

https://dspace.org/

Positive D-dimer results in a private hospital emergency department : an audit of patient management and outcomes (posed study)

Rudolph, Adriana Josina

2013-01-25
http://hdl.handle.net/10539/12303

Downloaded from a DSpace repository. https://dspace.org/

POSITIVE D-DIMER RESULTS IN A PRIVATE HOSPITAL EMERGENCY DEPARTMENT – AN AUDIT OF PATIENT MANAGEMENT AND OUTCOMES (POSED STUDY)

Adriana Josina Rudolph

A research report submitted to the Faculty of Health Sciences of the University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine (Emergency Medicine)

Johannesburg, 2011

DECLARATION

I, Adriana Josina Rudolph, declare that this research is my own work. It is submitted to the University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Emergency Medicine. It has not been submitted before for any degree or examination at this or any other University.

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I have followed the required conventions in referencing the thoughts and ideas of others.

I further declare that this research was approved by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, with clearance certificate number M10449.

_____

Adriana Josina Rudolph

_____ day of _____, 2011

DEDICATION

This dissertation is dedicated to

my husband Mario for his patience and understanding during the pursuit of this research

and my mother Annatjie for all the sacrifices she has made for my education

PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS STUDY

1. Adriana Rudolph, Johnny Mahlangu: *Positive D-dimer results in a private hospital emergency department – an audit of patient management and outcomes*. Poster presentation at the Laboratory Medicine Congress 2011, Sandton Convention Centre, Johannesburg, 31 August-4 September 2011
2. Adriana Rudolph, Johnny Mahlangu: *Clinical Utility of a D-dimer test in an Emengency Department.* Manuscript in preparation for submission to Blood Coagulation and Fibrinolysis Journal

ABSTRACT

Background: The D-dimer test is commonly requested in an emergency department to confirm or exclude clinically suspected venous thrombosis. In this setting, the D-dimer is used in conjunction with the Wells clinical score and other investigation such as duplex doppler, V/Q scan or CT scan to make a definitive thrombosis diagnosis. In a typical South African private hospital setting, such as Flora Clinic, it has not yet been established as to how many of the requested D-dimers are positive, what the impact and contribution of this result is on patient management and outcome in an emergency department. In the era of diagnostic test cost cutting and evidence based practice, this knowledge is important in informing rational decision making by emergency practitioners and also as part of auditing and improving the implementation of diagnostic pathways. The aim of this study was to establish the prevalence of D-dimer positivity in an emergency department, to determine in how many patients venous thrombosis was part of the documented differential diagnosis and if patients with a positive D-dimer test were managed in accordance with published clinical management recommendations.

Materials and methods: This study is a retrospective cross-sectional analysis. All D-dimer tests requested at Flora Clinic emergency department from 1 November 2008 to 31 May 2009 were reviewed. The percentage of positive results was calculated from the total D-dimer tests conducted by the laboratory, as requested from the emergency department during the defined

study period. Clinical notes and records of those patients with positive results were de-anonymised and de-identified, using a data capture sheet. The clinical notes of the patients with a positive D-dimer were reviewed to see what impact the D-dimer result had in the management and outcome of these patients in the emergency department.

Results: There were 365 D-dimer tests conducted in the Flora Clinic emergency department, within the study period. Out of these 145 patients had a positive D-dimer test, of which 144 met further inclusion criteria. The study population had a mean age of 62 years with 53% men in the study sample. Twenty two patients' patient records were missing. They still formed part of the intent-to-treat analysis, although the data were not available beyond demographic data collection. The prevalence of a positive D-dimer test, out of all D-dimer tests conducted, between 1 November 2008 and 30 May 2009 within the Flora Clinic emergency department was 39%. The diagnosis of venous thrombosis was considered in 25% of patient records. The higher the D-dimer level the more likely the emergency practitioner was to admit the patient to hospital. No association could be found between age or sex and D-dimer value. No patient record had a formal pre-test probability evaluation recorded, although some elements of the Wells Score were recorded in all the clinical notes. Among the special investigations requested in the emergency department, 11% were in accordance with published treatment protocol. Out of these 3% involved chest imaging. In 10% of the patient records the management initiated in the emergency department was according to recognised treatment protocol.

Conclusion: The study results suggest that the assessment of pre-test probability is not done in a formalised manner and that positive D-dimer tests are either misinterpreted or that the emergency practitioners do not have sufficient knowledge regarding the correct management of a positive D-dimer test. The study identified the current trend of practice among emergency practitioners in the South African environment. Further studies evaluating the reasons for and methods to improve the under-utilisation of both clinical prediction rules and established treatment protocols will be useful.

ACKNOWLEDGEMENTS

I would like to express gratitude and sincere thanks to the following people and organisations:

My supervisor, Professor Johnny Ndoni Mahlangu, for his patience, support and valuable input during the execution of the research.

Dr. Marelise Enslin, Dr. Peter Cole and laboratory personnel from Lancet Laboratories for allowing me access to their database of laboratory results and assistance in pulling the results needed for the study.

Dr. Justin Gavanescu, hospital manager from Flora Clinic for his permission to conduct the study, utilising patient information from patients who presented at the Flora Clinic emergency department.

Mr. Eustasius Musenge, biostatistician at the University of the Witwatersrand, for his help, advice and guidance in the analysis of the data obtained from the study.

TABLE OF CONTENT

CONTENT **PAGE**

DECLARATION ii
DEDICATION iii
PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS STUDY iv
ABSTRACT v
ACKNOWLEDGEMENTS viii
LIST OF FIGURES xii
LIST OF TABLES xiii
LIST OF ABBREVIATIONS xiv
1.0 INTRODUCTION 1
1.1 General introduction to venous thrombosis (VT) 1
1.1.1 Epidemiology of VT 1
1.1.2 Pathophysiology 2
1.1.3 Predisposing factors for development of VT 3
Category 5
Risk factors 5
Hereditary 5
Antithrombin deficiency; Protein C deficiency 5
Protein S deficiency; Factor V Leiden, Activated Protein C resistance (APCR);
Prothrombin gene mutation; 5
Dysfibrinogenemia; Plasminogen deficiency 5
Acquired 5
Reduced mobility; Advanced age; Cancer; Acute medical illness; Major surgery;
Trauma; Spinal cord injury; Pregnancy and postpartum; Polycythemia vera;
Antiphospholipid antibody syndrome; Central venous catheterisation; Limb
Immobiliser or cast 5
Probable 5
Elevated lipoproteins; Low tissue- factor pathway inhibitor 5
1.2 Diagnosis of VT 6

1.2.1 Clinical presentation 8
1.2.2 Assessment of clinical probability 9
1.2.3 The D-dimer test 15
1.2.4 Differential diagnosis for a positive D-dimer test 22
1.2.5 Imaging 25
1.3 Treatment of VT 27
2.1 Prevalence of a positive D-dimer tests in the ED 29
2.2 Epidemiology of VT in the ED population 30
2.3 Current ED practice for clinical probability assessment of VT 30
2.4 Current ED practice for diagnostic testing and management of VT 31
2.4 Rationale for the current study 33
2.5 Aims of the current study 34
3.0 MATERIALS AND METHODS 35
3.1 Study design 35
3.2 Human research ethics clearance 35
3.3 Setting of the study 36
3.4 Selection of patients for the study 36
3.5 Sample size calculation 37
3.6 Data collection 37
3.6.1. D-dimer test result 37
3.6.2. Clinical notes 38
3.6.3. Data collection sheet 39
3.7 Statistical analysis 40
4.0 RESULTS 41
4.1 Study population selection 41
Figure 4.1 Study population selections 42
4.2 Study population demographics 43
4.3 Study population D-dimer values 43
4.4 Differential diagnoses in patients with a positive D-dimer test 48
4.5 Utility of the Wells Score in patients with a positive D-dimer test 53
4.6 Management of patients with a positive D-dimer test 58
4.7 Outcome of patients with a positive D-dimer test in the ED 64
5.0 DISCUSSION AND CONCLUSION 69

5.1 Demographic data 69
5.2 Prevalence and predictors of a positive D-dimer test 70
5.3 Differential diagnoses considered in the ED 70
5.4 Utility of the Wells Score 71
5.5 Management of patients in the ED 72
5.6 Patient outcome in the ED 74
5.7 Limitations of the study 75
5.8 CONCLUSION 77
APPENDIX B: DATA COLLECTION SHEET 79
REFERENCES 85

LIST OF FIGURES

FIGURE **PAGE**

Figure 1.1 Diagnostic algorithm for suspected PE 7
Figure 1.2 Diagnostic algorithm for suspected DVT 7
Figure 1.3 Pathophysiology of clot formation 19
Figure 4.2 Categorisation of the differential diagnoses 49
Figure 4.3 Outcomes in the ED 65

LIST OF TABLES

TABLE **PAGE**

Table 1.1 Predisposing risk factors for the development of VT 5
Table 1.2 The Wells' Clinical Prediction Model for Suspected PE 10
Table 1.3 The Wells' Clinical Prediction Model for Suspected DVT 11
Table 1.4 Interpretation of the Wells Score 13
Table 1.5 Conditions leading to increased D-dimer values 24
Table 4.1 Study population D-dimer values 44
Table 4.2(a) Listing of differential diagnoses 50
Table 4.2(b) Most frequent differential diagnosis considered 54
Table 4.3 Wells Score elements for PE documented 56
Table 4.4 Wells Score elements for DVT documented 57
Table 4.5 Special investigations requested in Flora Clinic ED for patient with positive D-dimers 60
Table 4.6 Different treatments initiated in Flora Clinic ED in patients with positive D-dimers 61
Table 4.7 Detail of ED outcomes grouped under "Other" 65
Table 4.8 Procedures and outcomes post ED 66

LIST OF ABBREVIATIONS

CI	Confidence interval
CPR	Clinical prediction rule
CT	Computerised tomography
CUS	Compression venous ultrasonography
CXR	Chest radiograph
DVT	Deep venous thrombosis
ECG	Electrocardiogram
ED	Emergency department
ELFA	Enzyme-linked-fluorescent-assay
ELISA	Enzyme-linked-immuno-assay
EP	Emergency practitioner
ESC Task Force	The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology
INR	International normalised ratio
IV	Intravenous
IVC	Inferior vena cava
MRI	Magnetic resonance imaging
PE	Pulmonary embolism
SANAS	South African National Accreditation System
TEE	Transoesophageal echocardiography

TTE	Transthoracic echocardiography
USA	United States of America
VT	Venous thrombosis

CHAPTER 1

1.0 INTRODUCTION

1.1 General introduction to venous thrombosis (VT)

Venous thrombosis (VT) is a spectrum of diseases including deep vein thrombosis (DVT) and pulmonary embolism (PE) (Hargett&Tapson, 2008). PE is defined as the occlusion of the pulmonary arterial bed which may lead to acute life-threatening, but potentially reversible right ventricular strain and failure (The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology, 2008) (ESC Task Force, 2008). DVT is a term used to describe the formation of a thrombus in the deep venous system. These thrombi serve as the main source for pulmonary emboli. PE is a diagnosis often missed in the emergency department (ED) because it presents with non-specific signs and symptoms not easily assigned to the illness (ESC Task Force). PE and DVT are conditions at different ends of the same disease spectrum (Tapson, 2008).

1.1.1 Epidemiology of VT

According to United States of America (USA) statistics collected between 1979 and 1999, PE has a prevalence of 0,4% among hospitalised patients. In view of its non-specific clinical presentation it is difficult to determine the prevalence accurately. This is supported by data from Sweden where PE

was considered to be the main cause of death in 13,1% of cases. The incidence of PE within the same period and population was only 2%. (ESC Task Force, 2008).

