

Thesis manuscript for Master of Science in Epidemiology

**Diagnosing DVT in the Emergency Department: Combining
clinical predictors, d-dimer and bedside ultrasound.**

Student:

Gabriel E. Blecher MBBS(Hons) PDM FACEM

Thesis supervisors:

Dr. Ian Stiell, MD MSc FRCPC

Dr. George Wells, PhD

Other thesis committee members:

Dr. Phil Wells MD MSc FRCPC

*Professor, Chief & Chair, Department of Medicine, The Ottawa Hospital & University of
Ottawa.*

Dr. Michael Woo MD CCFP(EM) RDMS

Emergency Medicine Ultrasonography Fellowship Program Director

Abstract

I assessed the accuracy of two clinical prediction rules, the d-dimer blood test and point of care ultrasound for diagnosing lower limb deep vein thrombosis.

Emergency physicians were trained in ultrasound and prospectively scanned emergency department patients with suspected deep vein thrombosis. Accuracy of the Wells and AMUSE rules and the ultrasound result was compared to radiology-performed ultrasound and a 90-day clinical outcome. Univariate and multivariate analyses were performed assessing which factors were associated with the outcome.

The sensitivity and specificity of the Wells score for the clinical outcome was 85.7% and 68.5%; the AMUSE score 85.7% and 54.4%. Ultrasound had a sensitivity of 91.7% and specificity of 91.7% for radiology-diagnosed thrombus and 78.6% and 95.0% for clinical outcome. The odds ratio of a positive outcome with a positive ultrasound was 65.1.

After receiving the ultrasound training program, emergency physicians were unable to demonstrate sufficient accuracy to replace current diagnostic strategies.

Executive Summary

Statement of the problem

Emergency physicians regularly see patients who present with leg pain or swelling and may have deep vein thrombosis. The gold standard test, ultrasound performed by an expert, is often unavailable out of hours and so physicians use other diagnostic tools including clinical prediction rules, the d-dimer blood test and point of care ultrasound. I assessed the accuracy and usefulness of two clinical prediction rules, a blood test and point of care ultrasound for diagnosing acute lower limb deep vein thrombosis.

Methods of investigation

Staff physicians underwent training in how to perform lower limb venous ultrasound. Prospectively patients presenting to the emergency department over a six-month period with possible deep vein thrombosis were enrolled. Demographic and clinical data and a d-dimer result were collected. Physicians recorded ultrasound images of each patient assessing for the presence or absence of thrombosis. The primary analysis assessed the accuracy of bedside ultrasound against a composite outcome, which included 90-day follow up. Test characteristics of the Wells and AMUSE rules were also calculated against two outcomes – radiology-performed ultrasound and the composite outcome. An exploratory analysis was also performed using univariate and multivariate techniques assessing which factors were associated with the composite outcome.

Results

The Wells and the AMUSE scores have comparable accuracy: sensitivity of 85.7% for both, 68.5% specificity for the Wells and 54.4% specificity for the AMUSE rule. Point of care ultrasound was 91.7% sensitive for thrombosis diagnosed by radiology-performed scan and 91.7% specific. It was 78.6% sensitive and 95.0% specific for thrombosis when compared against a composite outcome of initial radiology-performed scan plus delayed clinical follow up. Multivariate analysis showed that the odds of a positive composite outcome with a positive point of care scan were 65.1 (95% CI 12.8 – 330.8).

Conclusion

Training emergency physicians to perform a limited ultrasound examination of the lower limb to diagnose proximal deep vein thrombosis is possible. The training program as conceived and carried out in this project is insufficient for achieving clinically acceptable sensitivity. If a training and quality assurance program could demonstrate sensitivity close to the current gold standard of radiology-performed ultrasound, emergency physician-performed ultrasound may in the future replace clinical decision rules, d-dimer and radiology-performed ultrasound.

Acknowledgements

I wish to acknowledge my supervisors Dr. Ian Stiell and Dr. George Wells, for their helpful advice from the initial stages of deciding on an appropriate topic for study, to assisting in the logistics of the study to the preparation and continual revision of this manuscript. George in particular assisted with some statistical issues encountered during the analysis phase.

Dr. Michael Woo greatly assisted with the running of the training day and constantly reviewed the ultrasound images for adequate image quality throughout the study. Dr. Paul Pageau took over the local management of the project and encouraged physician participation after I left Canada. Additionally without the assistance of the entire medical, nursing and support staff of The Ottawa Hospital Emergency Departments I would not have been able to carry out this project.

I also acknowledge my wife Romy for stoically putting up with the rigors of the thesis process.

Table of Contents

Abstract.....	ii
Executive summary.....	iii
Acknowledgements.....	v
Table of contents.....	vi
List of tables.....	viii
List of figures.....	ix

Chapter 1

1.1 Introduction to the Thesis.....	10
1.2 Introduction to deep vein thrombosis.....	10
1.2.1 Definition.....	10
1.2.2 Epidemiology.....	12
1.2.3 Clinical presentation.....	13
1.2.4 Investigation.....	13
1.2.5 Treatment.....	15
1.3 Statement of the problem in the Emergency Department.....	17
1.4 Review of previous studies.....	18
1.5 Clinical risk prediction scores.....	21
1.6 Rationale for the study.....	22

Chapter 2: Goals and Objectives..... 24

Chapter 3: Methods..... 26

3.1 Study design.....	26
3.2 Study period.....	26
3.3 Study centre.....	26
3.4 Study population.....	26
3.4.1 Inclusion criterion.....	26
3.4.2 Exclusion criteria.....	26
3.5 Design of case record forms and study database.....	27
3.6 Patient selection.....	27
3.7 Study flow.....	28
3.8 Standardized Patient Assessment.....	28
3.8.1 Patient assessment.....	28
3.8.2 Ultrasound training.....	28
3.8.3 Quality assurance.....	29
3.8.4 Data recorded.....	29
3.9 Outcome measures.....	32
3.10 Data analysis.....	33
3.10.1 Descriptive statistics.....	33
3.10.2 Contingency tables.....	33
3.10.3 Univariate analysis.....	34
3.10.4 Multivariate analysis.....	34
3.10.5 Sample size for study.....	34
3.11 Ethical concerns.....	34

Chapter 4: Results..... 36

4.1 Univariate analysis.....	40
4.2 Multivariate analysis.....	41

Chapter 5: Discussion..... 43

5.1 Interpretation of the results versus the objectives.....	43
--	----

5.1.1 Objective 1	43
5.1.2 Objective 2	46
5.2 Comparison with previous literature findings	49
5.3 Limitations	51
5.3.1 Indeterminate scans.....	52
5.3.2 Image review.....	52
5.3.3 Follow up.....	52
5.3.4 Expert sonographers.....	52
5.3.5 Previous DVT.....	53
5.3.6 Missed objectives.....	53
5.4 Strengths of the study.....	54
5.5 Clinical implications.....	55
5.5.1 Objective 1	55
5.5.2 Objective 2	58
5.6 Research implications and future directions	60
5.7 Conclusions.....	61
Tables and Figures.....	63
References	79
Appendices	
Appendix 1 : Case record form – Thrombosis Unit Suspected DVT Referral.....	83
Appendix 2: Case record form - DVT in the ED study	84

List of Tables

Table 1: Test characteristics in studies assessing the accuracy of ultrasound performed by emergency physicians

Table 2: Clinical characteristics of the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Table 3: Bedside ultrasound characteristics of cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Table 4: Outcomes of patients in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Table 5: Comparison of patients with low-risk (≤ 1) and high-risk (≥ 2) Wells score against 90-day outcome (N=103)

Table 6: Comparison of patients with low-risk (≤ 3) and high-risk (≥ 4) AMUSE score against 90-day outcome (N=104)

Table 7: Comparison of emergency physician-performed against radiology-performed ultrasound results in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=64)

Table 8: Details of false negative and false positives scans

Table 9: Comparison of determinate bedside ultrasound result versus 90-day outcome in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=94)

Table 10: Univariate associations in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis between predictive elements and 90-day outcome (N=103)

Table 11: Multivariate associations in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis between predictive elements and 90-day outcome - maximum likelihood estimates

List of Figures

Figure 1: Risk factors for development of deep vein thrombosis

Figure 2: Number of bedside scans by difficulty category of cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Figure 3: Proposed patient flow diagram

Figure 4: Number of bedside scans performed by physician in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Figure 5: Patient flow diagram for the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Chapter 1: Introduction

1.1 Introduction to the Thesis

This thesis attempts to find the best way for emergency physicians to diagnose deep vein thrombosis using a combination of three diagnostic tools. Deep vein thrombosis (DVT), or blood clot forming in the deep veins, most commonly affects the lower limb, and is a serious health problem. This is because the thrombus (clot) can dislodge and embolise (travel) into the pulmonary (lung) circulation where it can obstruct blood flow to the lungs, which can be fatal. A blood clot in the pulmonary circulation is known as pulmonary embolism.

Currently deep vein thrombosis is usually diagnosed by ultrasound, performed by technologists and interpreted by physicians. In this thesis I will examine whether emergency physicians can themselves perform ultrasound to accurately diagnose the condition, and whether the accuracy is improved by adding a blood test, and “clinical decision rules.” A decision rule is a tool that aids clinicians in making bedside diagnostic and therapeutic decisions. Because technologist-performed ultrasound is rarely available 24 hours a day, it would be ideal if an emergency physician could confirm or refute the diagnosis during a single visit to the hospital.

1.2 Introduction to deep vein thrombosis

1.2.1 Definition

Deep vein thrombosis is a common and important medical problem. Thrombus can spontaneously form in the larger veins of the lower limb, obstructing blood flow from the leg back to the heart. Rudolf Virchow described the classic triad of factors leading to formation of thrombus: abnormal blood flow, abnormal blood vessel wall and abnormal blood coagulation (clotting) function.¹ The clinical risk factors of deep vein thrombosis, described below, can all be related to these three root causes. When these factors are present, the natural balance between fibrin formation (a component of thrombus) and fibrinolysis (thrombus breakdown) is disrupted, leading to the formation and propagation of thrombus.

¹ Virchow R. *Abhandlungen zur wissenschaftlichen medicin*. Frankfurt (Germany): Meidinger Sohn & Co.; 1856.

Thrombus formation in the “deep veins” of the lower limb is known as deep vein thrombosis, as opposed to superficial thrombophlebitis, which affects the superficial veins. The distinction is important, as thrombus in the smaller, more superficial veins does not carry the same risk of propagation or embolism of deep vein thrombosis. Superficial thrombophlebitis is usually treated with anti-inflammatory medication and requires no further investigation or treatment. An exception to this is when the vein segment affected approaches a junction with a deep vein. Some practitioners may treat these in the same way as deep vein thrombosis because of the risk of extension into the deep system.

Although 90% of deep vein thrombosis occurs in the lower limbs, less commonly it does affect other areas of the body, including veins in the arm, head and neck, pelvis and rarely other locations. (1) Apart from arm vein thrombus, which is diagnosed similarly to leg thrombus, when other areas are affected the signs may be subtle and will require special tests for confirmation.

Acutely, lower limb deep vein thrombosis causes swelling, pain and discolouration. The natural history is either progression or resolution, although in Western medicine the condition is either treated or closely observed. In the long term, it can cause “post-thrombotic syndrome,” which affects 23-60% of individuals with deep vein thrombosis within 2 years. (2) The formation of thrombus damages the vein valves and increases venous collateral circulation, leading to venous hypertension (elevated pressure). Over time, this manifests as swelling, hyperpigmentation, venous ulcers, rash and discomfort. Venous ulcers heal slowly, are difficult to treat and are a significant cost burden on healthcare systems. (2)

The major mortality associated with deep vein thrombosis is when thrombus embolises (travels) towards the heart and lungs, where it lodges in the pulmonary arteries, known as pulmonary embolism. It obstructs blood flow from the heart to the lung, which causes impaired blood oxygenation, resulting in symptoms of breathlessness, chest pain and cough. Because the whole blood volume must flow through the pulmonary circulation and in adults there is no

bypass route, severe obstruction will cause hypoxia, (low blood oxygenation) hypotension (low blood pressure) and ultimately cardiac arrest causing death.

