning or CTPA according to local availability. Patients were diagnosed with PE if the V/Q lung scan was high probability for PE or if the CTPA was of sufficient quality and demonstrated an intraluminal filling defect involving a segmental or larger vessel. PE was excluded if the V/Q lung scan was normal. Patients with non-diagnostic V/Q lung scans, negative CTPA or non-diagnostic CTPA underwent up to three serial compression ultrasounds of both legs and were considered to have PE excluded if serial ultrasounds were normal. DVT, and therefore PE, was diagnosed if there was evidence of a non-compressible segment involving the popliteal and/or common femoral vein.

Although CPTP was not used as part of the diagnostic management algorithm, all components of the Wells PE score were routinely collected. All patients in the SIMPLE study were followed for 3 months for recurrent VTE. Patients presenting with symptoms of DVT or PE were evaluated with objective testing (Table A1). An independent central committee who were not involved in the patient's care interpreted all radiologic tests during follow-up.

Table A1

Investigations Used during Follow-up in the SELECT and SIMPLE Studies

Patients with Symptoms of DVT	
Diagnostic for DVT	CUS: new noncompressible segment Venography: constant intraluminal filling defect
Excludes DVT	CUS: fully compressible proximal leg veins on serial CUS Venography: normal study in patients with equivocal findings on CUS
Patients with Symptoms of PE	
Diagnostic for PE	V/Q scan: (a) high probability perfusion defect or (b) non-diagnostic result and new non-compressible segment on serial CUS or (c) non-diagnostic result, normal CUS and constant intraluminal filling defect on venography or (d) non-diagnostic result, normal CUS and constant intraluminal filling defect on pulmonary angiogram or (e) non-diagnostic result, normal CUS and new intraluminal filling defect of the main, lobar or segmental level vessels on CTPA (SELECT study only) CTPA: (a) new intraluminal filling defect of the main, lobar or segmental level vessels (b) non-diagnostic result and new non-compressible segment on serial CUS (c) non-diagnostic result, normal CUS and constant intraluminal filling defect on venography (d) non-diagnostic result, normal CUS and constant intraluminal filling defect on pulmonary angiogram
Excludes PE	V/Q scan: (a) normal study or (b) non-diagnostic results and fully compressible proximal leg veins on serial CUS (c) non-diagnostic results, normal CUS and normal bilateral venography study (d) non-diagnostic result, normal CUS and normal pulmonary angiogram (e) non-diagnostic result, normal CUS and normal CTPA (SELECT study only) CTPA: (a) normal study and fully compressible proximal leg veins on serial CUS or (b) non-diagnostic results and fully compressible proximal leg veins on serial CUS (c) non-diagnostic results, normal CUS and normal bilateral venography study (d) non-diagnostic result, normal CUS and normal pulmonary angiogram

Appendix B: Defining an Acceptable NPV

Before analyzing the data, I predefined an acceptable NPV. Multiple methods of determining an acceptable NPV have been described in the literature. I

incorporated two methods of estimating an acceptable NPV: 1) calculating a “*test threshold*”, and 2) determining the false negative rate of a criterion standard diagnostic test.

(1) Calculating a Test Threshold

Pauker and Kassirer defined the *test threshold* as “the probability of disease at which there is no difference between the value of withholding treatment and the value of performing a test”.⁸⁰ If the probability of disease is less than the test threshold, then either 1) the risk of harm from the test outweighs the value of the test result, or 2) the positive predictive value of a positive result would be too low to justify treatment.

Using the equations derived by Pauker and Kassirer, Kline et al. estimated the test threshold for using CTPA to investigate PE.²⁷ Their estimate incorporated the sensitivity of CTPA, the risk of adverse events with CTPA and the probability of benefit and harm from anticoagulation for PE. They calculated a probability of disease of 2% as the test threshold, where patients with a probability of disease below this level would not benefit from further testing with CTPA. I calculated a similar threshold for DVT using CUS as the diagnostic test.

Therefore, the NPV of a D-dimer strategy was considered acceptable if it corresponded to a probability of disease that was less than the test threshold of 2%.

(2) Determining the False Negative Rate of a Criterion Standard Diagnostic Test

The traditional criterion standard for diagnosis of DVT and PE is venogram and pulmonary angiogram respectively. It is widely accepted that a normal venogram excludes DVT and a normal good quality pulmonary angiogram excludes PE. The rate of VTE during three months of follow-up in patients in whom anticoagulation was withheld after a normal venogram or pulmonary angiogram is less than 2%.^{81,}

⁸² Because the rate of VTE diagnosed during follow-up can be considered to be the false negative rate, the NPV of the criterion standards for diagnosis of DVT and PE is 100% minus the false negative rate, or 98%.

An NPV of 98% has been suggested by both methods as being acceptable. Therefore, a D-dimer strategy in the current analysis was considered to have an acceptable NPV if the lower bound of a 95% CI around the NPV estimate was at least 98% or higher. My analysis focuses only on NPV. Consequently, I did not define the PPV required to rule in VTE and justify treatment.