PE is a complication of between 60-80% of DVTs, of which 50% will present asymptomatically. Despite being the 3rd most common cause of death in hospitalised patients, the diagnosis is still missed in up to 70% of cases. (Bulger,Jacobs&Patel, 2004). Among patients who develop PE between 7 to 11% will have a fatal event (ESC Task Force, 2008).

1.1.2 Pathophysiology

The main source of pulmonary emboli is thrombi from the deep venous system. In the 19th century Virchow identified a triad of predisposing factors for the formation of a venous thrombus (Ouellette, 2011). These include venous stasis, intimal blood vessel changes and changes to coagulation protein properties. Once these predisposing factors are present a platelet nidus forms near a valve in the lower extremities. A thrombus is formed with the aggregation of more platelets, as well as fibrin deposits (Ouellette, 2011).

When a part of this thrombus breaks off from its original location it is referred to as an embolus. The embolus has the potential to travel via the bloodstream to remote parts of the body and occlude veins. This process is referred to as embolisation. Throughout the process of thrombus

formation the endogenous thrombolytic system helps with partial dissolution of the thrombus (Ouellette, 2011).

A PE mainly originates from thrombi in the deep venous system of the lower extremities. From there an embolus travels to the lung. Large thrombi will lodge at the bifurcation of the main pulmonary artery causing hemodynamic compromise. Smaller thrombi end their journey in the peripheral lung vessels causing pleuritic chest pain, among other symptoms. (Ouellette, 2011).

Large and multiple thrombi have the potential to increase pulmonary vascular resistance to a level which cannot be overcome by the right ventricle. This can lead to sudden death. Alternatively patients can present with syncope or hypotension, which can progress to shock and death secondary to right ventricular failure. (ESC Task Force, 2008).

1.1.3 Predisposing factors for development of VT

PE and DVT have the same predisposing factors (ESC Task Force, 2008). Although VT can occur in up to 20% of patients without any identifiable risk factors, one or more of these are usually identified (Goldhaber,Visani&De Rosa, 1999). VT may be a result of hereditary risk factors, acquired risk factors or an interaction between hereditary and acquired factors. Some of these risk factors are presented in Table 1.1.

The incidence of VT increases with age. About 65% of patients diagnosed with PE are 60 years and older. Eight-fold higher rates are seen in patients over 80 years compared to those younger than 50 years. (Hansson, Welin, Tibblin et al., 1997).

Kabrhel et al. also found an association between physical inactivity and the incidence of PE. In a study population of 69 950 females, they found that the risk of PE was more than twice in women who spent most of the day sitting compared to those who were more active (Kabrhel, Courtney, Camargo et al., 2010).

The identification and estimation of the significance of predisposing factors may be helpful in both the assessment of clinical probability for diagnostic purposes, as well as for making decisions regarding primary prevention (ESC Task Force, 2008). VT has the potential to recur, especially in patients where the thrombosis was not provoked by an event like surgery, trauma, immobilisation, pregnancy or female hormonal intake (Eichinger, Heinze, Jandeck et al., 2010) . Using a scoring system, incorporating factors like sex, location of the initial DVT and D-dimer level, might be useful, in these patients, to predict further recurrences (Eichinger et al., 2010).

Table 1.1 Predisposing risk factors for the development of VT

(Modified from Tapson, 2008)

Category	Risk factors
Hereditary	Antithrombin deficiency; Protein C deficiency Protein S deficiency; Factor V Leiden, Activated Protein C resistance (APCR); Prothrombin gene mutation; Dysfibrinogenemia; Plasminogen deficiency
Acquired	Reduced mobility; Advanced age; Cancer; Acute medical illness; Major surgery; Trauma; Spinal cord injury; Pregnancy and postpartum; Polycythemia vera; Antiphospholipid antibody syndrome; Central venous catheterisation; Limb Immobiliser or cast
Probable	Elevated lipoproteins; Low tissue- factor pathway inhibitor

1.2 Diagnosis of VT

Due to the non-specific signs and symptoms with which patients with VT can present, patients are diagnosed through having a high index of suspicion and through utilisation of clinical prediction tools to determine which group of patients will need special investigations to either confirm or exclude VT. The special investigations include both laboratory testing, as well as imaging techniques.

Through clinical evaluation of a clinical prediction tool the probability of VT is assessed. According to the calculated pre-test probability a certain pathway is followed on a diagnostic algorithm (see Figure 1.1 and 1.2 below). At the end of the diagnostic process the clinician will arrive at two possible endpoints: 'confirmed VT' or 'excluded VT'. 'Confirmed VT' is a probability of VT high enough to justify the need for further specific treatment. The term 'excluded VT' is a probability of VT low enough to justify withholding treatment in a patient with an acceptable low risk, despite a clinical suspicion of PE. (ESC Task Force, 2008).

To classify a diagnostic strategy for VT as safe, the overall post-test incidence of VT should be less than 1% with a negative predictive value of more than 99 to 100% during a three month follow-up period (Michiels, Gadisseur, van der Planken et al., 2006).

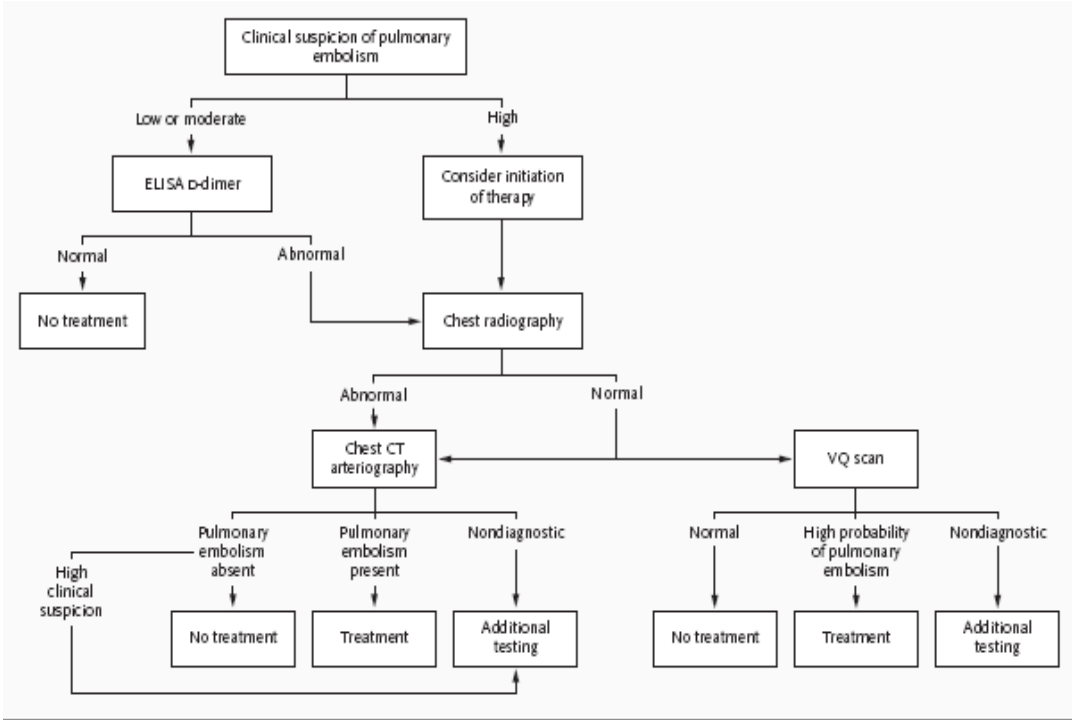


Figure 1.1 Diagnostic algorithm for suspected PE (Tapson, 2008)

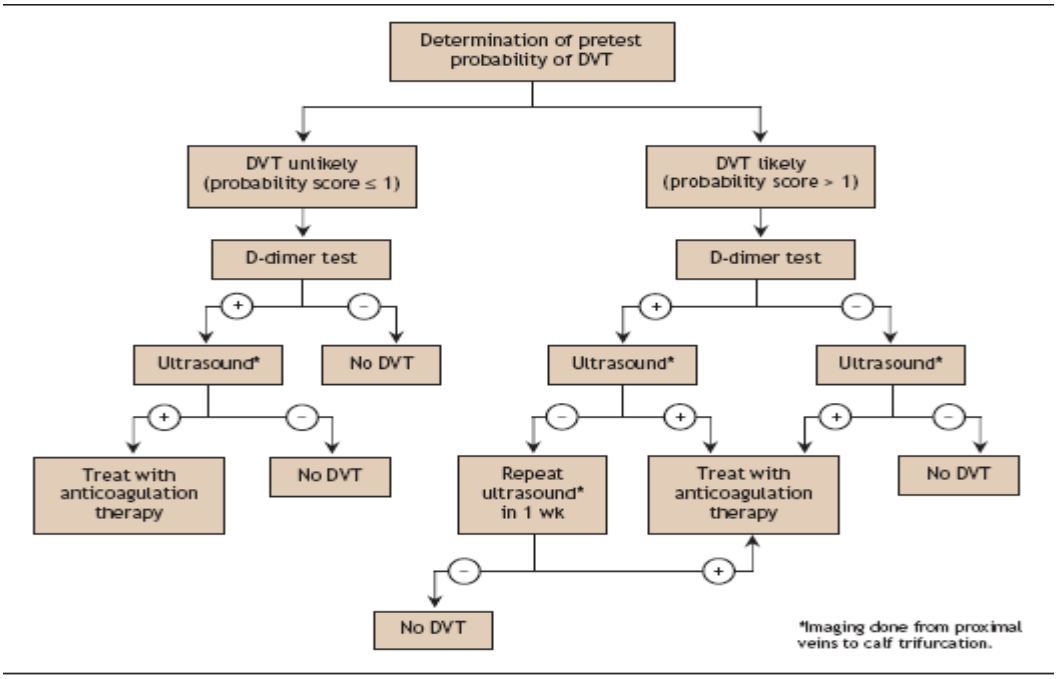


Figure 1.2 Diagnostic algorithm for suspected DVT (Scarvelis&Wells, 2006)

1.2.1 Clinical presentation

Being aware of the range of symptoms and signs of VT may reduce diagnostic delays; therefore it is important to select an appropriate diagnostic strategy as well as interpretation of the diagnostic test results (ESC Task Force, 2008).

Leg pain, swelling or warmth of the skin overlying a deep venous thrombus may serve as a clue that a patient has a DVT (Tapson, 2008). More than 90% of patients with PE will present with dyspnoea, tachypnoea or chest pain. Patients rarely present with syncope, but when it occurs it indicates severely reduced cardiopulmonary reserve. In the most severe cases shock and arterial hypotension may be present. (ESC Task Force, 2008). Pleurisy and haemoptysis occur mostly in patients with a secondary pulmonary infarction, usually caused by smaller peripheral emboli. Symptoms including cough, palpitations and light-headedness may also result from pulmonary embolism. (Tapson, 2008).

The results from routine testing done upon clinical presentation, including chest radiographs (CXR) and electrocardiogram (ECG) may also be non-specific. CXR is useful in excluding other causes of dyspnoea and chest pain. ECG changes of right ventricular strain are usually only seen in severe forms of PE. These include inversion of T waves in leads V1-V4, a

QR pattern in lead V1, the classic S1Q3T3 and a right bundle branch block. (ESC Task Force, 2008).

Clinical signs, symptoms and routine special investigations do not allow the exclusion or confirmation of VT. It should increase the index of suspicion, upon which further testing is needed. (ESC Task Force, 2008).

1.2.2 Assessment of clinical probability

Various clinical prediction rules (CPRs) have been developed to evaluate a patient's clinical probability of developing VT. The method that is most commonly used as a CPR is called the Wells score (Wells, Ginsberg, Anderson et al., 1998), including its variations, as outlined in Tables 1.2 and 1.3 below. The Wells' Clinical Prediction model makes provision for both suspected PE and DVT. The specific tool used for calculating the clinical probability is not so important, but rather the fact that a careful assessment, taking risk factors for the development of VT, into consideration. (Tapson, 2008).The interpretation of the Wells Score for both DVT and PE is shown in Table 1.4.