A distinction is made between proximal (above-knee) and distal (below-knee) lower limb deep vein thrombosis, because proximal thrombus is much more likely than distal to embolise. (3,4) There is approximately a 20% risk of distal thrombus progressing to involve the proximal veins (5,6) and the 3-month risk of thromboembolism in patients with suspected deep vein thrombosis but negative proximal leg ultrasound is around 1%. (7)

1.2.2 Epidemiology

Deep vein thrombosis is a common presentation in (Canadian) emergency departments. The estimated incidence of deep vein thrombosis is between 60 and 160 cases per 100,000 people, with approximately 260,000 cases occurring annually in the United States. (8,9) There is no significant difference in incidence between men and women. (10) The incidence increases with age, and sharply rises after age 45. (11) Deep vein thrombosis without embolism has been associated with morbidity due to local effects, but not mortality. Untreated deep vein thrombosis can however result in fatal pulmonary embolism, which occurs in an estimated 50,000 people per year in the US. (9) Not all cases of pulmonary embolism are associated with deep vein thrombus – in fact only 30%. (12,13) A population-based study of venous thromboembolism using hospital discharge diagnoses found a case fatality rate of 5% in diagnosed deep vein thrombosis (likely due to other causes) and 23% in pulmonary embolism. (14) Of patients diagnosed with pulmonary embolism in the emergency department with normal blood pressure, 3% die within 48 hours of diagnosis. Forty percent of survivors experience persistent pulmonary hypertension (elevated blood pressure in the pulmonary circulation) or right ventricular (cardiac) damage. (15)

There are several known risk factors for development of deep vein thrombosis, as shown in Figure 1. (1)

1.2.3 Clinical presentation

There are typical symptoms and signs on physical exam of deep vein thrombosis, but no one factor has high sensitivity or specificity. (16) Symptoms include swelling or a sense of fullness in the leg, or pain in the calf or thigh. Physical examination findings include unilateral leg oedema, tenderness, warmth, erythema, a palpable cord, and collateral superficial (non-varicose) veins. (16,17) The prevalence of each of these findings in a large study was 88%, 55%, 42%, 34% and 6%, respectively. (14) The classic Homan's sign (sharp calf pain on passive dorsiflexion of the foot) has proved to be insensitive and nonspecific. (18)

1.2.4 Investigation

There are several methods used to diagnose deep vein thrombosis. The previous criterion standard test, contrast venography, involves inserting a catheter into a leg vein, injecting contrast material, and taking X-ray images of the veins. Lack of opacification of a vein segment indicates DVT. The test is time-consuming, painful and has potential complications including the risk of contrast allergy, and infiltration of contrast into surrounding tissue. It necessarily involves a dose of radiation of 6 mSv. Because of these factors, it is today rarely performed.

In some countries, impedance plethysmography is utilised. This procedure is based on recording changes in blood volume of an extremity, which are directly related to venous outflow. A meta-analysis found it to be sensitive (88%; 95% CI 86-90%) and specific (90%; 95% CI 89-91%) for proximal vein thrombosis. It is insensitive for calf vein thrombosis, (sensitivity 28%; 95% CI 24-33%) nonocclusive proximal vein thrombus, and ileofemoral vein thrombosis above the inguinal ligament (groin crease). (19)

The most commonly used technique is ultrasonography, which has usurped venography as the practical "gold standard." (8) Ultrasound uses ultrasonic sound waves to produce an image of the underlying structures. Fluid-filled structures, including blood vessels, appear dark ("hypoechoic") on ultrasound. The diagnosis is made chiefly with use of compression sonography. Veins compress easily with direct probe pressure but arteries do not, so this helps identify the vein, and inability to completely compress the vein indicates

intraluminal thrombus. Several additional techniques are used to support the diagnosis of thrombosis; direct visualisation of white (“hyperechoic”) material within the vein lumen, augmentation and phasicity. Augmentation utilises the Doppler effect whereby squeezing the calf temporarily augments the flow in the vein and this is detected with the ultrasound probe using spectral Doppler. Normally the changes in pressure in the chest that occur with respiration cause phasic (intermittent) flow in the femoral vein. Absence of this phasic flow is taken to indicate an obstruction in the venous system proximal to the femoral vein, ie the pelvic or iliac veins. In the emergency department, compression sonography is the most commonly used technique, due to its simplicity and no requirement for Doppler functionality. The other techniques add time to the examination and are utilised primarily outside the emergency department setting.

There is practice variation regarding the technique; some centres perform ultrasounds limited to the trifurcation region of the calf veins and more proximally whilst others assess for thrombosis in calf veins as well. (20-26) This occurs because some centres believe it is important to diagnose and treat calf vein deep vein thrombosis and others do not.

Leg ultrasound is also used in diagnosing pulmonary embolism when it is impossible or impractical to directly image the chest. This may be because of a contraindication to the most widely used test, computed tomography pulmonary angiography (CTPA) such as contrast allergy or renal impairment. In these conditions, it is unsafe using iodinated intravenous contrast, which is necessary to opacify the pulmonary vessels and detect thrombus. It may also be because of lack of access in a particular hospital to CTPA, or the other test used, ventilation-perfusion (“VQ”) nuclear imaging. As mentioned, using leg ultrasound alone to diagnose pulmonary embolism is not a sensitive technique as only 30% of emboli are associated with lower limb thrombus.

Because of limited access to ultrasound after hours (22-24), a blood test (d-dimer) is commonly used to exclude deep vein thrombosis in those patients with a low risk of the disease, obviating the need for ultrasound. D-dimer is a

breakdown product of thrombus, detectable in minute quantities on blood testing. A small but detectable level is present in healthy individuals, but increasing values correlate with thrombus volume. (27) Conditions associated with elevated d-dimer apart from thrombosis include cancer, late pregnancy, recent surgery or trauma, sepsis, cardiac or renal failure, acute coronary syndromes, acute non-lacunar stroke and sickle cell crises. (28-32)

There are several types of blood test techniques used to detect d-dimer, however they can all be classed as either ELISA (enzyme-linked immunosorbent assay) or a form of agglutination – either latex or whole blood. Most quantitative tests in current usage have high sensitivity but low-intermediate specificity; hence the test is used to rule out rather than rule in the diagnosis. Tests can be qualitative (giving a binary result), quantitative or semi-quantitative. Correlation between different assays is poor and it is not currently possible to standardize the results from different assays, making it difficult to extrapolate results from one setting to another. Additionally the performance characteristics vary according to the cut-off value chosen; decreasing the value increases sensitivity at the expense of specificity. The VIDAS ELISA and whole blood agglutination techniques, two of the most widely studied in deep vein thrombosis diagnosis, have sensitivities of 98-100% and 85% respectively, and specificities of 40% and 70%, respectively.

1.2.5 Treatment

Deep vein thrombosis is treated to reduce the risk of post-thrombotic syndrome and pulmonary embolism. The treatment of isolated calf vein deep vein thrombosis is highly variable with no clear evidence to guide treatment. Some centres do not treat it; some re-scan the patient to detect thrombus progression, some treat with aspirin and others with full anticoagulation. There is no evidence-based guide to appropriate duration of treatment. Superficial thrombophlebitis is generally not treated with anticoagulation, with the possible exception of when the proximal long saphenous vein is involved, as in 8% of cases it may extend into the femoral vein, increasing the risk of thromboembolism. (33)

Above-knee deep vein thrombosis is treated as an outpatient with anticoagulation (usually oral warfarin or Coumadin) because of the risk of

potentially fatal PE. This has been dogma for decades, however no randomized controlled trial has ever been performed proving the usefulness of anticoagulation, and it was accepted as standard therapy before the widespread use of current diagnostic modalities. As thrombus formation occurs because of an imbalance in endogenous fibrin formation and breakdown (fibrinolysis), the cornerstone of treatment is pharmacologic anticoagulation. Anticoagulants work by inhibiting the clotting cascade and shifting the imbalance back in favour of fibrinolysis. Initially, injectable anticoagulants are often used, e.g. heparin or low molecular-weight heparin. Generally a patient is then switched to warfarin, which is given in oral form, but does require frequent laboratory monitoring of the degree of anticoagulation. This is because the degree of anticoagulation is sensitive to many factors including diet and antibiotic usage. Treatment duration for uncomplicated first-episode lower limb deep vein is usually 3 months. This may be extended to 6 months or even lifelong therapy depending on the presence of ongoing risk factors, for example active malignancy, second episode of thrombosis or genetic prothrombotic conditions. (34) Patients with deep vein thrombosis are usually managed as outpatients rather than with hospital admission, as the medication is administered orally and no specific in-hospital treatment is required.

An exception to standard treatment is when a patient is unable to be safely anticoagulated – for example, recent major head trauma. In this case, a device known as an IVC (inferior vena cava) filter may be deployed. This is a fine basket-like device inserted via endovascular approach by interventional radiologists into the IVC to “filter out” any thromboemboli before they reach the lung. This does not prevent embolism from other areas, e.g. upper limb, reaching the lung. Another exception is during pregnancy, because warfarin is proven to cause birth defects. Pregnant patients suffering thrombotic disorders are maintained on injectable heparin throughout the pregnancy.

Another treatment option is thrombolysis – administering “clot-busting” medications either systemically, or via a catheter directed into the thrombus. Recanalization of the occluded vein occurs faster with the addition of systemic thrombolysis, but it is unclear whether this reduces the risk of post-thrombotic

syndrome on the long term. Thrombolysis is also associated with increased bleeding, the most concerning location being intracranial, hence it is only recommended in the case of massive deep vein thrombosis, which is associated with phlegmasia cerulean dolens. (34) This is when venous obstruction of the major deep veins and collateral veins leads to a sharp rise in venous pressure, massive interstitial fluid shifts, decreased arterial perfusion, compartment syndrome, and gangrene with potential limb loss. (1)

Treatment of pulmonary embolism is similar to that of deep vein thrombosis as the conditions share similar pathophysiology. Initial treatment is with injectable anticoagulants, and then patients are generally switched to oral warfarin. Duration is longer than in lower limb thrombosis, but again depends on the risk of recurrence and of bleeding. Three months is recommended when the event was provoked by a major reversible risk factor such as surgery, 3-6 months when provoked by a minor transient risk factor and 6 months or lifelong therapy when unprovoked or associated with an irreversible risk factor. (35)

When the degree of pulmonary vascular occlusion is severe, pulmonary embolism can be treated with thrombolysis. Again the risk of intracranial haemorrhage must be balanced against the benefit of faster thrombus dissolution. Current recommendations are that thrombolysis should be used in patients with haemodynamic compromise, generally meaning a systolic blood pressure of below 90 mmHg. (36)

1.3 Statement of the problem in the ED

Formal ultrasonography is generally performed in the radiology department or vascular laboratory, is time-consuming and is generally unavailable out-of-hours. This is problematic in the emergency department, where patients present at all hours of the day with possible deep vein thrombosis. Out of hours, when formal ultrasonography is unavailable, the common practice is to risk stratify patients and to anticoagulate high-risk patients by administering low molecular weight heparin until the definitive investigation can be performed. (37,38) This significantly delays patient disposition and exposes patients to the small but significant risks of anticoagulation. (24,25) These include life-threatening

spontaneous haemorrhage into the brain and gastrointestinal tract as well as less clinically important haemorrhage in other locations.