The aim of a CPR is to simplify complex clinical scenarios into subgroups of risk. It quantifies each element of the history, physical examination and

basic laboratory and radiology results and weights it toward the role it plays in the diagnosis. A CPR is especially useful in optimising the diagnosis, where the diagnosis is uncertain. (Hargett&Tapson, 2008)

Table 1.2 The Wells' Clinical Prediction Model for Suspected PE

(Scarvelis&Wells, 2006)

Clinical factor	**Points scored**
Clinically suspected DVT	3.0
Alternative diagnosis less likely than PE	3.0
Tachycardia	1.5
Immobilisation/surgery in previous four weeks	1.5
History of DVT or PE	1.5
Hemoptysis	1.0
Malignancy (treatment within 6 months/ palliative)	1.0

Table 1.3 The Wells' Clinical Prediction Model for Suspected DVT

(Hargett&Tapson, 2008)

Clinical Finding	**Points Scored**
Active malignancy (ongoing treatment, or within the last 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden for ⩾ 3 days, or major surgery within the last 12 weeks using general or regional anaesthesia	1
Local lower extremity tenderness along the deep venous system	1
Swollen thigh and calf	1
Calf swelling ⩾ 3 cm larger than asymptomatic leg (measured 10	1

cm below the tibial tuberosity)

Clinical Finding	**Points Scored**
Unilateral pitting oedema of the symptomatic leg	1
Unilateral dilated superficial veins (non-varicose) of the symptomatic leg	1
Previously documented DVT	1
Alternative diagnosis at least more likely that DVT	-2

Table 1.4 Interpretation of the Wells Score (Hargett&Tapson, 2008)

Scoring method	**Score**	**Interpretation**
Wells Score for PE		
Traditional interpretation		
	> 6.0	High (59% based on pooled data)
	2.0 - 6.0	Moderate (29% based on pooled data)
	< 2.0	Low (15% based on pooled data)
Alternate interpretation		
	> 4.0	PE likely. Consider contrast enhanced computed tomography (CTA) and D-dimer testing . CTA -, D-dimer +: do ventilation perfusion scan. CTA -, D-dimer -: diagnosis excluded

Scoring method	Score	Interpretation
	⩽ 4.0	PE unlikely. Consider D-dimer to rule out PE. • D-dimer -: PE ruled out • D-dimer +: Request CTA • CTA -: PE excluded CTA +: PE confirmed
Wells Score for DVT		
	≥ 2	DVT likely
	≤ 1	DVT unlikely

A complete history and thorough clinical examination should be done on all patients with a suspected VT. If VT remains a clinical probability, a formal pre-test probability assessment should be done, with a validated model (Hargett&Tapson, 2008).

Should the results from the pre-test probability testing indicate a low or moderate clinical probability for VT; a D-dimer test should be done to assess the need for diagnostic imaging. Patients from this group with a positive D-dimer should all undergo chest imaging. (Hargett&Tapson, 2008).

The D-dimer test has a low negative predictive value in patients with a high probability for PE, and therefore it should not be requested in this patient group. Patients with a high probability for PE should undergo imaging directly. (ESC Task Force, 2008).

1.2.3 The D-dimer test

The D-dimer test is widely available and used in al spheres of clinical practice to exclude clinically suspected DVT and PE (Tita-Nwa, Bos, Adjei et al., 2010).

The D-dimer is a unique marker for a degradation product of fibrin created when cross-linked fibrin is broken down by plasmin. To further understand the concept of its formation, one has to understand the physiology behind

blood clot formation. A blood clot is formed when thrombin converts fibrinogen in plasma to fibrin monomers. (Adam,Key&Greenberg, 2009).

Simultaneously thrombin activates factor XIII. The activated factor XIIIa then cross-links with the fibrin monomers to form a cross-linked soluble fibrin polymer. These soluble fibrin polymers will further cross-link to ultimately form an insoluble fibrin polymer. Plasmin acts on both the soluble and insoluble fibrin polymer in a process of degradation. This degradation process release a fibrin degradation product called the D-dimer antigen. The initial fragments are of a higher molecular weight, followed by a further plasmin-mediated degradation process that ultimately produces the terminal D-dimer-E-complex which contains the D-dimer antigen. (Adam et al., 2009) (See Figure 1.3 below).

It is uncommon to detect circulating terminal fibrin degradation products in human plasma, whereas the soluble high molecular fragments (D-dimer antigens) can be measured in plasma. The D-dimer test measure an epitope on the degradation products of factor XIIIa, cross linked by fibrin. There are several methods of doing that. All the tests use monoclonal antibodies that detect an epitope present in the factor XIIIa-cross linked fragment-D-domain of fibrin. Each monoclonal antibody, recognises a different epitope on the degradation product, thus different D-dimer tests have different specificities. Every assay also has a different format, calibration standard and different instrumentation. Therefore it is important

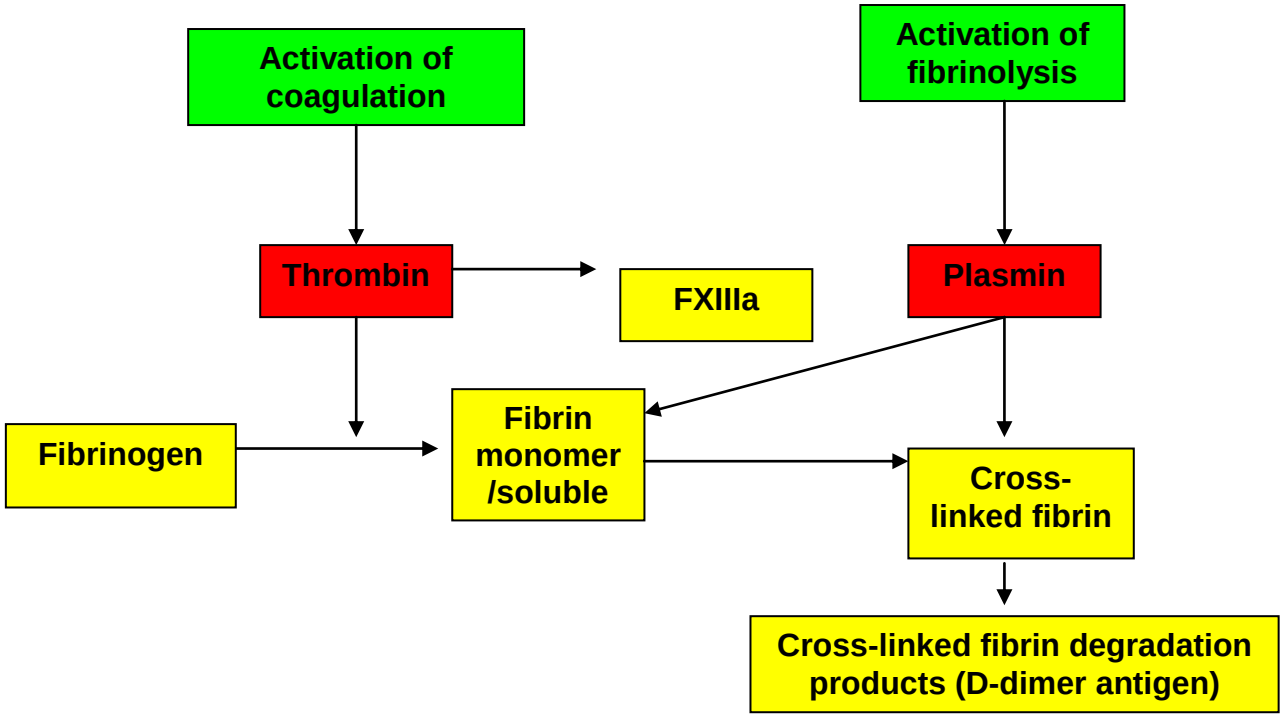
for an emergency practitioner (EP) to be familiar with the standards of the D-dimer assay that is used to produce the results, at the institution where he is practising. Efforts have been made by the International Society of Thrombosis and Haemostasis Scientific Standardisation Subcommittee to standardise assay results, but due to differences in the D-dimer analyte, it has not been successful yet. (Adam et al., 2009).

D-dimer values start rising the first day after the onset of symptoms of a VT, reaching a maximum 2-4 days after the onset of symptoms. Although levels drop thereafter a D-dimer test can remain positive for more than 12 days after the onset of symptoms (Goldin, Pasvolsky, Rogowski et al., 2011).

The first D-dimer tests were performed through a latex agglutination process. Latex beads were coated with the DD-3B6 antibody and added to the medium. When sufficient D-dimer antigen is present agglutination will be initiated. These early tests required personnel to visually report the degree of the agglutination process. Furthermore the test could only be performed in plasma, and only detected the D-dimer where plasmin has degraded the cross linked insoluble protein. (Adam et al., 2009). Subsequently automated latex agglutination was developed that reported the rate at which antibody coated particles aggregated when in contact with D-dimer antigen. These showed different specificities depending on if they were reacting with high or low molecular weight fibrin degradation products.

Another method the enzyme-linked-immuno-assay (ELISA) was initially developed for research purposes. The D-dimer antigen is captured on a plate, which is then followed by tagging the antigen with an antibody detection system. The method is extremely sensitive, but was initially time consuming until it was gradually automated for clinical use. Technological advances have led to the gold standard ELISA-based assays. These use an enzyme-linked-fluorescent-assay (ELFA) in their endpoint detection. They have equivalent sensitivity to ELISA testing but can be performed faster and detect D-dimer antigen at even lower levels (between 0-1000 µg/ml) (Adam et al., 2009).

Figure 1.3 Pathophysiology of clot formation (Modified from Wakai,Gleeson&Winter, 2003)



.

Other methods of D-dimer testing include immuno-filtration that can yield results within two minutes – a definite advantage in a clinical setting. These maintain a good sensitivity compared to ELISA testing. Apart from the above mentioned methods whole blood agglutination also exists. These are not as sensitive, but are fast and have a limited need for sophisticated laboratory equipment. (Adam et al., 2009).

The laboratory from which the data for the study was obtained uses the Vidas D-dimer exclusion test. It is an immuno-enzymatic elimination of fibrin degradation products in human serum using ELFA. It is reported to have an overall sensitivity, regardless of pre-test probability of between 98.4-100% and a specificity of between 34.2-41.3%. (Perrier, 2004). It is advised by the manufacturer, that the test always be used in conjunction with the pre-test probability (ex. Wells score), for the optimal results.

Each of the different tests has their own sensitivity and corresponding specificity. A D-dimer test should at least have a moderately high sensitivity for it to be used safely as a negative predictive marker in the diagnostic algorithm. A positive D-dimer result should always be followed up by further confirmatory or exclusion tests. (Hargett&Tapson, 2008).

The ELISA and ELFA tests have a higher sensitivity than the whole blood agglutination test – 95% vs. 85%, but in return a lower specificity – 50% vs. 70%(Adam et al., 2009). The implication of this is that the first will yield more false positive results, making it an ideal screening test, but not a good confirmatory test. Using the ELISA and ELFA, is ideal in a setting where a VT is expected, but once a positive result is obtained, further confirmatory tests are needed. Again, it emphasises the importance that the EP should be familiar with the properties and limitations of the D-dimer test used in the environment where he practices, in order to interpret it correctly.

There are conditions that can lead to an increase in D-dimer value without a PE being present (false positive). These include advanced age, pregnancy, recent trauma or surgery, malignancies and the presence of haematomas and infections. (Wakai et al., 2003). Unfortunately, patients presenting with PE often have these underlying conditions, predisposing them to its development. Clinical trials have demonstrated that the D-dimer test in isolation is not sufficient to make the diagnosis of PE (Kruip, Slob, Schijen et al., 2002). The D-dimer should always be used as part of a clinical algorithm which also incorporates the pre-test probability for the condition.