Current risk stratification techniques involve measuring serum d-dimer, scoring the patient on a clinical prediction rule, such as the Wells score, or combining the two. (39) The Wells score involves completing a 10-item questionnaire, which includes history and examination findings, to produce a dichotomous risk prediction for deep vein thrombosis – likely or unlikely. (17,40) This particular scoring system has been well validated in 14 studies. (41) Other prediction rules exist, but have not been adequately prospectively validated. (8)

A newer application of ultrasound in the ED is emergency physician-performed ultrasound with the aim of excluding proximal leg deep vein thrombosis. This has the potential advantage of speed and safety. Published research has found that examinations take between 3.5 and 13 minutes to complete. (42-44) In-hours, the patient does not require transport out of the unit, thus speeding up the disposition decision. Out of hours, patients can avoid the risks of anticoagulation by having proximal leg deep vein thrombosis excluded before leaving the hospital. As yet, there is no standard technique accepted by all emergency physicians practicing bedside ultrasound. Some continuously interrogate the vein between the groin and knee and others use a “2-point” technique, which itself can consist of a number of anatomical locations. The two points scanned are the femoral vein and the popliteal vein, because isolated superficial femoral vein thrombosis is uncommon: 1/146 in one study and 6/131 in another. (45,46) Most studies do not use augmentation, as it has not shown to improve the accuracy of the exam. (47)

1.4 Review of previous studies

In the last decade there have been 7 prospective cohort studies assessing the accuracy of ultrasound performed by the emergency physician, and one systematic review. The major weaknesses of the studies have been a reliance on a small number of highly trained experts performing the scans, inadequately described methods of patient selection and the primary outcome being a second ultrasound scan rather than a clinically meaningful outcome.

Blaivas (42) published a study in 2000 with 112 patients scanned in the ED, with 34 positive for deep vein thrombosis. All had formal ultrasound within 8 hours performed by the vascular lab. The ED scans were performed by 5 physicians, 3 of whom were RDMS certified. This stands for Registered Diagnostic Medical Sonographer, signifying a high level of expertise in ultrasound. The femoral and popliteal veins were imaged, but the exact location was not specified. Augmentation manoeuvre was used. The agreement between the two scans was 98% (95% CI 95.4-100%).

In 2001 Frazee (48) published his series of 76 patients who were compression scanned by 6 emergency physicians. Comparison was made against vascular laboratory ultrasound. Again the exact locations where the common femoral and popliteal veins were imaged were not described. Augmentation, colour Doppler flow void, visible thrombus, dilated veins and valvular incompetence were all used to make the diagnosis. The sensitivity was 88.9% (95%CI 65.3-98.6) and specificity 75.9% (95%CI 62.8-86.1).

Jang (43) in 2004 published a study of 8 emergency residents performing bedside US for proximal leg DVTs. Anatomical location of images obtained was not reported. The criterion standard was venography when available; otherwise ultrasound or CT venography was used. Seventy-two patients were enrolled and the sensitivity was 100% (95%CI 82.2-100) and specificity 91.8% (95%CI 79.5-97.4)

A study in 2004 by Theodoro et al (49) used 5 physicians; three resident, one ultrasound fellow and one staff physician. The proximal vein was imaged 2cm distal to the bifurcation of the superficial and deep femoral veins, and the popliteal vein was imaged until the trifurcation. No augmentation was used, however Doppler was used to aid vessel identification. A 99% agreement between ED and radiology-performed ultrasound was found for the 156 patients enrolled.

Jacoby et al (50) in 2007 published a study using 2-point compression with similar specifications to the Theodoro study. Augmentation, colour Doppler and respiratory variation were used to assist in making the diagnosis. There were 6

residents scanning patients in the vascular lab rather than in the ED. Comparison was the vascular technician using the same machine. Over 3 months, 121 limbs were scanned, with overall sensitivity of 89% (95% CI 55-100).

A 2008 meta-analysis by Burnside et al (51) found emergency physician-performed ultrasound to have a sensitivity of 95% (95% CI 87-99) and specificity of 96% (95% CI 87-99). There was however significant heterogeneity in the results; the largest study included (Magazzini) used a different technique whereby the leg was scanned from the groin to the ankle. Excluding this study may have altered the result of the meta-analysis significantly.

Kline's group in 2008 published a study of 183 patients scanned by emergency physicians and residents who completed a training course. (52) None were RDMS-certified. The course consisted of a 1-hour lecture and a minimum of 5 proctored scans on healthy volunteer models. The outcome measure was a combination of positive radiology-performed ultrasound and planned anticoagulation for greater than 89 days or an autopsy report confirming DVT or PE. They found a sensitivity of 70% (95% CI 60-80) and a specificity of 89% (95% CI 83-94).

The results of these previous studies are listed in Table 1.

In practice d-dimer is often used together with ultrasound in a diagnostic strategy for deep vein thrombosis. Bernardi published a prospective cohort study in 1998 in which patients underwent a proximal leg US and if negative for deep vein thrombosis, a d-dimer. (20) It is not stated who performed the ultrasounds, but presumably it was not ED staff. If the d-dimer was negative, patients were followed up at 3 months, or if positive, had a repeat US after one week. If this scan was normal, patients were followed up at 3 months. 946 patients were recruited, 27.5% of who had a deep vein thrombosis on initial scan. The cumulative incidence of deep vein thrombosis or PE in the follow up period was 3 patients, or 0.4%.

In 2008 he published a randomised study (53) comparing 2-point US with whole-leg US. Again this study was not ED-based, as the scans were performed in ultrasound laboratories. Those that had a normal 2-point scan had a d-dimer

performed, and if positive, were re-scanned at one week. Patients with negative d-dimers were followed up at 3 months. Patients randomised to the whole-leg strategy with normal initial scans were simply followed up. 2098 patients were randomised, and the thromboembolism rate at follow up was 0.9% in the 2-point strategy and 1.2% in the whole-leg strategy, which was statistically insignificant.

1.5 Clinical risk prediction scores

Several systems have been developed to aid clinicians in risk stratifying patients with regard to deep vein thrombosis. The best known is the Wells score, which combines nine items derived from clinical assessment to give a risk score. It originally stratified risk into low, intermediate and high risk, but was later dichotomised into low or high risk. When applied in practice, the high-risk score confers a likelihood ratio of 5.2 of a patient having deep vein thrombosis, while a low risk score has a likelihood ratio of 0.25. (54) The rule has low interobserver variability; the kappa for comparison of pretest probability between nurses and physicians is 0.75. (40) The rule has been extensively prospectively validated in multiple populations. (55) The limitations are that it has not been validated in pregnant women, patients with previous venous thromboembolism, patients using anticoagulants for over 48 hours or in patients aged over 60. (54) It also includes a subjective element of considering an alternative diagnosis.

Other scores have been developed in attempt to reduce the number of items that comprise the score. The Kahn, St. Andre and ambulatory Constans scores have four, six and five items respectively. The area under the receiver operating curve is often used in assessing the accuracy of the rules in classifying patients. The area was 0.76 (95% CI 0.70–0.81) for the Wells rule, 0.57 (95% CI 0.50–0.63) for the Kahn rule, 0.67 (95% CI 0.61–0.73) for the St. Andre rule and 0.79 (95% CI 0.74–0.84) for the Constans rule. Although the Constans rule seems the most accurate, none of the rules other than the Wells have been validated prospectively. (8)

The AMUSE score was developed in the Netherlands for use in primary care because the Wells criteria were developed in a tertiary care setting and have a miss rate of 2.9% in low risk patients in the primary care population. (56,57) The

AMUSE score differs from the Wells rule in that it incorporates the result of the d-dimer assay and removes the subjective element “alternative diagnosis more likely.” It has been demonstrated to have good performance: in patients assessed as low risk (score \leq 3) for having deep vein thrombosis and not further investigated or treated, 1.4% [95% CI 0.6 – 2.9] developed venous thromboembolism during a 3 month follow up period. (57)

1.6 Rationale for the study

Patients suspected of having lower limb deep vein thrombosis are often referred to emergency departments for investigation. Current diagnostic protocols are inefficient and resource-intensive. In assessing low-risk patients, many protocols utilise d-dimer tests that delay decision-making whilst waiting for a result and therefore delay patient disposition. Because of the poor specificity of the test, many patients are referred for formal ultrasound performed outside the emergency department. This process significantly extends the length of stay in the emergency department. Most departments do not have 24-hour access to formal ultrasound and patients who are assessed as high-risk or have an abnormal d-dimer receive antithrombotic therapy until the definitive test is performed. This exposes them to the discomfort of injections, the inconvenience of needing to return to the hospital for further testing and the small risks of bleeding.

As bedside ultrasound skills by non-specialist physicians have become widespread in emergency departments, the time is ripe for the process of investigating suspected deep vein thrombosis to be made more efficient.

Current evidence indicates that the accuracy of emergency physician-performed ultrasound compares favourably to radiology-performed ultrasound. (51) To justify routine use of ultrasound by emergency physicians in excluding lower limb DVT, evidence must prove not only comparable accuracy, but also safety using clinically relevant outcomes. One clinically relevant outcome is that after leaving the emergency department having DVT excluded, the patient suffers no venous thromboembolic event, or death, for 90 days after the ED visit. This

outcome is commonly used in venous thromboembolism research to ensure that a deep vein thrombosis, or subsequent pulmonary embolism, was not missed on the initial visit. When studies compare emergency physician-performed to radiology-performed ultrasound, there is a risk that both the emergency physician and the radiologist missed a thrombosis. Outcomes that occur after 90 days are presumed not to have been present at the initial visit, and hence are not considered “missed” events.

New evidence must be incorporated into current clinical practice. Most departments’ protocols for investigating suspected deep vein thrombosis use a combination of clinical decision rule, d-dimer and ultrasound. Thus any new evidence must be able to be integrated into this environment. Practically, this means new research should incorporate the clinical decision rule and d-dimer in addition to ultrasound.

This study will do precisely that: use a combination of clinical, laboratory and bedside information to exclude lower limb deep vein thrombosis, and serious complications, out to 90 days. This study is needed in order to enable emergency physicians to effectively evaluate suspected deep vein thrombosis in an efficient manner. This will avoid the serious and long-term complications of untreated DVT, as well as avoid the risks of unnecessary anticoagulation.

It is possible that bedside ultrasound plus a clinical decision rule, without a d-dimer, is a safe strategy for investigating DVT. If this is true, it could reduce patients’ length of stay in the emergency department and avoid anticoagulation without compromising safety. Such an outcome would be welcomed in emergency departments where patient length of stay is an important marker of efficiency.

Chapter 2: Goals and Objectives

Objectives:

1. To compare the accuracy of emergency physician-performed ultrasound for diagnosing DVT against two outcomes: the criterion standard of a radiology department-performed ultrasound scan; and a clinical outcome of any venous thromboembolism occurring within 90 days.
 - a. To develop and implement a training program for emergency physicians to use bedside ultrasound to exclude proximal lower limb deep vein thrombosis
 - b. To prospectively enrol a cohort of patients presenting to the emergency department where the possibility of lower limb deep vein thrombosis is considered
 - c. To have emergency physicians complete a case record form comprising several clinical characteristics which will enable calculation of the Wells and AMUSE risk stratification scores
 - d. To have emergency physicians perform a focussed bedside ultrasound intending to exclude proximal lower limb deep vein thrombosis and record the result on the case record form
 - e. To measure interobserver variability of the bedside ultrasound result by having a second physician repeat the scan on a proportion of the cohort
 - f. To determine the acceptability of emergency physician-performed ultrasound to emergency physicians and to determine the level of comfort using a diagnostic strategy to exclude proximal leg DVT in the ED
 - g. To obtain follow up data, consisting of diagnosed deep vein thrombosis and pulmonary embolism, death due to venous thromboembolism and adverse events on enrolled patients, utilising medical imaging reports, medical record review, telephone follow-up and clinical documentation through the Thrombosis Unit

- h. To compute the test characteristics of emergency physician-performed ultrasound versus the criterion standard of radiology staff-reported ultrasound scans for the diagnosis of proximal leg deep vein thrombosis
- i. To compute the test characteristics of emergency physician-performed ultrasound versus the clinical outcome at 90 days, using the data collected in (g) above

2. To assess the ability of the combination of a clinical prediction rule elements, d-dimer result and emergency physician-performed ultrasound to effectively exclude the primary outcome of a diagnosis of venous thromboembolism in a 90-day follow up period.