In a study done involving 3306 patients, it was found that a low probability for PE and a negative D-dimer test was effective in excluding PE. During

the 3 month follow-up the incidence of thromboembolism was 0,5% (van Belle, Buller, Huisman et al., 2006). In a study looking at patients with a high clinical probability for PE, the D-dimer test had a better negative predictive value than the Wells criteria, but the accuracy of the diagnosis was improved by using both together (Soderberg, Brohult, Jorfeldt et al., 2009). A prospective study done by Kline on 2302 patients, showed that the post-test prevalence of PE among low-risk patients with negative D-dimer test results were 0,7% (95% CI, 0,6-1,7) without using a clinical prediction tool (Kline, Runyon, Webb et al., 2006). Reviewing current literature shows that the D-dimer test does assist with the diagnosis of PE. It has a strong negative predictive value, but a positive D-dimer test should always be followed up with further confirmatory testing to reach the diagnosis of a VT.

1.2.4 Differential diagnosis for a positive D-dimer test

There are many conditions associated with fibrin formation, explaining the limited specificity of the D-dimer test. The formation and lysis of fibrin are part of the inflammatory response, acute phase response and a plays a role in the production of various systemic inflammatory mediators. (Wakai et al., 2003). Therefore a positive D-dimer test should always be viewed within the patient's clinical context, with the doctor carefully considering other diagnoses than VT (Table 1.5).

The increase of the D-dimer value in non-pathological conditions, like increased age, compromises the specificity of the D-dimer value as a tool to rule out DVT and PE in certain patient groups, like the elderly (Tita-Nwa et al., 2010).)

Table 1.5 Conditions leading to increased D-dimer values (Wakai et al., 2003).

Non-pathological	**Pathological**
• Cigarette smoking • Increasing age • Functional impairment • Race – black population • Pregnancy • Post-surgical	• Trauma • Pre-eclampsia • Malignancy • Infection • Sickle cell disease • Disseminated intravascular coagulation • Arterial or venous thrombosis • Atrial fibrillation • Acute coronary syndromes • Stroke • Acute upper gastrointestinal haemorrhage

1.2.5 Imaging

In the presence of a positive D-dimer test, the next step to confirm or exclude a VT is requesting the appropriate imaging technique. Most of the confirmation through imaging can either be completed or initiated within the ED.

Although the CXR is usually normal it is useful to exclude other clinical diagnoses (ex. Pneumonia) and should be done as a baseline imaging test. During the later stages a CXR may show signs associated with a pulmonary infarct which include, a Westermark sign (dilatation of the pulmonary vessels and a sharp cut-off), a small pleural effusion, elevated diaphragm or atelectasis. (Ouellette, 2011).

In patients where a PE is suspected CT angiography has become the gold standard imaging test. Ventilation-perfusion (V/Q) scanning is still utilised, but due to the high proportion of inconclusive results CT angiography is the preferred method, where available. Pulmonary angiography is a reliable test, but due to the fact that it is invasive it is usually reserved for cases where either the CT angiography or V/Q scanning is inconclusive. (ESC Task Force, 2008).

In 90% of patients a PE originates from a lower limb DVT and concomitant evidence of a DVT is usually found in 70% of patients with a PE. Due to the high sensitivity and specificity (>90%) of lower limb compression venous ultrasonography (CUS) it has largely replaced the need for venography to diagnose DVT. It can also be used to reduce false negative results from when using a single-detector CT for the diagnosis of PE. (ESC Task Force, 2008).

Different imaging modalities can be utilised to diagnose aortic dissection. These methods include: transthoracic /transoesophageal echocardiography (TTE /TEE), CT, magnetic resonance imaging (MRI), aortography and intravascular ultrasound. Each of them has their own advantages and disadvantages. TEE and TTE can be used in the ED or operating theatre with good accuracy, keeping the limitations in mind. CT is most often used. It has sensitivity of >90% and specificity of >85%, but is limited in diagnosing aortic regurgitation, intimal tears and subtle aortic dissection. MRI has the highest accuracy for detecting all forms of aortic dissection. Its use in the ED is mainly limited by availability. Aortography is not a technique utilised in the ED, but is the standard technique for guiding interventions in aortic dissection. (The Task Force on Aortic Dissection European Society of Cardiology., 2001).

Due to the costs and time needed to perform imaging, appropriate imaging studies, which support the findings on clinical history and examination, should be requested.

1.3 Treatment of VT

Although the EP will not be involved in the long-term treatment of patients with VT, they might initiate definitive treatment upon confirmation of the diagnosis in the ED. Therefore the EP should have a basic knowledge of the treatment modalities for VT.

Patients with suspected DVT or PE should receive full anticoagulation with parenteral heparin, either low-molecular weight or unfractionated heparin. Diagnostic investigations should not delay empirical anticoagulant therapy. Heparin activates antithrombin III which slows the progression of a DVT and reduces pulmonary emboli. Although it does not dissolve the existing clot, it allows the fibrinolytic system to function unopposed . (Tapson, 2008). Oral anticoagulation in the form of warfarin can be started from day one. Heparin is continued for at least five days, until the international normalised ratio (INR) is between 2.0 to 3.0 (Tapson, 2008).

Despite outpatient anti-coagulation therapy with low-molecular weight heparin shown to be effective and safe in clinical trials, Spencer et al. found the morbidity and mortality of outpatient therapy to be higher than reported in clinical trials. They found that co-morbidities including cancer, severe infections and congestive heart failure were associated with poorer outcomes, making admission of these patients for therapy advisable. (Spencer, Goldberg, Lessard et al., 2010).

Other treatment modalities include thrombolytic therapy and surgical care in the form of inferior vena cava (IVC) interruption or IVC filters. These are not always considered as standard therapy, but used in specific clinical situations. (Tapson, 2008).

VT, especially PE is one of the major diagnostic problems in the ED, due to a combination of high incidence but with a non-specific clinical presentation. The 30-day mortality of PE has been reported to be around 7,2%, emphasising the importance of prompt diagnosis and treatment (Martinez Izquierdo, Pallas Villaronga, Clemente Rodriguez et al., 2010).

CHAPTER 2

2.0 DIAGNOSIS AND TREATMENT OF VT IN THE ED

2.1 Prevalence of a positive D-dimer tests in the ED

Corwin et al. (2009) reported a prevalence of 39% positive D-dimer tests in a population with a low clinical suspicion of VT. Kline et al. (2006) supported this figure in another study. They found a prevalence 29,9% (690/2302) in symptomatic patients evaluated for PE in the ED.

In a study conducted in an American ED, a slightly higher prevalence of 44% was found. Out of the 44% of patients with a positive D-dimer test, PE was confirmed in 11% of these patients. The main aim of their study though, was to evaluate factors associated with a positive D-dimer test. Female sex, increasing age (from 4^{th} to 5^{th} decade), surgery, immobility and pregnancy were all strongly associated with a positive D-dimer. Active malignancy was associated with a positive D-dimer test, but not inactive malignancy. They also found that several factors associated with PE were not associated with a positive D-dimer test. These included smoking, obesity, thrombophilia and a family history of VT. (Kabrhel et al., 2010).

2.2 Epidemiology of VT in the ED population

In a retrospective analysis of ED records in Australia the mean age of patients diagnosed with PE within the ED was 60,4 years. Among these patients 54,4% were female. Among the patients admitted from the ED there were 5,6% in-hospital deaths. (Jelinek, Ingarfield, Mountain et al., 2009).

A Spanish review found the mean age of patients to be older, at 70,8 years. They evaluated 30-day mortality which was found to be 7,2%. (Martinez Izquierdo et al., 2010)

2.3 Current ED practice for clinical probability assessment of VT

The ED is where patients with VT often present for the first time. As previously discussed these patients often present with non-specific signs and symptoms, which can be misleading to the EP. This combined with the fact that PE has a high mortality of up to 10% in the first hour, emphasises the importance of an accurate diagnostic strategy, which takes a CPR into account.(Ouellette, 2011).

A study conducted in the Netherlands, showed the importance of doing a CPR. They found that VT was diagnosed in 1,1% of patients with a low clinical probability of VT compared to 9,3% of patients with a high clinical probability of VT. This shows the importance of considering a CPR before D-dimer testing, both to minimise unnecessary testing and to ensure that the diagnosis of VT is not missed. (Gibson, Sohne, Gerdes et al., 2008).

In a retrospective analysis of 100 randomly selected ED records, the documentation of a CPR was evaluated. Only records, in which VT was considered as a diagnosis, were included in the study (97 records). Out of the 97 records a CPR was documented in only 35 patient records. The authors concluded that CPR was not utilised in the majority of cases where VT was suspected. (Smith, Mensah, Sameer et al., 2008).

2.4 Current ED practice for diagnostic testing and management of VT

In another retrospective review the diagnostic process EPs followed in patients with both a low and high clinical suspicion for PE was evaluated. They found that in 42% of patients with a low clinical probability of PE and a positive D-dimer, there was an omission to request a CT. According to diagnostic protocol all these patients should have received a CT scan. They calculated that this caused a potential of a missed diagnosis of PE in 12 patients. In the same publication they reported the discharge diagnoses

among the 605 (42%) of patients who did not receive a CT scan, but had a positive D-dimer. (Corwin, Donohoo, Partridge et al., 2009). Although most of these can also cause a rise in the D-dimer value, the consideration of the diagnosis alone does not exclude the possibility of a PE.

Corwin et al. (2009) also recorded the discharge diagnoses in patients in whom a D-dimer test was done. An unspecified diagnosis described as other was considered in the majority of patients. Chest pain or dyspnoea not otherwise specified was the second most common diagnosis in this group, followed by chronic obstructive pulmonary disease or asthma. Pneumonia, congestive cardiac failure, cardiac arrhythmia, myocardial infarction, acute cholecystitis and pericarditis were the other diagnoses considered.

In a similar review done by Smith et al. (2008) in Canadian EDs, 7 out of 12 (58,33%) patients with a positive D-dimer test received a subsequent imaging test. There were 15 patients with a negative D-dimer test that received imaging unnecessarily. Among the 97 patients included in the study they found that management of 25% of patients were not according to established management protocols.

2.4 Rationale for the current study

Published data on ED practices in the diagnosis and management of VT have shown a lack of utilisation of a CPR and treatment decisions in disagreement with established management protocols for VT. Currently, all published data on ED practices in the diagnosis and management of VT come from countries outside of South Africa.

The D-dimer test is widely available within the South African ED environment and often utilised by EPs. The prevalence of a positive D-dimer test within the South African ED is not known. It would be of value to know if this correlates with the prevalence found in publications from other countries, where the demographic characteristics of patients might differ.

The limited time a patient spends in the ED provides a short, but critical window of opportunity for the EP to diagnose VT. With the knowledge that the early diagnosis of VT within the ED environment can reduce VT mortality, it would be valuable to evaluate the current practice of South African EPs in the diagnosis and management of VT, in order to identify if a need exists for improvement of their current practice. The evaluation of the current practice will incorporate the utilisation of a CPR, the actions taken in reaction to a positive D-dimer test, including both diagnostic testing and treatment initiated within the ED.

Because resources are limited, doctors are forced to consider the diagnostic and management costs of patients. On the other hand doctors also strive to adhere to practices supported by evidence based medicine. This emphasises the importance of adhering to a diagnostic approach, which ensures accurate diagnosis of conditions without the overuse of resources.

2.5 Aims of the current study

The aims of this study are

- To establish the prevalence of a positive D-dimer test in a South African private ED.
- To document the differential diagnosis considered in patients with a positive D-dimer test.
- To compare the management of patients with a positive D-dimer test in a private ED to published clinical management recommendations.
- To establish the clinical utility of the Wells Score in patients with a positive D-dimer test.
- To document the clinical outcome of patients with a positive D-dimer test within the private ED.

CHAPTER 3

3.0 MATERIALS AND METHODS

3.1 Study design

This is a retrospective cross-sectional uncontrolled study that compared the management of patients with a positive D-dimer test, in a single private South African hospital ED, to international published ED management standards.

3.2 Human research ethics clearance

Permission to use the patient and laboratory records for this study was sought from the institutional protocol review committee prior to study initiation. As this was a retrospective analysis of patient records no patient informed consent form was required prior to data access. Permission to utilise the data was obtained from the management of Lancet laboratories and the hospital manager at Flora Clinic. Unconditional ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee, clearance certificate number M10449, which is included as appendix A of this dissertation.

3.3 Setting of the study

The entire patient records analysed in the study was obtained from Flora Clinic ED situated in Johannesburg, Gauteng, South Africa. Flora clinic is a private hospital with a 24 hour ED facility, which manages both trauma and medical emergencies, for patients choosing to utilise private healthcare.

Laboratory data was obtained from Lancet Laboratories, an independent South African National Accreditation System (SANAS) accredited laboratory, contracted to do all laboratory diagnostic tests on patients presenting to the Flora Clinic ED.

3.4 Selection of patients for the study

The study population included all patients who presented at the Flora Clinic ED, in whom a D-dimer test was done during the seven month study period, which was from 1 November 2008 to 31 May 2009. The study population included patients with medical as well as surgical conditions.

Both male and female patients, above 18 years of age, were included in the study population. Patients below 18 years of age were excluded from the study, as most of the conditions associated with a raise in the D-dimer test do not occur frequently within the paediatric population.

3.5 Sample size calculation

Sample size calculation was based on the desired precision of the primary outcome, which was the proportion of charts with documentation of the pre-test probability scores and management of positive D-dimer tests against published protocols.

Assuming that the ED visit documentation rate was approximately 75% we determined that we would need to review 63 charts to produce a confidence interval (CI) for our estimate of the primary outcome that would not be wider than 5%. The study sample was increased to 100 to allow for an unknown documentation rate.

3.6 Data collection

3.6.1. D-dimer test result

All D-dimer test results requested on patients in the Flora Clinic ED from 1 November 2008 up to 31 May 2009 were obtained from the Lancet laboratory. Lancet laboratories use the Vidas D-dimer test method. It is an immuno-enzymatic elimination of fibrin degradation products in human serum, using ELFA. It is reported to have an overall sensitivity, regardless

of pre-test probability of between 98.4-100% and a specificity of between 34.2-41.3% (Perrier, 2004). These performance characteristics make it an excellent screening test.

D-dimer test results were divided into positive or negative according to the Vidas test reference ranges established by Lancet laboratory. All results ≥ 0,5 ug/ml were reported as positive. Results < 0.5 ug/ml was classified as negative. Results were entered into an excel spreadsheet.

3.6.2. Clinical notes

The clinical notes and special investigation report forms, present in the patient files of patients with positive D-dimer tests, during the defined study period were also reviewed. Should patient records be missing in patients where the laboratory results were available, the patients were still included in the study. In these instances, demographic data could still be obtained from the laboratory results and were included in the data analysis. Data analysis that depended on data captured from the clinical notes could not be obtained and therefore these patients' data were excluded from all analysis that relied on data from the patient records as source.

The management of these patients within the ED and special investigations requested in response to the positive D-dimer result were evaluated. The elements of the Wells Score noted in the clinical notes of emergency EPs working at Flora Clinic ED, in patients who had a positive D-dimer test, during the study period were also recorded and the total percentage of Wells Score elements mentioned in the clinical notes was calculated per element.

Subsequently the outcomes of patients with a positive D-dimer test, within the ED were also determined. The clinical notes were evaluated to see which differential diagnosis was considered for each patient and which special investigations were requested within the ED.

3.6.3. Data collection sheet

The collected data were transferred onto a data collection sheet (Appendix B). To ensure patient confidentiality, the data sheet was anonymous with patient names and other personal identification details removed and replaced by a study number. All data sheets were kept separate from all the mentioned results for the purpose of analysis and reporting of data.

Reporting of data was done on all patients eligible for the study, as defined by the inclusion and exclusion criteria during the defined study period. All data captured on the data collection sheets were inserted into 2X2 tables using excel spreadsheets.

3.7 Statistical analysis

Descriptive and inferential statistics were used to explore and analyse the data respectively. Measures of central tendency (mean, median and mode) and measures of variability (standard deviation and range) were used to describe continuous variables. Frequency distribution tables were used to describe categorical variables. To compare pairs of categorical variables the Chi-Square and where appropriate the Fischer's exact test were used. The student's t-test was used to analyse pairs of a continuous variables.

The 95% confidence intervals and standard deviation for all the results were calculated. Statistical significance was ascertained at the 5% level, at which level a p-value of less than 0.05 would show statistical significance.

A biostatistician was consulted to assist with complex statistical analytical processes.

CHAPTER 4

4.0 RESULTS

4.1 Study population selection

The results from the study population selection process are depicted graphically in Figure 4.1 below. Between 1 November 2008 and 31 May 2009 there were 365 D-dimer tests requested in the Flora Clinic ED. Among these 220 (60%) of the results were negative and the balance positive (40%). One patient with a positive D-dimer test was below 18 years of age, and therefore excluded from the study. In 144 (99%) of patients with a positive D-dimer test, all the inclusion criteria were met. Out of the 144 patients who met the inclusion criteria 122 (85%) patient records were available for further data analysis. There were 22 (15%) patient records that could not be located at the time of the study, and as outlined in section 3.6.2, these patients had to be excluded from data analysis which relied on the patient records as main source. Demographic data, available on the pathology reports could still be used for the 22 patients with missing patient records.

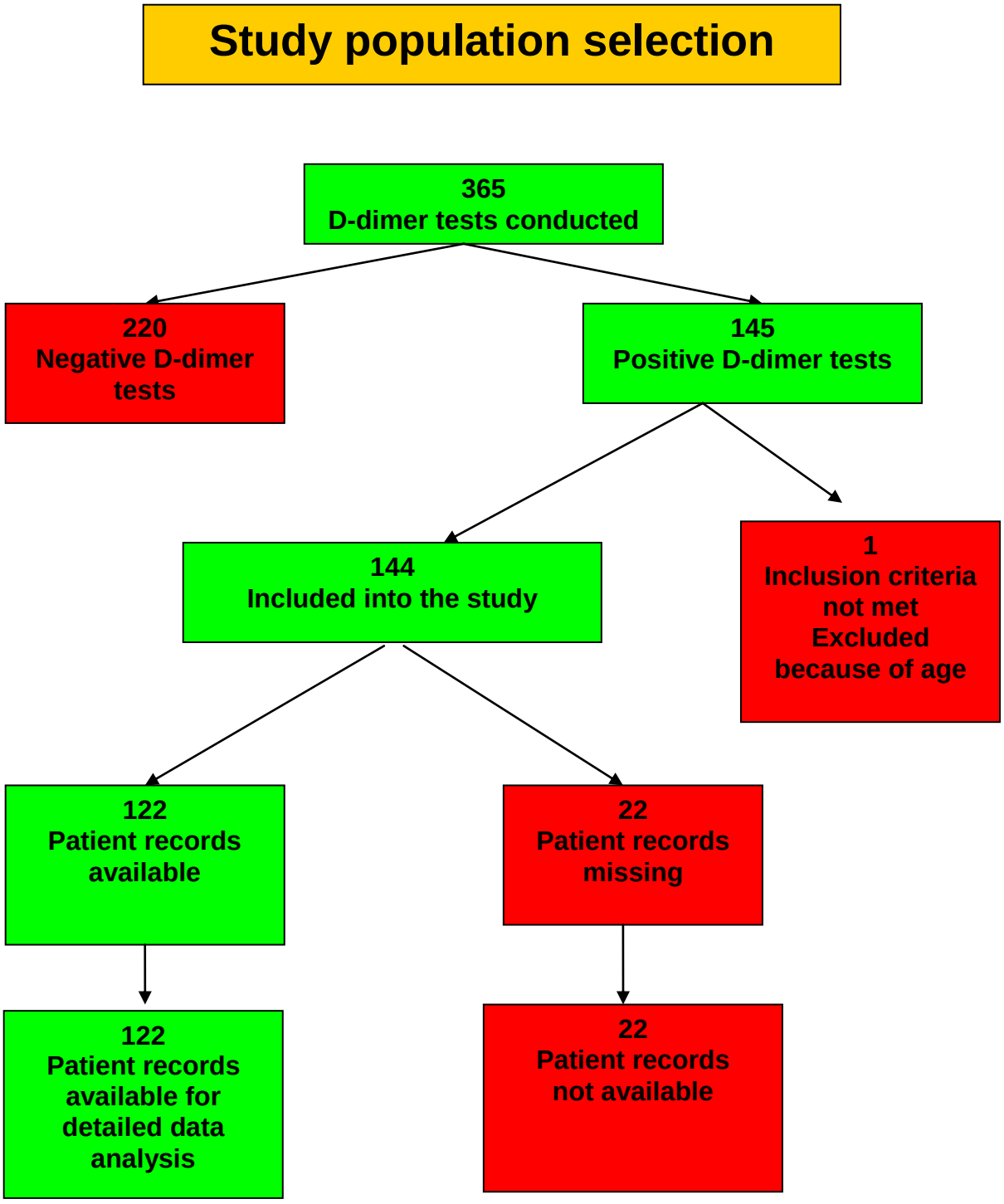


Figure 4.1 Study population selections

4.2 Study population demographics

The mean age of the 144 patients with positive D-dimer tests, who met the inclusion criteria, was 62 years with a range from 19-94 years. In the selected study population there was a slight predominance of males comprising 76 (53%) subjects. Patient records were analysed sequentially according to study number.

4.3 Study population D-dimer values

The prevalence of a positive D-dimer test among adult patients presenting in the Flora Clinic ED in whom a D-dimer test was requested, within the specified study period, was 39%.

The D-dimer values of the study population, at the time of presentation in Flora ED, are shown in Table 4.1 below. The mean D-dimer value in the study population was 2,58 µg/ml with a range of 0,51-41,40 µg/ml.

Table 4.1 Study population D-dimer values

Patient study number	D-dimer value (ug/ml)	Patient study number	D-dimer value(ug/ml)
1	1.59	**73**	1.39
2	0.79	**74**	3.68
3	6.15	**75**	2.15
4	4.93	**76**	1.45
5	1.47	**77**	0.71
6	1.08	**78**	1.00
7	1.67	**79**	1.35
8	0.67	**80**	1.24
9	0.59	**81**	1.35
10	0.83	**82**	1.44
11	0.64	**83**	0.55
12	1.23	**84**	0.52
13	1.01	**85**	0.74
14	1.10	**86**	9.09
15	1.25	**87**	0.61
16	3.02	**88**	10.00
17	2.38	**89**	0.98
18	0.81	**90**	4.48
19	1.75	**91**	28.65
20	0.53	**92**	1.15
21	8.84	**93**	1.46

Patient study number	D-dimer value (ug/ml)	Patient study number	D-dimer value(ug/ml)
22	1.38	**94**	1.50
23	1.12	**95**	4.10
24	1.12	**96**	0.68
25	1.07	**97**	2.20
26	1.08	**98**	0.98
27	1.66	**99**	0.77
28	1.40	**100**	0.69
29	0.87	**101**	0.57
30	0.74	**102**	1.79
31	0.59	**103**	0.53
32	0.58	**104**	1.85
33	5.19	**105**	0.61
34	1.59	**106**	0.55
35	1.40	**107**	3.91
36	1.21	**108**	0.75
37	1.59	**109**	0.53
38	6.85	**110**	0.82
39	0.57	**111**	0.84
40	1.58	**112**	0.62
41	0.70	**113**	1.82
42	0.57	**114**	1.12
43	1.72	**115**	7.91

Patient study number	D-dimer value (ug/ml)	Patient study number	D-dimer value(ug/ml)
44	1.03	**116**	2.49
45	2.36	**117**	0.53
46	0.58	**118**	2.67
47	0.52	**119**	4.90
48	0.98	**120**	5.61
49	0.61	**121**	1.14
50	0.69	**123**	1.80
51	1.49	**124**	4.19
52	2.07	**125**	3.37
53	1.73	**126**	6.03
54	1.11	**127**	0.90
55	8.42	**128**	0.66
56	1.63	**129**	1.09
57	0.73	**130**	6.54
58	14.70	**131**	0.70
59	0.60	**132**	1.07
60	6.85	**133**	2.88
61	2.03	**134**	5.14
62	0.81	**135**	6.06
63	0.63	**136**	0.55
64	4.54	**137**	41.40
65	1.70	**138**	1.74

Patient study number	D-dimer value (ug/ml)	Patient study number	D-dimer value(ug/ml)
66	0.51	**139**	0.71
67	2.31	**140**	8.27
68	0.96	**141**	0.80
69	0.56	**142**	2.71
70	8.00	**143**	1.43
71	0.77	**144**	1.05
72	1.20	**145**	5.73

4.4 Differential diagnoses in patients with a positive D-dimer test

There were 163 differential diagnoses entries in the clinical notes. In ten (7%) of the patient records no differential diagnosis was documented. There were on average 1,13 differential diagnoses per patient record documented.