- a. To compare the accuracy of the Wells and AMUSE scores for predicting the primary outcome. I have chosen this comparison because of the reported improved accuracy of the AMUSE score in a primary care setting and its lack of extensive validation outside the Netherlands.
- b. To have emergency physicians measure a d-dimer and record the result on a data collection form
- c. To perform an exploratory univariate analysis with predictor variables being clinical decision rule elements, d-dimer and emergency physician-performed ultrasound results and the outcome variable being thromboembolism at 90 days
- d. To perform a multivariate analysis with predictor variables derived from the univariate analysis and the outcome being thromboembolism at 90 days

Chapter 3: Methods

3.1 Study design

A prospective cohort study was conducted that enrolled a convenience sample of emergency department patients with leg pain or leg swelling, in whom the attending physician considered the diagnosis of DVT.

3.2 Study period

Recruitment commenced on October 26, 2010 and ceased on April 27 2011, which is a six-month period.

3.3 Study centre

The study setting was the two emergency departments of The Ottawa Hospital, Ottawa, Ontario with a combined annual volume of 130,000 attendances. The Department is affiliated with the University of Ottawa, and maintains an active research program.

3.4 Study population

3.4.1 Inclusion criterion

Patients aged 18 or over with the chief complaint of lower limb pain or swelling above the ankle and in whom the attending physician considered the possibility of deep vein thrombosis.

3.4.2 Exclusion criteria

- D-dimer or ultrasound has been previously performed to investigate the current complaint. Knowledge of these test results is likely to influence the physicians' performance and interpretation of the bedside ultrasound.
- Cognitive impairment: any condition that makes communication difficult, including developmental delay, acquired brain injury or substance intoxication. Patient cooperation during the scan and telephone follow up are both important components of the study and require adequate communication.
- Pregnancy: d-dimer levels rise consistently throughout gestation, making interpretation problematic
- Inability to follow up: homelessness, incarceration or terminal illness

- Previous history of deep vein thrombosis: some thromboses become chronic and differentiating acute from chronic clot on ultrasound is difficult
- Above-knee amputation of the symptomatic lower limb
- Patient complaint of chest pain or shortness of breath where the possibility of pulmonary embolism is considered by the physician. Using bedside lower limb ultrasound in the diagnosis of pulmonary embolism is beyond the scope of the present study.

3.5 Design of case record forms and study database

The case record form consists of two forms. The first has been in use at The Ottawa Hospital for some time and is used to refer patients with suspected venous thromboembolism to the Thrombosis Clinic. [Appendix 1] It has the information required to calculate the Wells score, as well as space to notate the d-dimer result, left/right side, referring physician information, campus and other information required for patient management.

The second form was designed specifically for this study and includes the ultrasound result data and additional clinical risk factors needed to calculate the AMUSE score. [Appendix 2]

All data was entered into a Microsoft Excel spreadsheet. (Microsoft Corporation, Redmond WA) The database was housed on a server located at the Ottawa Hospital Research Institute.

3.6 Patient selection

Emergency physicians and residents selected patients for inclusion in the study. The cohort was a convenience sample of all patients presenting with possible deep vein thrombosis to The Ottawa Hospital Emergency Department. Not all staff physicians were trained in the ultrasound technique and hence were unable to enrol patients. The decision on whether to recruit a patient into the study was left to the discretion of the physician.

3.7 Study flow

The proposed patient flow in the study is depicted by the flow chart in Figure 3.

3.8 Standardized Patient Assessment

3.8.1 Patient assessment

Either a staff or resident emergency physician assessed patients. All physicians were certified by either the Royal College of Physicians and Surgeons in Canada and/or the College of Family Physicians of Canada, and residents were enrolled in either of the RCPSC or CFPC programs in emergency medicine. Physicians taking part in the study were certified to perform DVT ultrasound exams from the trifurcation to the femoral vein after successful completion of the training program.

Results of the assessment, both clinical and radiological, were recorded in a standardized data collection form. (Appendices 1 and 2)

3.8.2 Ultrasound training

Prior to commencement of the study, expressions of interest regarding further ultrasound training were sought from the staff and residents already credentialed in ultrasound use in the emergency departments. Those who agreed to participate received detailed training in performing bedside ultrasound to exclude above-knee DVT and image manipulation and storage. The Emergency Medicine Ultrasonography director and Ultrasound Fellowship director (RDMS-qualified) developed the training program. This occurred on October 25, 2010. It was a 3.5-hour session held in the University of Ottawa Simulation Centre and comprised a didactic lecture on theory and technique followed by a 2-hour scanning workshop. Skill acquisition of each participant was tested using real-time performance assessment during scanning of 10 healthy volunteer models. It has been shown that emergency residents can learn the technique in two hours. (43) There is no literature that authoritatively concludes how many scans are required to achieve competency in the technique.

Only physicians that completed the training program were authorised to enrol patients. A small number of physicians subsequently completed an equivalent training program and were able to recruit patients.

The technique taught was the so-called “2-point” compression ultrasonography. This involves images the lower limb veins in short axis, with the corresponding artery in view. Force is applied downwards on the probe to collapse the normal vein and saving the image. The screen needs to be split in order for the non-compressed and compressed image to be visible side-by-side. Non-compressibility of the vein indicates intraluminal thrombus.

The two points assessed were the femoral vein and the popliteal vein. In fact we mandated five images in total that needed to be saved: common femoral vein (CFV) above the sapheno-femoral junction (SFJ), CFV at the SFJ and the CFV below the SFJ. The popliteal vein, behind the knee, was assessed in the popliteal fossa distal to the superficial femoral vein, and again as it divides into the major calf veins. This is known as the “trifurcation,” as the popliteal vein divides into anterior and posterior tibial veins and the peroneal vein, although the anatomy is highly variable.

3.8.3 Quality assurance

There was ongoing evaluation of the quality of the patient assessments judged by completeness of data collection sheets and compliance in enrolling eligible patients. Saved ultrasound images were regularly reviewed for adequacy by the Emergency Medicine Ultrasonography director and the Ultrasound Fellow and feedback was given to each physician sonographer.

3.8.4 Data recorded

Demographic information and bedside ultrasound result

Demographic information captured included age, sex and contact details to enable telephone follow-up.

Additionally the following ultrasound data was recorded:

- Date of scan
- Limb scanned (left or right)

- Result: positive, negative or indeterminate. Encouragement was given to participants during the training and regularly throughout the study to make a concerted effort to assign a positive or negative result to the scan.
- Physician name to enable identification for trend analysis
- Start and finish times of scan to enable calculation of scan duration
- Degree of difficulty on a 5-point Likert scale and reason for difficulty e.g. patient obesity, restricted mobility, pain, or other

Clinical risk prediction data

Information was recorded that enabled calculation of two clinical prediction scores, the Wells and AMUSE scores. These both combine historical information and examination findings.

The revised Wells score: (17,41)

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as deep-vein thrombosis; alternative diagnosis specified	-2

A Wells score of <2 indicates DVT is unlikely; a score of ≥ 2 indicates DVT likely.

The AMUSE score: (57,58)

Clinical characteristic	Score
Male sex	1
Use of hormonal contraception	1
Active cancer in past 6 months	1
Surgery in previous month	1
Absence of leg trauma	1
Distension of collateral leg veins	1
Difference in calf circumference of ≥ 3 cm	2
Abnormal d-dimer assay	6

A score of ≤ 3 signifies low risk. Prior to study commencement, the participating physicians were reminded of the importance of completing the clinical aspects of the data collection form before obtaining the d-dimer result or performing the

bedside ultrasound. This was to ensure that the investigation results did not influence the subjective clinical assessment.

D-dimer result

The Ottawa Hospital uses a latex-agglutination quantitative assay (HemosIL D-Dimer Kit, Beckman Coulter, Brea, CA). A value of less than 300 μ g/L is considered a negative predictor for deep vein thrombosis and pulmonary embolism. Although the case record form includes space for the physician to note the d-dimer result, for accuracy reasons the data was recorded directly from the hospital's clinical information system.

3.9 Outcome measures

The primary outcome was a composite of diagnosis of a proximal lower-limb DVT or PE or death from venous thromboembolism within 90 days of presentation to the emergency department. In other words, any patient that was diagnosed on the index presentation to the emergency department, or at any time within the 90-day follow up period, or died of thromboembolism during follow up, was counted as a positive outcome. This was defined by any of the following:

- Positive ultrasound for proximal lower-limb deep vein thrombosis reported by a staff radiologist. This includes thrombus (either occlusive or non-occlusive) reported anywhere in the deep vein system from the popliteal to the common femoral vein. Thrombus in the trifurcation or inferior to it, without involvement of the popliteal vein was not considered an outcome, nor was thrombus in the great saphenous vein.
- Commencement of anticoagulation or placing of an IVC (inferior vena cava) filter for the purposes of treating a diagnosed deep vein thrombosis.
- Positive CTPA (computed tomography pulmonary angiogram) or high probability VQ (ventilation-perfusion) scan reported by a staff radiologist or nuclear medicine physician.
- Autopsy result consistent with fatal PE, or on clinical grounds when no autopsy available.

Patients recruited who did not have DVT excluded during ED assessment were referred to The Ottawa Hospital Thrombosis Unit for follow up. For patients lost to follow up from the Thrombosis Unit, liaison was made with the Ontario Coroner's office to determine cause of death if relevant. The outcome at 90 days was determined by a combination of accessing the hospital clinical information system (database) and contacting participants via telephone.

Secondary outcomes include test characteristics of emergency physician-performed bedside ultrasound, performance of the Wells and AMUSE rules with regard to the primary outcome and scan duration. The result of the bedside ultrasound was compared to both the radiology-performed ultrasound and the primary outcome to calculate sensitivity, specificity, positive and negative predictive values.

3.10 Data analysis

All data analyses were performed using SAS statistical software. (Version 9.2; SAS Institute, Inc.)

3.10.1 Descriptive statistics

The characteristics of the cohort were described with simple descriptive statistics including frequencies, percentages, means, medians, standard deviations and interquartile ranges.

3.10.2 Contingency tables

The following comparisons were made: the Wells score against the primary outcome; the AMUSE score against the primary outcome; emergency physician-performed ultrasound against radiology-performed ultrasound; emergency physician-performed ultrasound against primary outcome. Sensitivity, specificity, positive and negative predictive values with large-sample 95% confidence intervals were calculated.

3.10.3 Univariate analysis

Associations between possible predictors of the outcome were analysed with the chi square test or Fisher exact test as appropriate.

3.10.4 Multivariate analysis

Predictor variables that had a p-value of less than 0.20 on the univariate test were entered into the multivariate analysis. For the multivariate analysis, stepwise logistic regression was used, with a p-value of 0.20 required for entry into the model and a p-value of 0.05 required for a variable to remain in the model.

3.10.5 Sample size for study

The sample size for this Master's thesis was determined based on feasibility. More specifically, it was the number of cases that that could be enrolled in the 6-month period.