The differential diagnoses were categorised according to the main organ system involved, as shown in Figure 4.2. The actual differential diagnoses and their frequencies are shown in Table 4.2. In 36 (25%) of the patient records, VT was considered as one of the differential diagnoses and it constituted 22% of all the differential diagnoses considered. Among the other diagnoses considered acute myocardial infarction (12 patients) was the most frequent, with respiratory tract infection, including pneumonia second (10 patients) (Table 4.2b).

Of the 163 entries 61% (99 entries) were of conditions that could be associated with an increased D-dimer titre. These constituted 18 out of the 48 different differential diagnoses considered (38%).

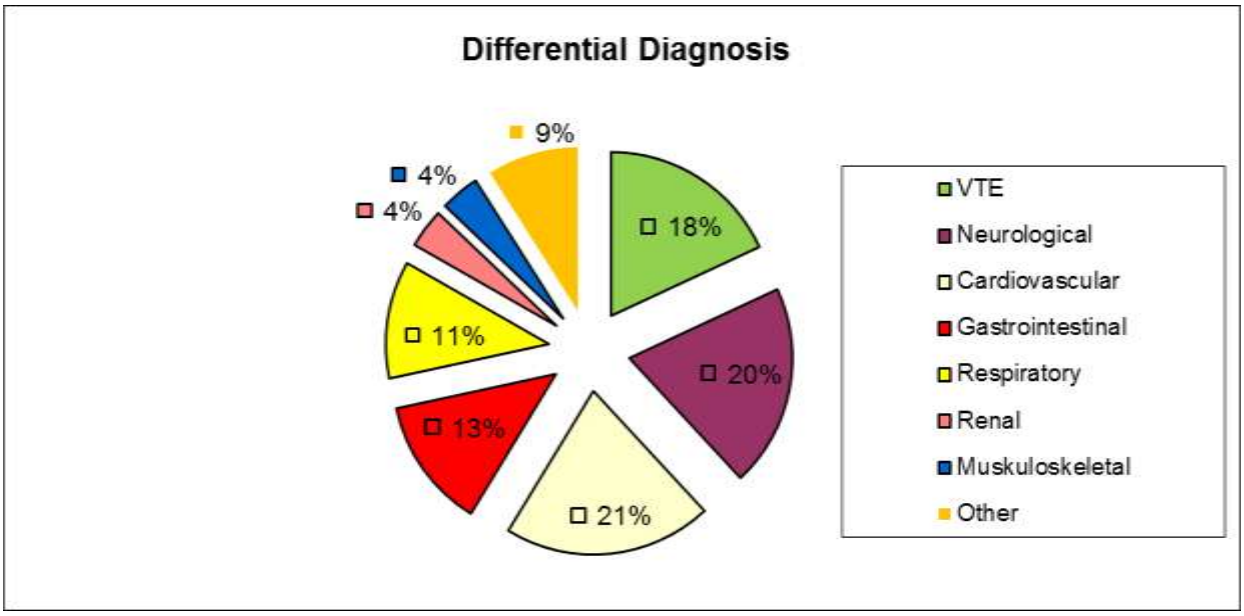


Figure 4.2 Categorisation of the differential diagnoses

Table 4.2 (a) Listing of differential diagnoses

System	Category	Frequency
-	-	-
Neurological		31
-	Cerebrovascular incident	8
-	Seizure/Epilepsy	7
-	Transient ishaemic attack	4
-	Anxiety	3
-	Syncope	3
-	Dizziness	2
-	Intracranial bleed	2
-	Confusion	1
-	Hemorraghic brain metastases	1
Cardiovascular		68
-	VT	36
-	Acute myocardial infarction	12
-	Unstable angina	5
-	Hypertension	4
-	Atrial flutter/atrial fibrillation	2
-	Congestive cardiac failure	2
-	Hypovolaemic/septic shock	2
-	Arterial occlusion of foot	1

-	Dissecting aortic aneurysm	1
-	Heartblock	1
-	Venous stasis leg	1
-	Ventricular tacycardia	1
-	-	-
Gastrointestinal		20
-	Gastritis/Peptic ulcer	5
-	Hiatus hernia/dyspepsia	4
-	Oesophagitis	4
-	Cholecystitis/gallstones	2
-	Dehydration	2
-	Partial bowel obstruction	1
-	Strangulated hernia	1
-	Sub-acute abdomen	1
-	-	-
Respiratory		18
-	Pneumonia/Respiratory tract infection	10
-	Dyspnea/pulmonary edema	2
-	Unspecified chest pain/pleurisy	2
-	Bronchitis	1
-	Bronchospasm	1
-	Pulmonary collapse	1
-	Sinusitis	1

-	-	-
Renal		6
-	Pyelonephritis/urinary tract infection	5
-	Renal failure	1
-	-	-
Muskuloskeletal		6
-	Cellulitis/soft tissue infection	3
-	Baker's cyst	1
-	Lumbar disc prolapse	1
-	Thoracic spine arthritis	1
-	-	-
Other		14
-	Injury/Trauma	5
-	Cancer	3
-	Hyperglycaemia	3
-	Polypharmacy	1
-	Hypoglycaemia	1
-	Iron deficiency anemia	1
Total	-	163

Table 4.2(b) Most frequent differential diagnoses considered

Differential diagnosis	Frequency
VT	36
Acute myocardial infarction	12
Pneumonia/Respiratory tract infection	10
Cerebrovascular incident	8
Seizure/Epilepsy	7
Pyelonephritis/urinary tract infection	5
Injury/Trauma	5
Unstable angina	5
Transient ishaemic attack	4
Hypertension	4
Hiatus hernia/dyspepsia	4
Oesophagitis	4

4.5 Utility of the Wells Score in patients with a positive D-dimer test

The patient records were evaluated for any entry, by the attending doctor in ED, that relates to the criteria on either the Wells Score for DVT or PE (see Table 1.2 and 1.3). The presence of each element of the Wells score was evaluated, regardless of the value allocated to that specific element or the differential diagnosis considered.

The number of entries per Wells Score element is shown in Table 4.3 and 4.4 for PE and DVT respectively. In 79% (113 entries) of the patient records an alternative diagnosis less likely than PE was considered, making it the most frequent element from the Wells Score for PE documented. Haemoptysis was only documented in 1 (0,69%) patient record, making it the least documented element from the Wells Score for PE.

There were 312 entries across the 144 patients included that related to one of the Wells Score elements for PE, with an average of 2,17 entries per record. The highest amount of elements documented per record was 6, while some of the records had no entries.

On the Wells Score for DVT an alternative diagnosis more likely than DVT was considered in 106 (74%) patient records, being the element documented most frequently. The element from the Wells Score for DVT documented the least was unilateral pitting oedema of the symptomatic leg, with only 3 (2%) entries. There were 250 entries in the 122 that could be linked to the Wells Score elements for DVT, with an average of 1,74 entries per record. The highest number of elements documented per record was also 6, with 0 entries being the lowest.

In none of the records where VT was considered as a diagnosis could a formal documentation of any pre-test probability evaluation be found and therefore there weren't any records where all elements were considered once the diagnosis of VT was considered.

Table 4.3 Wells Score elements for PE documented

Clinical factor	**Clinical note entries**	**% of clinical notes in which mentioned**
Clinically suspected DVT	14	9
Alternative diagnosis less likely than PE	113	79
Tachycardia	108	75
Immobilisation/surgery in previous four weeks	51	35
History of DVT or PE	12	8
Haemoptysis	1	0.69
Malignancy (treatment within 6 months/ palliative)	13	9
Total entries	**312**	

Table 4.4 Wells Score elements for DVT documented

Clinical factor	Clinical note entries	% of clinical notes in which mentioned
Active malignancy	13	9
Paralysis, paresis or recent plaster immobilisation lower extremities	41	29
Recently bedridden ≥ 3 days, or major surgery within last 12 weeks	42	29
Local lower extremity tenderness along deep venous system	10	7
Swollen thigh and calf	10	7
Calf swelling ≥ 3 cm larger than asymptomatic leg	4	3
Unilateral pitting oedema of the symptomatic leg	3	2
Unilateral dilated superficial veins symptomatic leg	14	10
Previously documented DVT	7	5
Alternative diagnosis at least more likely that DVT	106	74
Total entries	**250**	

4.6 Management of patients with a positive D-dimer test

The management of patients in the Flora Clinic ED was evaluated through looking at both special investigations requested in the ED and treatment initiated in the ED. These were compared to international published protocols for the management of both DVT and PE (see Figures 4.3 and 4.4). The decision, if the special investigations and treatment compared to international published protocols, was based on clinical judgement and if the outcome of the special investigations was taken into account to decide whether the treatment given was according to published protocols.

There were 16 special investigations requested according to published protocols, in 15 different patient records. The details of the special investigations requested are reflected in Table 4.5 below. In 10 (63%) the results confirmed a VT, through the results of 5 (31%) tests VT could be excluded and in one (6%) case the results were not available.

In 15% (22 patient records) no treatment was initiated. In the remaining 100 records, where treatment was documented, 15 (10% of total patient records evaluated) were according to published protocols. The detail of all the treatment given in the ED is given in Table 4.6 below. There were a total of 40 different treatments given, with intravenous (IV) fluid therapy being the

treatment given most commonly, in 44 (31%) of patients. Intravenous paracetamol, given in 23 (16%), was the pain relief given most frequently. There were an average of 1,53 different treatment entries per patient record.