The sample size for a definitive study of this question is primarily determined by the required 95% confidence limits around a high degree of sensitivity for the outcome. For example, collecting 60 cases positive for the primary outcome could yield a decision strategy that is 100% sensitive with a 95% CI of 94-100%. A recent systematic review (51) identified positivity rates of deep vein thrombosis in similar studies ranging from 7 to 32%. Thus a conservative estimate of the expected incidence of the primary outcome is 15%, and so the definitive study would need to enrol 400 patients to yield 60 with a positive primary outcome. At the two EDs, we believe that 400 eligible patients are seen each year but anticipate that enrolment into the study would be 50% of eligible patients. Hence, approximately 24 months would be required to complete a definitive study.

3.11 Ethical concerns

The study protocol was submitted to the Research Ethics Board of The Ottawa Hospital and was approved on September 14, 2010 as protocol 2010535-01H.

As for prior studies on clinical decision rules, the requirement for informed consent was waived for this study. (59,60) The study is an observational one conducted in a context of an established follow up system for deep vein thrombosis, albeit with one added investigative procedure. Ultrasound is a non-invasive, painless and safe investigation, with established widespread use in clinical medicine. As in previous studies deriving rules for imaging the ankle and knee joints, cervical spine, and head, normal patient management will not be altered. Patients are not being subjected to new therapy, invasive procedures, undue risk or discomfort beyond that which would normally be required in the course of patient care. All personal identifiers will be kept strictly confidential and stored separately from the clinical information collected. Once this information is no longer required, it will be deleted from the database. An information card both in English and French was distributed to all enrolled patients informing them of their participation in the study and to expect a follow up telephone call in 90 days.

Chapter 4: Results

The characteristics of the patient group are provided in Table 2. From October 26, 2010 to April 30, 2011, 104 patients were recruited. Ideally basic descriptive data would have been collected on patients who were not recruited into the study. This would enable determination of whether or not there were systematic differences between the patients recruited and patients not recruited.

Unfortunately due to resource limitations, this was not done. The cohort in the study was generally middle-aged and relatively healthy, as evidenced by the mean age (58) and small number of patients with significant comorbidities. There were large differences in the proportion of patients fulfilling the risk factors included in the Wells score. Only 3.9% had lower limb immobilization whereas 43.6% had pitting edema confined to the symptomatic leg. Only one patient had a previous deep vein thrombosis, because these patients were largely excluded from the study. It was clarified to the physicians during the study that the exclusion of previous thrombosis referred to the symptomatic limb only. It is likely, however, that nearly all potential subjects with any previous thrombosis were excluded by the physicians. A large proportion of patients (47%) had a d-dimer above the upper limit of normal, confirming the poor specificity of the test.

The characteristics of the bedside scans performed in the emergency departments are shown in Table 3. Physicians were able to complete the bedside ultrasound scan in a median time of ten minutes. The self-rated median difficulty score was 2 on a 5-point scale, where 1 represented “very easy” and 5 “very difficult.” Not all patients had a radiology-performed scan after the emergency physician-performed scan; in fact 40 did not. This occurred because it was not feasible to mandate a formal ultrasound test for patients deemed to be at very low risk of venous thrombosis. These patients would ordinarily be discharged from the department and no follow up would occur. Amongst the patients who did have formal ultrasound scans, this occurred an average of one day after their

bedside scan. Reflecting the large number of physicians, each performed an average of 3.5 scans during the course of the study. Staff physicians performed the majority of scans (89.4%), which was expected given the training was directed primarily towards staff as opposed to residents.

In Figure 2 it is apparent that the distribution of scan difficulty, as reported by the physicians, was not a normal one. The physicians rated their scans towards the easier end of the spectrum, as 62% were rated 1 (very easy) or 2 (easy), and only 5.8% were characterized as 5 (most difficult).

It was expected that the distribution of scans by physician would be uneven as the investigators were expected to recruit more than the non-investigators. The residents are indicated in figure 4 by physician numbers 1, 6 and 14. The primary investigator (physician 2) and the ultrasound fellowship director (physician 17) were responsible for performing 9.6% and 17.6% respectively of all scans.

Although the patient load at each campus was similar, the physicians at the General campus recruited 34 (32.7%) patients, whilst 70 patients (67.3%) were recruited at the Civic campus.

In Table 4, the outcomes for the patients in the cohort are provided. Hospital admission was rare (1.0%) in the cohort as was death (1.9%). Only 63 patients had both formal and bedside ultrasounds, hence the reduced denominator for the 18.8% of formal scans that were positive. Two patients developed lower limb venous thrombosis or pulmonary embolism during the follow up period, thus a total of 14 (13.5%) of patients were positive for the primary 90-day outcome.

Figure 5 shows the patient flow throughout the study. Four patients inadvertently did not have a d-dimer performed, and 40 patients did not have a radiology-performed ultrasound scan. Amongst these 40 patients, 2 patients died, 4 were completely lost to follow up and one was known to be alive but was uncontactable. The four who were completely lost to follow up all had low-risk

Wells scores and negative d-dimers. An assumption was made that none of the patients missing outcome data experienced a primary outcome. A sensitivity analysis was considered to examine the effects on the results, however it was not considered useful due to the small numbers in the cohort.

The characteristics of the Wells score in the cohort are detailed in Table 5. A Wells score of ≥ 2 was 85.7% sensitive (95% CI 57.2 – 98.2%) when compared against the composite outcome, comprised of positive radiology-performed initial ultrasound or development of venous thromboembolism and deaths due to venous thromboembolism during the follow up period. The confidence interval was wide due to the small number of cases, in particular the number of outcomes. Specificity was unimpressive at 68.5% (95% CI 57.8 – 78.0%), but this is in keeping with a clinical decision rule that aims for sensitivity over specificity. The negative predictive value of 96.8% (95% CI 89.0 – 99.6%) means that a low-risk Wells score reasonably accurately predicts the absence of an event in the 90-day period.

In Table 6 the characteristics of the comparison decision rule are shown. The sensitivity of the high-risk AMUSE rule for the 90-day outcome was identical to that of the Wells score – 85.7% (95% CI 57.2 – 98.2%). This is unsurprising, given the small numbers of positive outcomes in the study. Of the 14 patients with positive outcomes, both rules classified 12 patients as high risk. Wide confidence intervals again relate to the limitation of small numbers. Specificity was 54.4% (95% CI 43.6 – 65.0%), which is more than 10% lower than the Wells score. The negative and positive predictive values were not greatly different between the two scoring systems.

Table 7 shows the operating characteristics of the emergency physician-performed compared to the radiology-performed ultrasound. The bedside ultrasound had similar sensitivity to the two clinical decision rules (91.7%, 95% CI 61.5 – 99.8%) but had substantially higher specificity of 91.7% (95% CI 80.0 – 97.7%). This led to not only a good negative predictive value of 97.8% (95% CI 88.2 – 99.9%) but also a superior positive predictive value of 73.3% (95% CI

44.9 – 92.2%). Four scans, about 6% of all scans, were considered indeterminate by the physician, so a decision was made to exclude these cases from the analysis. This was done because there was no clinically sensible way to include them. The recorded images alone did not contain enough information to retrospectively assign a binary result to them, and the data of interest were the physicians' determination of the result. Images were recorded primarily for quality assurance purposes. One could assume that the indeterminate scans were all positives or all negatives however this would not be a realistic clinical decision for any investigation result that was indeterminate.

There were five emergency physician-performed ultrasound scans that had discrepant results to the radiology-performed scans. Table 8 provides the details of these scans. Four of the errors were false positives, where the emergency physician felt the images showed a thrombosis, and the radiologist disagreed after performing their own scan. The more concerning error was the single false negative, where a thrombus seen on the radiology-performed scan was missed by the emergency physician. The difficulty rating of the scans varied from 4 (difficult) to 1 (very easy). All the operators were staff physicians and were mostly inexperienced with the technique. The patients' age ranged from 34 to 85, and four the five errors occurred in females.

Regarding the false positive scans, two of the saved images demonstrated thrombus in the great saphenous vein. Although the femoral and great saphenous veins are distinguishable on ultrasound, it is likely the physicians' limited scanning experience and lack of familiarity with the anatomy contributed to the errors.

It is worthwhile exploring the false negative case in more detail. The patient was an 85-year-old woman who was scanned 3 months after the study commenced. The physician considered it an easy scan (rating of 2) and it took 15 minutes to complete. Her Wells score was 2 ("likely") and her d-dimer was positive at 2320. The formal scan revealed an occlusive thrombus extending from the trifurcation to just below the sapheno-femoral junction. On reviewing the saved bedside

images, it was apparent that the femoral artery and vein were not identified; rather the vein imaged and compressed in the groin was the long saphenous vein, leading to the false impression of a negative scan. This scan was the first performed in the study by the operator, who prior to study commencement had not done any lower limb ultrasonography. He recruited three patients to the study.

Table 9 details the characteristics of point of care ultrasound when compared with the composite outcome. The sensitivity of bedside ultrasound for deep vein thrombosis drops from 91.7% (95% CI 61.5 – 99.8%) when the outcome is radiology-performed scan to 78.6% (95% CI 49.2 – 95.3%) when the outcome is the composite outcome which includes follow-up. Note that 10 of 104 cases were excluded in this analysis due to the bedside scan results being indeterminate. Specificity was 95.0% (95% CI 87.7 – 98.6%). One explanation for the reduced sensitivity is that in this dataset all the cases that had not yet reached 90 days of follow up at the time of analysis were considered a negative response. Additionally there was one case that was negative for thrombosis on both bedside and formal sonography, as defined by thrombus at the trifurcation or more proximally. There was however thrombus in the calf veins, which at The Ottawa Hospital is not considered a deep vein thrombosis. The patient had a follow-up scan one week later, organized by the Thrombosis Unit, and the thrombus had progressed proximally. The patient was then treated for true deep vein thrombosis with anticoagulation.

4.1 Univariate analysis

Some of the Wells score elements were significantly associated ($p < 0.05$) with the primary outcome whilst others were not. The associations are detailed in Table 10. One of the strongest negative associations was when an alternative diagnosis was considered as likely or more likely than that of deep vein thrombosis. This equates to the physician's overall impression of deep vein thrombosis not being the explanation for current symptoms. There were only two positive cases compared to 49 negative cases when an alternative diagnosis was considered

more likely than thrombosis. Interestingly this is the most subjective of all the components of the score, as it uses physician gestalt rather than a measurable quality. The strongest association was entire leg swelling, with a p-value of <0.0001. The final significant association was when pitting edema was confined to the symptomatic leg, which had a p-value of 0.0035. Lesser associations were seen with previous DVT (p=0.1359), localized tenderness along the distribution of the deep venous system (p=0.0658) and calf swelling 3cm more than the asymptomatic side (measured 10cm below tibial tuberosity), which had a p-value of 0.1093. It is noteworthy that many of the traditional risk factors for venous thromboembolism, when considered in isolation, were not significant associations in this dataset. The two additional contributors to the AMUSE score (use of hormonal contraception and absence of leg trauma) were both non-significant.

Both the d-dimer and bedside ultrasound results were strongly associated with a positive outcome. A d-dimer result of ≥ 300 $\mu\text{g/L}$ had a p-value of 0.0107 and a positive bedside ultrasound of <0.0001. A sensitivity analysis was conducted to determine the potential impact of the indeterminate scan results on accuracy. They were assigned as all positive results, and then again as negative results, and the analysis re-run. The strength of the association remained unchanged regardless of the treatment of indeterminate scans.

4.2 Multivariate analysis

The covariates from the univariate analysis that had significant associations (as defined by a p-value of less than 0.20) were entered into the multivariate model. Thus the following variables were entered into the model:

- Previous DVT
- Localized tenderness along the distribution of the deep venous system
- Entire leg swollen
- Calf swelling 3cm greater than the asymptomatic side
- Pitting edema confined to the symptomatic leg

- Alternative diagnosis as likely or greater than that of DVT
- D-dimer result ≥ 300 $\mu\text{g/L}$
- Bedside ultrasound result

The model considered was a stepwise logistic regression, with significance level of 0.20 for a covariate to enter the model and 0.05 to remain in the model.

Table 11 gives the results of the multivariate model. Only one covariate remained significant after multivariate analysis – the result of the bedside ultrasound scan. The beta coefficient was 4.18, with the corresponding odds ratio of 65.1, and 95% confidence intervals 12.8 to 330.8. Most apparent is the high odds ratio of 65.1 with wide confidence intervals, suggesting an unstable estimate. This result warrants further analysis. Both the small cohort size and the small number of “positives” (i.e. subjects that had a primary outcome), explain the wide confidence interval. There are 10 missing values in this analysis as the ‘indeterminate’ results were excluded. This increased the standard deviation and thus widened the confidence interval.

The area under the curve of the model was 0.866, signifying good fit. The Hosmer-Lemeshow goodness-of-fit test was unable to be applied because the predictor variable (ultrasound result) has only 2 levels. The levels were DVT seen, or not seen.

Chapter 5: Discussion

In this study, it has been shown that the Wells score and the AMUSE score for predicting lower limb deep vein thrombosis have comparable accuracy in a Canadian emergency department setting: sensitivity of 85.7% for both with 68.5% specificity for the Wells and 54.4% specificity for the AMUSE rule. Point of care ultrasound was 91.7% sensitive for thrombosis diagnosed by radiology-performed scan and 91.7% specific, which is somewhat lower than previously reported. False negatives are most likely due to operator inexperience. Point of care ultrasound was 78.6% sensitive and 95.0% specific for thrombosis when compared against a composite outcome of initial radiology-performed scan plus delayed clinical follow up. The reduced sensitivity is mainly related to thrombosis that may not be apparent on initial imaging but progresses proximally to become apparent later. Multivariate analysis showed that the odds ratio of a positive composite outcome with a positive point of care scan was 65.1 (95% CI 12.8 – 330.8). This strong relationship meant that the d-dimer result and elements of the clinical prediction rules were not independently associated with the outcome. Essentially when the d-dimer was positive, the bedside ultrasound was also positive, but the ultrasound was a more powerful predictor of thrombus. With appropriate training and quality assurance, emergency physician-performed ultrasound for lower limb deep vein thrombosis can be performed accurately.

5.1 Interpretation of the results versus the objectives

5.1.1 Objective 1

1. To compare the accuracy of emergency physician-performed ultrasound against the criterion standard of a radiology department-performed ultrasound scan.

- a. To develop and implement a training program for emergency physicians to use bedside ultrasound to exclude proximal lower limb deep vein thrombosis

The training program was successfully designed and delivered to the physician group in October 2010. During the study period there was no official retesting of the material covered, however image quality was good and no physicians consistently produced poor quality scans.

- b. To prospectively enrol a cohort of patients presenting to the emergency department where the possibility of lower limb deep vein thrombosis is considered

Patients presenting to the Ottawa Hospital Emergency Departments during the study period were successfully recruited. As resources were limited, there was no research assistant available in the Department to facilitate recruitment. Certainly those subjects recruited represented a proportion of the total eligible for recruitment. Several factors contributed to this, including physicians who were under a heavy clinical load and not always receptive to carrying out research. Another important factor was the small number of physicians who were trained to perform the scans. Of about fifty staff physicians, sixteen were trained, and one left the group shortly after the training. Resource limitations were the reason not all staff could be trained in the technique, and this obviously affected the ability to capture all eligible subjects. Overnight, medical staffing is considerably reduced, so when the clinical load was high, enrolment in the study is likely to have suffered.

- c. To have emergency physicians complete a case record form comprising several clinical characteristics which will enable calculation of the Wells and AMUSE risk stratification scores

The physicians generally completed the case record forms adequately. A small number of forms initially had fields missing and these data were completed after communicating with the physician shortly after the recruitment date. The scanned medical record was inspected in other cases so that missing data fields could be completed.

- d. To have emergency physicians perform a focussed bedside ultrasound intending to exclude proximal lower limb deep vein thrombosis and record the result on the case record form

The performance and recording of the scan was successfully carried out in the majority of cases. Not all images were reviewed, as the plan was only to review cases where the bedside ultrasound result differed from the formal result. The interpretation of the images by the attending physician was the primary data point, as ultrasound is a dynamic process and the still images capture only a fraction of the information available to the sonographer.

- e. To measure interobserver variability of the bedside ultrasound result by having a second physician repeat the scan on a proportion of the cohort

Although measurement of interobserver variability was planned for the study, unfortunately this did not occur. This was primarily due to very few instances where another physician trained in the technique was available to repeat the scan.

- f. To determine the acceptability of emergency physician-performed ultrasound to emergency physicians and to determine the level of comfort using a diagnostic strategy to exclude proximal leg deep vein thrombosis in the emergency department

Ultimately the concern was that because physicians already were under pressure from both a clinical and research standpoint, data forms may be incompletely filled out and recruitment would be poor. Thus the decision was made not to require the physicians to answer additional questions on their comfort level with the procedure.

- g. To compute the test characteristics of emergency physician-performed ultrasound versus the criterion standard of radiology staff-reported ultrasound scans for the diagnosis of proximal leg deep vein thrombosis

The cohort of emergency physicians achieved acceptable sensitivity when measured against radiology-performed ultrasound for below-knee deep vein thrombosis. Sensitivity and specificity both above 90% is significantly better than a screening test such as d-dimer, which tends to have very high sensitivity but poor specificity. The negative predictive value of a bedside scan of 97.8% is reassuring particularly given the limited training the staff were given and the lack of ongoing quality assurance and testing of skill maintenance. The more interesting test characteristics are those relating to the comparison of bedside ultrasound against the primary composite outcome, which includes 90-day follow up. The sensitivity falls to 84.6%, however the specificity is impressively high at 95%. As a comparison, the sensitivity of radiology-performed ultrasound for the primary outcome is 85.7% (95% CI 57.2 – 98.2%) and specificity 100% (95% CI 92.9 – 100.0%). This is because deaths were considered to be outcomes, and small thrombosis in the calf can always progress to an outcome. The negative predictive value of 97% for the bedside test is almost identical to the comparison against radiology-performed scan. This is the key statistic that adds important evidence to the move to point-of-care testing. Emergency physicians aim to rule out serious conditions and then discharge patients, rather than tailoring specific treatment to subtly different variants of a condition. This is best left to experts in thrombosis. In a patient diagnosed with a thrombosis by an emergency physician, it is likely a confirmatory, more detailed scan will be performed in conjunction with a consult with a thrombosis expert to decide on appropriate therapy. If emergency physicians are to regularly discharge patients with “no thrombosis” after a bedside ultrasound, they must be confident that a negative result is accurate.

5.1.2 Objective 2

2. To assess the ability of the combination of a clinical prediction rule, d-dimer result and emergency physician-performed ultrasound to effectively exclude the primary outcome of a diagnosis of venous thromboembolism in a 90-day follow up period.

- a. To compare the accuracy of the Wells and AMUSE scores for predicting the primary outcome.

It has been shown that the Wells and the AMUSE scores have comparable sensitivity and specificity when measured against a composite clinical outcome. Although the Wells score has been extensively validated in many settings, the AMUSE score has not. The rule has been successfully validated outside the setting it was originally developed in and found that its performance was similar to the Wells score in my cohort of emergency department patients. The sensitivity was, however, significantly reduced from that found (94.9%) in the validation study of 1028 patients in a Dutch primary care setting. (57)

- b. To have emergency physicians measure a d-dimer and record the result on a data collection form

The serum d-dimer level was measured in 100 of 104 patients (96.2%), which is a good proportion in a study without dedicated research assistants ensuring fidelity of data in real-time. There were a greater number of data forms that had missing d-dimer results, however these were completed after accessing the hospital pathology database system.

- c. To obtain follow up data, consisting of diagnosed deep vein thrombosis and pulmonary embolism, death due to venous thromboembolism and adverse events on enrolled patients, utilising medical imaging reports, medical record review, telephone follow-up and clinical documentation through the Thrombosis Unit

Not all patients could be contacted for telephone follow up despite multiple attempts. As noted, to facilitate data analysis, those that were unable to be contacted, or those that had not yet reached their follow-up date, were assumed not to have had an outcome. Only a small number of overall patients in the study had documented follow-up review with the Thrombosis Clinic, as patients that have a low clinical risk for DVT and a negative d-dimer, as well as those with a negative radiology-performed ultrasound are generally not referred for follow

up. The medical notes in the Thrombosis Clinic were hand-searched for outcome data. No autopsy results were available, so deaths were adjudicated on clinical grounds as to whether they constituted an outcome or not.

- d. To perform a univariate analysis with predictor variables being pre-test probability, d-dimer and emergency physician-performed ultrasound results and the outcome variable being thromboembolism at 90 day follow up

In fact rather than pre-test probability, the predictor variables used were the elements of both clinical decision rules. Both rules were designed to be used in practice with a decision on whether to proceed with further investigations based on a binary result of low risk/not low risk. The univariate analysis showed that few of the elements of the clinical prediction rules in isolation are predictive of an outcome. In fact the item most strongly associated with an outcome was the most subjective, i.e. "alternative diagnosis as likely or greater than that of DVT." Of note the associations between the investigation results (d-dimer and bedside scan result) were significantly stronger than the elements of the prediction rules.

- e. To perform a multivariate analysis with predictor variables derived from the univariate analysis and the outcome being thromboembolism at 90 days

On multivariate analysis, the strength of the relationship between the bedside scan result and the primary outcome was unexpectedly strong. The odds ratio of 65 is very unusual in this type of research, considering a usual odds ratio would be in the single digits. The strong relationship is not undermined by the wide confidence intervals, as the 95% confidence interval for the odds ratio does not include unity. The wide confidence interval is expected given the small number of positive outcomes. A likely explanation for the dominance of the ultrasound over clinical data points is the lack of specificity of clinical symptoms and signs. There are many possible causes of a swollen leg and many patients with cancer do not have lower limb venous thrombosis but few conditions that restrict compression of a vein on an ultrasound image.

5.2 Comparison with previous literature findings

As seen in Table 1, the sensitivity and specificity in my study is comparable to that previously reported in the literature. As with some of the published studies, low numbers of positive (for thrombosis) scans translates to wide confidence intervals. This study had small numbers – a total of 94 conclusive bedside scans were performed, of which 15 were considered positive by the physician.

The systematic review by Burnside et al in 2008 (51) found a pooled sensitivity of 95% and a pooled specificity of 96%, compared with 91.7% and 91.7% respectively in my study. Whether a diagnostic test is ready for widespread adoption depends partly on these test characteristics, as well as other factors including cost effectiveness, acceptability to patient and clinician and availability.