Table 4.5 Special investigations requested in Flora Clinic ED for patient with positive D-dimers

	Number	As % of patient records
Investigations mentioned		
Repeat D-dimer	1	0.69
Abdominal sonar	1	0.69
VQ scan	1	0.69
CT angiogram chest	1	0.69
CT chest	3	2
Duplex doppler	6	5
CT brain	1	0.69
Chest X-ray	1	0.69
Venogram	1	0.69
Total	**16**	**11**

Table 4.6 Different treatments initiated in Flora Clinic ED in patients with positive D-dimers

Category	Treatment strategy in ED	Number recorded
Pain relief		
	Paracetemol IV (Perfalgan)	**23**
	Tramadol IV	**5**
	Parecoxib IV	**8**
	Pethidine IV	**1**
	Lentogesic® p.o	**1**
	Synap Forte® p.o	**2**
	Ketorolac IV	**1**
	Myprodol® p.o	**1**
Antispasmodics		
	Hyoscine IV	**3**
Antibiotics		**8**
Anticoagulation/fibrinolytics		
	Streptokinase IV	**1**
	Enoxaparin	**9**
	Aspirin p.o	**17**
	Warfarin p.o	**2**
	Heparin IV	**1**

Category	Treatment strategy in ED	Number recorded
Ventilation/Respiratory support		
	Intubation	**3**
	Oxygen per face mask	**10**
	Nebulisations: Ipratropium/Salbutamol	**1**
Electrolytes/Metabolic/Fluid		
	Potassium	**1**
	IV fluid therapy	**44**
	Insulin	**2**
Sedatives		
	Hydroxyzine p.o	**1**
	Lorasepam IV	**5**
	Diazepam IV	**1**
	Midazolam IV	**2**
	Promethazine	**1**
Anti-arrhythmic		
	Amiodarone IV	**1**
Antacid therapy		
	Esomeprazole IV	**18**
Anti-emetics		
	Metoclopramide IV	**9**
	Procholrperazine IV	**1**

Category	Treatment strategy in ED	Number recorded
	Odansetron IV	**1**
Anti-epileptics		
	Phenytoin IV	**1**
Corticosteroids		
	Hydrocortisone IV	**1**
	Decadron IV	**1**
Diuretics		
	Furosemide IV	**2**
Other		
	Transfer to other facility	**2**
	PE excluded	**1**
	Repeat D-dimer	**2**
	TNT	**7**
	Ice packs	
	Compression bag	**1**
	Elevation of leg	**1**
	NG Tube	**1**
No treatment		**18**

4.7 Outcome of patients with a positive D-dimer test in the ED

The final outcome of treatment in the ED is reflected in Figure 4.3 below. The majority (55%) of patients were admitted to hospital for further specialist treatment. Among the outcomes 9 (6%) patients did not fall into a specific outcome category. The details of the other outcomes are given in Table 4.7 below.

In 23 (16%) of the patient record a recording could be found of the procedures planned after discharge from the ED. Out of the 23 records, three had recorded the outcome of these clinical tests or procedures conducted post ED discharge. The details of these procedures and outcomes are shown in Table 4.8 below.

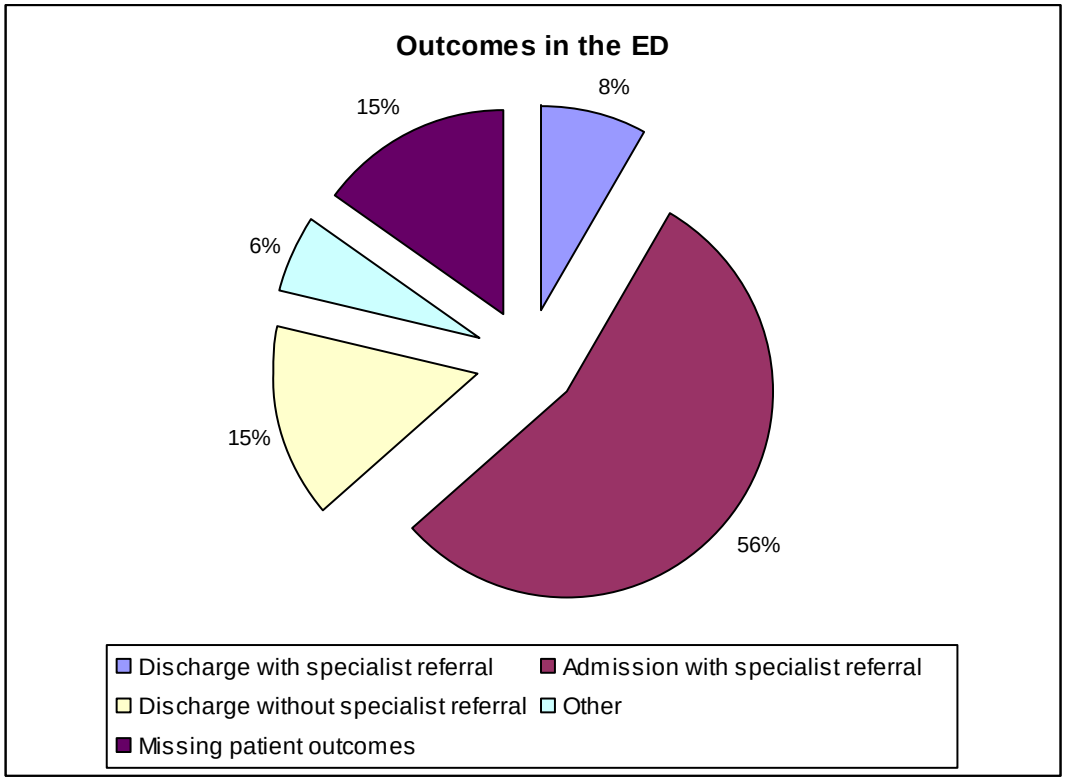


Figure 4.3 Outcomes in the ED

Table 4.7 Detail of ED outcomes grouped under "Other"

Detail of other outcomes	**Number**
Follow up in the ED for re-evaluation	2
Telephonic consultation with specialist	5
Venogram booked as out patient	1
Referral to another hospital due to financial reasons	1
Total	**9**

Table 4.8 Procedures and outcomes post ED

Outcome in ED	**Details of clinical procedures planned post ED**	**Outcome**
Admitted with specialist referral	Admitted for ventilation post intubation	unknown
Admitted with specialist referral	Admitted for intensive care monitoring	unknown
Admitted with specialist referral	Admitted to intensive care for repeat blood tests and isosorbide dinitrate infusion	unknown
Admitted with specialist referral	Admitted work-up and confirmation of pulmonary embolus diagnosis	unknown
Discharged without specialist referral	VQ scan done in casualty - PE excluded	PE excluded
Admitted with specialist referral	Admit for repeat D-dimer test	unknown
Discharged without specialist referral	Spiral CT chest was done	unknown
Admitted with specialist referral	Intensive care observation	unknown
Admitted with specialist referral	For intensive care monitoring	unknown

Outcome in ED	**Details of clinical procedures planned post ED**	**Outcome**
Follow-up for in ED for re-evaluation	Venogram	unknown
Telephonic consultation with specialist	Spiral CT chest	Normal
Admitted with specialist referral	Admitted for pain relief, surgical consultation	unknown
Discharged with specialist referral	To omit Warfarin tablet, repeat PI in 2 days	unknown
Admitted with specialist referral	To high care on an insulin sliding scale	unknown
Admitted with specialist referral	Admit and place nasogastric tube	unknown
Referral to another hospital due to financial reasons	For transfer and specialist treatment at state hospital	unknown
Admitted with specialist referral	Admitted and CT scan performed	Dissecting aortic aneurysm diagnosed
Discharged with specialist referral	Follow up with cardiologist	unknown
Admitted with specialist referral	Admitted to high care for observation	unknown

Outcome in ED	**Details of clinical procedures planned post ED**	**Outcome**
Admitted with specialist referral	For CT scan chest, administration of low molecular weight heparin	unknown
Discharged with specialist referral	For stress ECG	unknown
Admitted with specialist referral	For IV antibiotics	unknown
Admitted with specialist referral	For repeat D-dimer	unknown

CHAPTER 5

5.0 DISCUSSION AND CONCLUSION

5.1 Demographic data

This study provides demographic data on patients with a positive D-dimer test, no current publications mentioned demographic characteristics in this subset of patients, which makes this data unique. The mean age of 62 years of patients with a positive D-dimer test, in this cohort, is much higher than values reported by for example Kline et al. (2006), who reported a mean age of 44,7 years among patients in whom a D-dimer test was requested in the ED. This would support the data which stated that the incidence of a positive D-dimer test increases with age (Harper, Theakston, Ahmed et al., 2007). Although this possibility exists within this cohort, the demographics of patients with a negative D-dimer test were not evaluated, so this could not be confirmed. Among the 144 patients with a positive D-dimer test, no association could be found between the actual D-dimer value and the age of the patient (P=0,22).

There were fewer females than males with a positive D-dimer test (47 vs. 53%). Although more males presented with a positive D-dimer test, no statistical gender difference could be found between actual D-dimer values once the D-dimer was positive (p=0.98). No published data could be found, to evaluate if this trend also exists in other studies.

5.2 Prevalence and predictors of a positive D-dimer test

The positive D-dimer prevalence of 39% compares to data published by Corwin et al. (2009) of 39%, evaluating the prevalence in an American ED. The prevalence was lower in another American publication which found that 29,9% of patients had a positive D-dimer test (Kline et al., 2006).

Although the main objective of this audit was not to find associated factors with positive D-dimer results we could test the association between the D-dimer value and available outcome and demographics. No association could be found between age or sex and how high the D-dimer value was. The only statistically significant association was between the D-dimer value and admission rates (p=0.02). The higher the D-dimer value, the more likely the EP was to admit the patient for further work-up and treatment. This differs from an evaluation by Kabhrel et al. (2010) which found multiple factors associated with a positive D-dimer test.

5.3 Differential diagnoses considered in the ED

The recording of the differential diagnoses in the majority of the clinical notes were made before the D-dimer test was either requested or the

results available. Thus in this study the differential was based on the clinical presentation of the patient alone. Keeping in mind that the differential, thus should have been based on a clinical probability assessment for VT, it was surprising to find that in only 25% of patient files VT was considered as a motivation for requesting a D-dimer test, as part of the diagnostic work-up. There were a substantial amount of other differentials considered (61% of differential entries) that could also be associated with a positive D-dimer test, but these in themselves could not serve as a motivation to request the D-dimer test, and should it be requested and found positive it should still be followed by appropriate imaging tests.

5.4 Utility of the Wells Score

Although the elements of the Wells Score were present in all the clinical records evaluated in this study, none of the clinical notes had a formal CPR evaluation recorded. This could be explained by various reasons, including calculation of a CPR by the EP without formal recording, or a lack of emphasis and awareness of the importance of CPR evaluation. The Flora Clinic ED is not linked to an academic centre, and being responsible for their own continued medical education, EPs practising here are not all exposed to an academic environment in which up-to-date information on

patient treatment and management is distributed frequently. The results from this cohort are in contrast to findings by Corwin et al. (2008), who found that 36% of records from EPs considering VT as a diagnosis contained a formal CPR recording.

In view of the non-specific nature of VT presentation and the difference between the incidences of VT in patients with a low versus a high clinical probability for VT (Gibson et al., 2008), the lack of CPR recording is alarming. The danger of under-diagnosis and maltreatment is increased. The assessment of a pre-test probability does not need the utilisation of extra recources and streamlines diagnostic and treatment decisions. Awareness, improved utilisation and recording of a CPR is needed among EPs practising in the Flora Clinic ED, to ensure appropriate management of patients with a positive D-dimer test result.

5.5 Management of patients in the ED

According to published international protocol all patients with a positive D-dimer test and suspected VT should undergo either CT imaging of the chest or limb ultrasonography, depending if the diagnosis of PE or DVT is considered. Among the patients in Flora Clinic ED 11% received a special investigation according to treatment protocol. These included other diagnostic modalities (ex. Chest X-ray), apart from a CT scan, which are

also within diagnostic and treatment protocols. Corwin et al. (2009) only evaluated patients with a possible PE. They determined that 58% of patients with a positive D-dimer test received a CT scan. For the purpose of comparison, only the % of patients who received chest imaging (3%) were compared to the data from the study done by Corwin et al. (2009). A difference of 54% was found between the % of chest imaging requested among EPs in the Corwin et al. (2009) publication and EPs at Flora Clinic. This has reached a statistical significance with a p-value of < 0.0001. Patient numbers in our study was much smaller and conducted over a shorter period of time, which could have had an influence on the results, but both studies were done in a single centre.

The 15% of patients where no treatment was initiated, could not be compared to any trend in published data, but might point to ignorance and a lack of understanding about the implications of a positive D-dimer test. Among patients in the Flora Clinic ED, only 10% of patients received treatment according to published treatment protocol, highlighting that education is needed among these EPs concerning patient management of suspected VT. This is much lower than Corwin et al. (2009) who established that 75% of patients in their study were managed according to treatment protocol.