The most important factor likely to affect sensitivity in this case is the training of the clinician performing the ultrasound. The one-day training course including lectures and scanning live models to enable refinement of the technique was the most intensive that could be delivered given the available resources. After 10 proctored scans, the physicians were able to begin recruiting patients for the study. The number of observed scans before an operator is considered proficient is a matter for debate. Various organisations including emergency medicine colleges and ultrasound bodies have specified differing minimum scan numbers required to meet accreditation requirements, however evidence linking minimum number of scans performed to competency is lacking. The Australasian Society for Ultrasound in Medicine requires 15 “validated” DVT scans for the purposes of obtaining the Certificate in Clinician Performed Ultrasound². The American College of Emergency Physicians suggests 25-50 scans per application.³ The Royal College of Radiologists suggests a minimum of 100 scans be completed.⁴ Given the one false negative scan in this cohort of 60 conclusive scans, the implication is that the training was inadequate. The format of lecture and scanning workshop is probably ideal, but insufficient to ensure adequate accuracy. The number of scans observed by an expert likely needs to be

² Website www.asum.com.au, accessed 17/6/2012

³ ACEP Policy Statement on Emergency Ultrasound Guidelines 2008

⁴ Ultrasound Training Recommendations for Medical and Surgical Specialties 2005

increased beyond 10. As mentioned, exactly what that ideal number is remains uncertain. It likely depends on the ultrasound experience the participants have prior to learning the new technique, as well as the quality of the teaching and the difficulty of the observed scans. To reinforce and maintain the learned skills, regular refresher courses could be run, or alternatively every scan could be over-read by an expert who gave feedback to the clinician. Clearly this approach would require significant resources.

In the training session, the people who volunteered to have their limbs scanned were medical students who were relatively simple to scan. All were compliant, none were obese, none had previous surgery or scars in the region and none had impaired mobility, all of which contribute in real life to difficulty identifying the anatomy. Having physicians complete proctored scans on real-life patients of varying degrees of difficulty would undoubtedly improve their skill level.

The more clinically relevant statistic is the accuracy of the ultrasound compared with longer-term follow up. When using a period of follow up to ensure no serious adverse events occur, the test characteristics are more robust and believable. Because thromboembolic events may occur in this follow up period, the test's sensitivity is likely to be less than when the comparison is made against an immediate radiology-performed scan. Indeed in the present study the sensitivity was 84.6% (95% CI 54.6 – 98.1%) and the specificity was 95.1% (95% CI 87.8 – 98.6%). Positive predictive value was 73.3% (95% CI 44.9 – 92.2%) and negative predictive value 97.5% (95% CI 91.2 – 99.7%) Contributing factors to the reduced sensitivity include cases where a below-knee thrombus was not diagnosed (due to the planned technique) on the index presentation but progressed to a proximal lower limb thrombus and was then diagnosed. This would be considered a “missed” event. A case of deep vein thrombosis may also truly not be present on the initial presentation and develop during the follow up period. This is likely to be less common than a thrombus that was not diagnosed on the initial visit and so the conservative approach is to include the event in the primary outcome.

The study published by Jeff Kline in 2008 used a 30-day follow up as the comparator, specifically a telephone interview and medical record review. Two authors adjudicated as to whether the primary outcome was positive or not based on review of radiology reports, autopsy reports and the medical record looking for planned anticoagulation for greater than 89 days or a planned vena caval filter. Even this was a 30-day rather than 90-day period, the sensitivity was still expectedly inferior to prior studies. These earlier studies compared the result of the emergency physician-performed scan against the radiology-performed scan, not against a clinical outcome with delayed follow up. The sensitivity was 70% (95% CI 60.0% – 80.0%) and specificity was 89% (95%CI 83% - 94%). The positive predictive value was 52.8% and negative predictive value 94.6%. This highlights the fact that using delayed clinical follow up rather than comparing against another test is a more robust research methodology, and will therefore reduce test performance.

5.3 Limitations

This study was conducted as part of a larger study aiming to recruit 60 positive cases of deep vein thrombosis. For the purposes of the thesis, recruitment was ceased on an arbitrary date, thus only 104 cases were included, and only 15 were considered positive by the physician performing the bedside scan. Unfortunately 10 cases were considered indeterminate by the physician, which further decreased the number available for analysis. The limited resources available for training hampered recruitment. Sixteen out of approximately 55 staff physicians were trained, due to restrictions on numbers because of time, space and financial constraints. Physicians who were already accredited by the department to perform ultrasound for other indications were preferentially given access to the workshop. This therefore selected a group of doctors who had higher than average skill in performing ultrasounds, although few had significant experience in lower limb venous ultrasound. To enhance external validity, doctors of all seniority levels and ultrasound experience ideally would have been trained and their experience level explicitly stated and possibly adjusted for in the analysis.

5.3.1 Indeterminate scans

The probable reason for 10% of scans being indeterminate is the relative lack of experience of the physicians with the technique. Although they all participated in a well-designed workshop with a practical component, when imaging real-life patients multiple factors contribute to the inability to confidently call a scan positive or negative and these usually relate to poor image generation. The physician factors that cause poor image quality include poor choices of depth of field, TGC controls and gain setting; not adequately visualising the required areas and inadequate familiarity with the anatomy. The patient factors that were not encountered in the initial workshop were obesity, tissue edema, restricted mobility, pain during the examination as well as patient non-compliance. Many of these issues would be improved with more frequent use of the technique, particularly with feedback from experts. Because emergency physicians see patients with such a broad range of problems, there may be periods of many months where they do not scan a lower limb for potential thrombosis and thus lose their skills. One way to address this problem would be with frequent refresher workshops, or even better, getting real-time and delayed feedback on each scan by an expert. This requires significant resource investment.

5.3.2 Image review

A decision was made not to review all images saved by the clinicians, rather only those with discrepant results to the formal scan. The reason for this again was limited resources, mainly the investigators' time. Again, ideally all images would have been reviewed to judge adequacy of the images and enable better feedback to all the clinicians to improve their technique.

5.3.3 Follow up

As outlined follow up was incomplete for 5 patients in the cohort. Outcomes were imputed to have not occurred, and this would have biased the test characteristics in the direction of greater accuracy.

5.3.4 Expert sonographers

A limitation common to many studies investigating point-of-care ultrasound is over-scanning by experts. Often the investigators are ultrasound fellowship-trained and have significantly greater experience in performing bedside ultrasound than the average emergency physician. Thus the results of studies

where these experts perform the majority of scans lack external validity. In the present study, the emergency ultrasound director and myself performed 27% of all scans. Thus an average emergency physician who does not have a large amount of experience cannot easily apply these results to their setting. It is difficult to avoid this issue unless those performing the research, who are usually very enthusiastic about ultrasound, avoid recruiting patients themselves.

5.3.5 Previous DVT

In the preparations for the study, it was decided that if a patient was previously diagnosed with a lower limb deep vein thrombosis, they should be excluded. The basis for this is that the thrombus may not fully resolve, and differentiating acute from chronic thrombus is challenging and beyond the scope of this study.

Unfortunately it was interpreted as a blanket exclusion and thus significantly reduced numbers, particularly those with a risk factor for a subsequent event. This could have been avoided by allowing patients into the study with previous thrombosis if the side was known, and the symptomatic leg on current presentation was the contralateral one. A greater number of positives would have been recruited and thus reducing some of the imprecision of the estimates.

5.3.6 Missed objectives

Some of the planned objectives were not met. Measuring interobserver variability would have allowed examination of how frequently emergency physicians agree on the result of a scan. Due to a high clinical workload during the study, there simply were not physicians free to perform another scan for the purposes of research. Encouraging them to perform the one scan for the study purposes was enough of a challenge without causing further distraction from their clinical work.

Another planned objective was measuring the acceptability to emergency physicians of using the technique to investigate patients with suspected venous thrombosis. This objective was not met, as the data collection sheet needed to be kept short enough so as not to discourage physicians from enrolling patients. The questions on acceptability were not included on the final data collection sheet thus this analysis was not performed.

Unfortunately resource limitations precluded gathering clinical details on those patients eligible but were not recruited. It is likely that a large proportion of eligible patients were not recruited because of the limited number of physicians trained in the ultrasound technique, as well as a high clinical load leading to missed opportunities. Additionally the lack of a research assistant on the floor to screen for potential recruits hindered the collection of data on “missed” patients.

5.4 Strengths of the study

This is the first observational study assessing the accuracy of the combination of a clinical prediction rule, d-dimer result and bedside ultrasound in diagnosing acute lower limb deep venous thrombosis in the emergency department. Several investigators have assessed combinations of diagnostic modalities (20,21,26) including ultrasound, d-dimer testing and clinical probability test but not in the emergency department setting. Emergency physicians did not carry out these studies and thus comparing their results with the present study is problematic. In the previously published studies it is either sonographers (technicians) or physicians specialising in vascular medicine who performed the tests; these practitioners are likely to have significantly more experience and skill in performing vascular ultrasound than an average emergency physician.

I have shown that adding d-dimer or a clinical prediction score to the bedside ultrasound result does not improve accuracy. The result is even more notable considering that the training for the physicians consisted of a standalone one-day course. The false negative rate would likely be further reduced had additional quality assurance occurred in tandem with more extensive training.

This study did follow up patients after discharge from the emergency department, which few studies have previously done. This required significant effort to phone the participants, often multiple times, in order to make contact. Without follow up, the true rate of missed venous thrombosis would be unknown.

As emergency physicians at the study sites staff the department twenty-four hours a day, the study was not biased by only recruiting during business hours.

This issue affects many studies where the staff who collect data are only available during business hours.

This is the first study to validate the AMUSE primary care rule outside of the Netherlands. Although the rule was developed for use in a general practice setting, there is nothing that prevents validation, and potential use, in an emergency department setting. Similarly for a rule to be accepted for widespread implementation, it should be validated in communities outside the one it was originally developed in. The AMUSE primary care score has been compared against the Wells score previously (61) in the Netherlands, where the AMUSE rule was developed. The comparison did use 90-day follow up using a patient questionnaire and general practitioner records, and outcomes that were judged by an independent adjudication committee. It found that over the 90-day follow up period, the two rules missed an equal number of patients who developed venous thromboembolism or death due to thromboembolic events.

5.5 Clinical implications

5.5.1 Objective 1

To compare the accuracy of emergency physician-performed ultrasound against the criterion standard of a radiology department-performed ultrasound scan.

Goals a-c have no particular clinical implication.

- d. To have emergency physicians perform a focussed bedside ultrasound intending to exclude proximal lower limb deep vein thrombosis and record the result on the case record form

In over 90% of the performed scans a decision was made regarding the presence or absence of thrombus. The ten scans, out of a total of 104, that were indeterminate can reasonably be explained by lack of experience. As the majority of physicians who were involved in the study did not have prior experience with

the technique, the only training they received was the one-day session prior to study commencement. Although physicians were not asked to record why their scans were indeterminate, it is most likely that the anatomy was not confidently identified. Physicians' skills with identifying the vessels in patients of all sizes would improve with experience. The clear implication is that the required number of proctored scans performed in order to safely make diagnostic-quality studies needs to be greater than ten.

- e. To measure interobserver variability of the bedside ultrasound result by having a second physician repeat the scan on a proportion of the cohort
- f. To determine the acceptability of emergency physician-performed ultrasound to emergency physicians and to determine the level of comfort using a diagnostic strategy to exclude proximal leg deep vein thrombosis in the emergency department

Future similar prospective studies need to allow sufficient resources to capture this extra information. Physician time is valuable in a busy department and the more data that is requested then the more time they spend not seeing patients. This could be addressed with a research assistant who would facilitate the data collection, freeing up physicians. Measuring interobserver variability of the ultrasound result requires "doubling-up" of the scanning time and thus a department must make a commitment to research at the expense of reduced physician efficiency.

- g. To compute the test characteristics of emergency physician-performed ultrasound versus the criterion standard of radiology staff-reported ultrasound scans for the diagnosis of proximal leg deep vein thrombosis

The major implication for the practice of emergency medicine is that it is possible for emergency physicians to diagnose lower limb venous thrombosis using point of care ultrasound. If a physician reaches a certain skill level and can

therefore perform the scan proficiently, adding more information to the diagnosis decision such as a d-dimer result or a scoring system does not further improve accuracy.