Not only do the EPs at Flora Clinic not record utilisation of a CPR, but once a positive D-dimer result is obtained it does not prompt appropriate diagnostic testing according to established protocols. The omission of utilising a CPR, could lead to unnecessary and random D-dimer test requests. Once a test is just requested randomly without clinical motivation it could lead to ignorance of the implications of such a test result. This could explain why the majority of EPs did not record appropriate action in response to the positive D-dimer test.

5.6 Patient outcome in the ED

Despite the lack of management according to published treatment protocols for VT the majority of patients (55%) with a positive D-dimer test were still admitted to hospital and referred for specialist treatment. As previously discussed the association was even stronger between admission and a higher D-dimer value. This might indicate that the EPs were at least considering the positive D-dimer test to be of enough importance for further work-up, that the positive D-dimer test could have accidentally been associated with other conditions that prompted admission or that they admit patients out of a fear of litigation.

Although patients with a positive D-dimer test was more likely to be admitted it must be highlighted that this still does not ensure the diagnosis

or exclusion of VT and does not support clinical practice in the best interest of the patient. A delay in the diagnosis of VT, leads to a delay in the initiation of life-saving treatment with a possible effect of patient mortality and morbidity.

5.7 Limitations of the study

- Due to limited access to clinical notes and laboratory results the study could only be conducted over a 28 week period. Therefore the study sample was small and no conclusion could be made about the trend the data follows over a long period of time.
- This study was conducted at a single centre, results might not be representative of patients seen in the rest of South Africa and therefore not be generalised.
- There were 22 clinical notes that could not be found in the patient files. Only demographic data and D-dimer values were available for these patients. They had to be excluded from all data analyses beyond that point. The absence of data from these 22 patients could have had an influence on the overall results found in the study.
- The differential diagnosis from one record could not be included due to illegibility of that entry in the clinical notes.

- Due to the retrospective nature of the study and the reliance on patient records for information, any outcomes or decisions that were not recorded in the notes could not be utilised as evidence.

- In most cases the patients were discharged from the ED before a final diagnosis was made. Therefore the final outcome of most of the patients was limited, not excluding the possibility that the diagnosis of VT could still be made.

5.8 CONCLUSION

The prevalence of a positive D-dimer test in patients presenting at Flora Clinic ED, of 39%, correlates with that found in some other publications. There was no formal evaluation of a pre-test probability in any of the clinical notes, in addition only 10% of patients received treatment according to published treatment protocols. This suggests that the assessment of pre-test probability is not done in a formalised manner and that a positive D-dimer test is either misinterpreted or that knowledge gaps exist among the EPs regarding the correct management of a positive D-dimer test. The study served in identifying the current trend of practice among EPs in the South African environment. Further studies evaluating the reasons for and methods to improve the under-utilisation of both CPRs and established treatment protocols will be useful.

APPENDIX A: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Adriana Josina Rudolph

CLEARANCE CERTIFICATE	**M10449**
PROJECT	Positive D-Dimer Results in a Private Hospital Emergency Department (ED): an Audit of Patient Management and Outcomes (POSED Study)
INVESTIGATORS	Dr Adriana Josina Rudolph.
DEPARTMENT	Division of Emergency Medicine
DATE CONSIDERED	30/04/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 11/04/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof JN Mahlangu

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX B: DATA COLLECTION SHEET

Patient number:

Demographic data:

Age (years)	
Sex (male/female)	

Inclusion criteria present:

The following criteria have to be present (mark with an X):

	Yes	No
Presented to Flora Clinic Emergency Department		
Presenting between November 2008 and May 2009.		
Patient $\geqslant$ 18 years of age		
Positive D-dimer test recorded		
Value of D-dimer test		

The answer to all of the above should be yes for the patient to be included

Total of inclusion criteria met:

Yes	No

Elements of the Wells score present in the clinical notes:

Wells Score in suspected PE:

	Considered In clinical notes (yes/no)
Clinically suspected DVT (as mentioned in clinical notes)	
Alternative diagnosis less likely than PE (as interpreted by investigator or mentioned in the notes)	
Tachycardia	
Immobilization/surgery in previous four weeks	
History of DVT or PE	
Haemoptysis	
Malignancy (treatment within 6 months/ palliative)	
Total of elements mentioned in patient score	

Wells Score in suspected DVT:

	Considered in clinical notes Y (yes) or N (no)

Active malignancy (on-going treatment or within last 6 months or palliative)	
Paralysis, paresis or recent plaster immobilisation of the lower extremities	
Recently bedridden for ⩾ 3 days or major surgery within the last 12 weeks using general anaesthesia	
Local lower extremity tenderness along the deep venous system	
Swollen thigh and calf	
Calf swelling ⩾ 3 cm larger than asymptomatic leg	
Unilateral dilated superficial veins of symptomatic leg (non-varicose)	
Unilateral pitting oedema of symptomatic leg	
Previously documented DVT	
Alternative diagnosis more likely than DVT considered	

<u>Differential diagnosis:</u>

Has there been any response documented in reaction to the positive D-dimer test?

Yes	
No	

If the answer is yes:

Was the diagnosis of VT (PE or DVT) considered by the attending doctor in the emergency department (mark with an X)?

Yes	
No	

List other differential diagnosis considered by the attending doctor in the emergency department (in the order mentioned in the notes):

1.	
2.	
3.	
4.	
5.	

<u>Patient outcome in the ED:</u>

Was any treatment initiated in response to the positive D-dimer test?

Yes	No

If the answer to the question is yes specify the treatment given:

1.	
2.	
3.	
4.	

5.	

Action plan post ED visit planned by the EP in response to the positive D-dimer test:

EP's action	Yes/No/Unsure
No further action upon positive D-dimer result	
Specialist referral	
Patient admitted	
Other: Specify 1. 2. 3.	

Was the action plan post referral or admission documented?

Yes	No

If the answer to the previous question was yes specify the action plan:

Special investigations requested EP in response to the positive D-dimer test:

Were any further special investigations requested?

Yes	No

If the answer is yes specify the following:

Test requested	Outcome
1.	
2.	
3.	

REFERENCES

Adam, S.S., Key, N.S. &Greenberg, C.S. 2009. D-dimer antigen: current concepts and future prospects. *Blood*,vol. 113,pp. 2878-2887.

Bulger, C., Jacobs, C. &Patel, N. 2004. Epidemiology of acute deep vein thrombosis. *Tech Vasc Interv Radiol*,vol. 7,pp. 50-54.

Corwin, M.T., Donohoo, J.H., Partridge, R., et al. 2009. Do emergency physicians use serum D-dimer effectively to determine the need for CT when evaluating patients for pulmonary embolism? Review of 5,344 consecutive patients. *Am J Roentgenol*,vol. 192,pp. 1319-1323.

Eichinger, S., Heinze, G., Jandeck, L., et al. 2010. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism. The Vienna prediction model. *Circulation*,vol. 121,pp. 1630-1636.

Gibson, N.S., Sohne, M., Gerdes, V.E., et al. 2008. The importance of clinical probability assessment in interpreting a normal D-dimer in patients with suspected pulmonary embolism. *Chest*,vol. 134,pp. 789-793.

Goldhaber, S.Z., Visani, L. &De Rosa, M. 1999. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*,vol. 353,pp. 1386-1389.

Goldin, Y., Pasvolsky, O., Rogowski, O., et al. 2011. The diagnostic yield of D-dimer in relation to time from symptom onset in patients evaluated for

venous thromboemolism in the emergency medicine department. *J Thromb Thrombolysis*,vol. 31,pp. 1-5.

Hansson, P.O., Welin, L., Tibblin, G., et al. 1997. Deep vein thrombosis and pulmonary embolism in the general population. 'The study of men born in 1913'

Arch Intern Med,vol. 157,pp. 1665-1670.

Hargett, W.C. &Tapson, V.F. 2008. Clinical probability and D-dimer testing: How should we use them in clinical practice? *Sem Resp Crit Care M*,vol. 29,pp. 15-24.

Harper, P.L., Theakston, E., Ahmed, J., et al. 2007. D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. *Int Med J*,vol. 37,pp. 607-613.

Jelinek, G.A., Ingarfield, S.L., Mountain, D., et al. 2009. Emergency department diagnosis of pulmonary embolism is associated with significantly reduced mortality: a linked data population study. *EMA*,vol. 21,pp. 269-276.

Kabrhel, C., Courtney, M., Camargo, C.A., et al. 2010. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Acad Emerg Med*,vol. 17,pp. 589-597.

Kline, J.A., Runyon, M.S., Webb, W.B., et al. 2006. Prospective study of the diagnostic accuracy of the simplify D-dimer assay for pulmonary embolism in emergency department patients. *Chest*,vol. 129,pp. 1417-1423.

Kruip, M.J., Slob, M.J., Schijen, J.H., et al. 2002. Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of

patients with suspected pulmonary embolism: a prospective management study. *Arch Intern Med*,vol. 162,pp. 1631-1635.

Martinez Izquierdo, M.T., Pallas Villaronga, O., Clemente Rodriguez, C., et al. 2010. Clinical presentation of pulmonary thromboembolism in an emergency department: comparison with previous studies. *Emergencias*,vol. 22,pp. 113-116.

Michiels, J.J., Gadisseur, A., van der Planken, M., et al. 2006. Different accuracies of rapid enzyme-linked immunosorbent, turbidimetric, and agglutination D-dimer assays for thrombosis exclusion: impact on diagnostic work-ups of outpatients with suspected deep vein thrombosis and pulmonary embolism. *Semin Thromb Hemost* vol. 32,pp. 678-693.

Ouellette, D. 2011. Pulmonary Embolism. Retrieved 25 July, 2011, from http://emedicine.medscape.com/article/300901.

Perrier, A. 2004. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management sutdy. *Am J Med*,vol. 2004,pp. 291-299.

Scarvelis, D. &Wells, P.S. 2006. Diagnosis and treatment of deep-vein thrombosis. *CMAJ*,vol. 175,pp. 1087-1092.

Smith, C., Mensah, A., Sameer, M., et al. 2008. Is pretest probability assessment on emergency department patients with suspected venous thromboembolism documented before SimpliRed D-dimer testing? *CJEM*,vol. 10,pp. 519-523.

Soderberg, M., Brohult, J., Jorfeldt, L., et al. 2009. The use of D-dimer testing and Wells score in patients with high probability for acute pulmonary embolism. *J Eval Clin Pract*,vol. 15,pp. 129-133.

Spencer, F., Goldberg, R., Lessard, D., et al. 2010. Factors associated with adverse outcomes in outpatients presenting with pulmonary embolism: the Worcester venous thromboembolism study. *Circulation*,vol. 3,pp. 390-394.

Tapson, V.F. 2008. Acute pulmonary embolism. *NEJM*,vol. 358,pp. 1037-1052.

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology 2008. Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*,vol. 29,pp. 2276-2315.

The Task Force on Aortic Dissection European Society of Cardiology. 2001. Diagnosis and management of aortic dissection. *Eur Heart J*,vol. 22,pp. 1642-1681.

Tita-Nwa, F., Bos, A., Adjei, A., et al. 2010. Correlates of D-dimer in older persons. *Aging Clin Exp Res*,vol. 22,pp. 20-23.

van Belle, A., Buller, H.R., Huisman, M.V., et al. 2006. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*,vol. 295,pp. 172-179.

Wakai, A., Gleeson, A. &Winter, D. 2003. Role of fibrin D-dimer testing in emergency medicine. *Emerg Med J*,vol. 20,pp. 319-325.

Wells, P.S., Ginsberg, J.S., Anderson, D.S., et al. 1998. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med*,vol. 129,pp. 997-1005.