If the d-dimer was no longer performed, it would likely speed up a patient's journey through the emergency department. Most departments draw the blood and then send the tube to the pathology department for processing. It commonly takes more than one hour for the physician to receive the result. Although rapid point-of-care systems are available, most emergency departments do not use them because of concerns of cost as well as reduced test performance compared with laboratory testing. The advantage of physician-performed ultrasound over a clinical risk score is that the result obtained is thrombus seen or not seen, compared with the low risk or not low risk categories generated by a risk score. Any result other than low risk will require further confirmatory testing, often including both a d-dimer and an ultrasound in a sequential fashion. The sensitivity and specificity for deep vein thrombosis in the present study of clinician-performed ultrasound was 79% and 95% respectively, whereas d-dimer has been shown to have a sensitivity of around 97% and specificity of 35-45%. This suggests that in the context of the presently described training program, a standalone negative scan is not sufficiently sensitive to exclude deep vein thrombosis. In a patient with a significant clinical probability of DVT, a negative bedside scan must be followed by further testing, ideally an ultrasound performed by an expert sonographer. The high specificity suggests that, in particular, in the context of a high pre-test probability, a positive scan should be considered reliable and anticoagulation commenced.

One of the most important issues to tackle before this practice becomes standard in emergency departments is training and quality assurance. The one false negative in this series was due to the practitioner's lack of experience with the anatomy. This kind of error would decrease with increased initial training, and to a greater degree with ongoing monitoring of scan quality. Thus an ideal departmental setup would be one where each scan is recorded, and constructive feedback is provided to the physician concerned for each inadequate scan. The ACEP (American College of Emergency Physicians) policy statement on

emergency ultrasound guidelines requires this quality assurance process for any ultrasound program. (62) Additionally, accreditation to perform the bedside scan as a single “rule-out” test enabling early discharge would be contingent on each physician producing a pre-specified number of adequate quality scans. Each scan must have accurate results as judged by agreement with the current standard of care in the institution concerned. Exactly what that number should be is unclear. One study showed that even after 20 scans, novice emergency physician sonographers were performing technically inadequate scans. (63) The ACEP policy statement reports that “a generally accepted number of 25-50 cases per application should follow didactic training,” (62) however they list no literature that proves this is the correct number required to achieve competence. It would appear that performing ten proctored scans, as was done in the present study, is insufficient to achieve competence, particularly when those scans were all technically easy. Future training programs should incorporate a more realistic mix of patients of various body habitus.

As noted earlier, very few cases of venous thrombosis were identified exclusively in the follow-up period. This suggests that the diagnosis can, and needs to be made during the first presentation. Where there is a reasonable clinical likelihood of disease, an initial negative point of care scan should not preclude further testing. If a patient has ongoing or progressive symptoms or signs, repeat ultrasound should be performed. Ideally an expert sonographer should perform this rather than an emergency physician given that no diagnosis was made on the index presentation. A repeat scan is also likely to capture thrombosis that was perhaps initially present only in the calf, which then propagated proximally to above the knee.

5.5.2 Objective 2

To assess the ability of the combination of a clinical prediction rule, d-dimer result and emergency physician-performed ultrasound to effectively exclude the primary outcome of a diagnosis of venous thromboembolism in a 90-day follow up period.

- a. To compare the accuracy of the Wells and AMUSE scores for predicting the primary outcome.

As the test characteristics of the two clinical decision rules were similar in this cohort, either rule could be used in similar populations to risk stratify such patients. The advantage of the Wells score is that it uses only clinical information, whereas the AMUSE rule requires the result of a d-dimer, which adds time to the workup.

- b. To have emergency physicians measure a d-dimer and record the result on a data collection form
- c. To obtain follow up data, consisting of diagnosed deep vein thrombosis and pulmonary embolism, death due to venous thromboembolism and adverse events on enrolled patients, utilising medical imaging reports, medical record review, telephone follow-up and clinical documentation through the Thrombosis Unit
- d. To perform a univariate analysis with predictor variables being pre-test probability, d-dimer and emergency physician-performed ultrasound results and the explanatory variable being thromboembolism at 90 day follow up

That few of the individual components of the decision rules had significant associations with the outcome is noteworthy. It suggests that the classical risk factors in isolation are insensitive for venous thromboembolic disease and are only useful in the setting of a validated decision rule.

- e. To perform a multivariate analysis with predictor variables derived from the univariate analysis and the outcome being thromboembolism at 90 days

The strong association between the bedside ultrasound and the primary outcome suggests that a patient with a positive ultrasound result is highly likely to have deep vein thrombosis. As noted below, if the physician performing the scan has a high level of training and experience, the accuracy of the test is greatly improved. Although the statistical strength of the association is strong, multiple issues mean that at present, replacing current diagnostic algorithms with bedside ultrasound is not possible. These issues include defining the ideal training requirements and how to incorporate current strategies (e.g. clinical prediction rules, d-dimer and radiology-performed ultrasound) with bedside ultrasound.

5.6 Research implications and future directions

This project suggests further work is required in order to make emergency physician-performed ultrasound an accepted standard of care. In the near term, the data collection process described in this thesis is still ongoing. A significantly higher number of positive scans is required in order to generate reasonably tight confidence intervals. The aim is to have 60 positive bedside scans in the cohort. Because this study excluded all patients with previous lower limb venous thrombosis, a large number of potential candidates were missed. The criteria are currently being modified so that patients with previous thrombosis in the same leg as the current presentation are excluded. This will hopefully allow a greater number of positive scans to be achieved in a shorter time period.

One of the most important issues to resolve is the training required to achieve competence. This incorporates both the initial training required, as well as continuous quality assurance programs. There is scope for a large project measuring competence progressively over a larger and larger series of proctored scans in order to determine an appropriate number of minimum scans that leads to competence. The learning process must incorporate a realistic mix of patients as described above. Carefully defined criteria of competence need to be pre-specified and measured. Ultrasound images ideally would be carefully labelled and saved to facilitate more than one rater to determine acceptability of each scan, as well as to measure inter-rater reliability.

A difficult issue to manage is the level of experience of the physician sonographer. If the experience level could be quantified, it could be adjusted for in the analysis. One way of achieving this would be to simply list the number of lower limb deep vein scans each operator had performed prior to commencing the training program. Another way would be to also incorporate not just previous specific experience with the technique, but overall ultrasound experience in terms of total number of scans performed, years of experience, or some other measure of expertise.

If this technique does become accepted, how it is incorporated into usual practice needs to be determined. For example, if the result of the bedside scan is negative, is the patient able to be discharged without follow up? Or will they require a further scan down the track? If the scan is positive, should the patient then proceed to formal ultrasonography? This is important, to more accurately define the anatomical extent of the thrombus, which is not done in the technique described. The extent of the thrombus is important, as it is one of the factors impacting on treatment decisions.

If acceptable accuracy can be shown in future studies, it would be helpful to perform a cost-effectiveness study. Because an emergency physician could perform the test more efficiently, it might one day replace the test performed by a radiology department.

5.7 Conclusions

Training emergency physicians to perform a limited ultrasound exam of the lower limb to diagnose deep vein thrombosis is possible. They are able to accurately visualize the deep venous system of the proximal lower limb to rule out clinically significant thrombosis that could lead to serious health outcomes if untreated. One of the most important issues that arose from this work is the determination of the initial and ongoing training that is required to achieve competence. It seems that a training program as planned and carried out in this project is insufficient for achieving high accuracy. The required sensitivity is dependent upon physician preference, but ideally for a condition with potential mortality, should approach 100% with a narrow confidence interval. Further

research should be directed to develop a training and quality assurance program that can demonstrate this level of accuracy, good specificity and cost-effectiveness.

Tables and Figures

Table 1: Test characteristics in studies assessing the accuracy of ultrasound performed by emergency physicians

Study, year	N (total)	N (events)	Sensitivity (95% CI)	Specificity (95% CI)
Blaivas, 2000	112	34	100% (89% - 100%)	99% (92% - 100%)
Fraze, 2001	76	18	89% (64% - 98%)	76% (63% - 86%)
Jang, 2004	72	23	100% (85% - 100%)	92% (80% - 97%)
Theodoro, 2004	156	32	100% (89% - 100%)	98% (94% - 100%)
Jacoby, 2007	121	9	89% (51% - 99%)	97% (92% - 99%)
Kline 2008	183	36	70% (60% - 80%)	89% (83% - 94%)
<i>Burnside, 2008*</i>	<i>936</i>	<i>132</i>	<i>95% (87% - 99%)</i>	<i>96% (87% - 99%)</i>

**Systematic review of all previous studies*

Table 2: Clinical characteristics of the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Characteristic	Patients (N=104)
Basic descriptors	
Age in years, mean (SD)	58.4 (16.6)
Range	19-88
Male sex (%)	44 (42.3)
Past medical history (%)	
Congestive heart failure	2 (1.9)
Peripheral vascular disease	3 (2.9)
Systemic lupus erythematosus	1 (1.0)
Current medications (%)	
Antiplatelet agent	22 (22.2)
Anticoagulant	5 (4.8)
Elements of Wells' decision rule (%)	
Previous deep vein thrombosis N=103	1 (1.0)
Active cancer (treatment ongoing or within 6 months or palliative) N=103	7 (6.8)
Paralysis, paresis or recent plaster immobilization of the lower extremities	4 (3.9)
Recently bedridden >3 days, or major surgery, within 4 weeks N=103	9 (8.7)
Localised tenderness along the distribution of the deep venous system N=103	43 (42.2)
Entire leg swollen N=103	28 (27.2)
Calf swelling 3cm> asymptomatic side (measured 10cm below tibial tuberosity) N=103	30 (29.4)
Pitting edema confined to the symptomatic leg N=103	44 (43.6)
Collateral superficial veins (non-varicose) N=103	13 (12.8)
Alternative diagnosis as likely or greater than that of DVT N=103	51 (49.5)
Additional elements of AMUSE score (%)	
Use of hormonal contraception N=103	6 (5.8)
Absence of leg trauma N=103	19 (18.5)
Laboratory investigations	
D-dimer result (median, IQR) N=100	<300 (288.5)
D-dimer result \geq 300 μ g/L (%) N=100	47 (47)

Table 3: Bedside ultrasound characteristics of cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Characteristic	Patients (N=104)
Time duration of scan in minutes, median (IQR) N=101	10 (9)
Difficulty of scan, physician-reported 1-5, median (IQR) N=103	2 (2)
Time interval from bedside to formal ultrasound in days, median (IQR) N=63	1 (1)
Number of scans performed per physician, median (IQR)	3.5 (4)
Staff physician operator (%)	93 (89.4)
Resident physician operator (%)	11 (10.6)

Table 4: Outcomes of patients in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

Outcome	Patients (N=104)
Hospital admission (%)	1 (1.0)
Bedside ultrasound positive (%)	15 (14.4)
Formal ultrasound positive (N=63) (%)	12 (18.8)
Death (%)	2 (1.9)
DVT or PE during follow up period (%)	2 (1.9)
Composite (initial plus 90-day) outcome positive (%)	14 (13.5)

NB the composite outcome is comprised of all cases of thrombosis diagnosed on formal ultrasound plus those diagnosed during the 90-day follow up period as well as deaths due to venous thromboembolism

Table 5: Comparison of patients with low-risk (≤ 1) and high-risk (≥ 2) Wells score against composite outcome (N=103)

	Composite outcome (+)	Composite outcome (-)
Wells score ≤ 1	2	61
Wells score ≥ 2	12	28

Sensitivity 85.7% (95% CI 57.2 – 98.2%)

Specificity 68.5% (95% CI 57.8 – 78.0%)

Positive predictive value 30.0% (95% CI 16.6 – 46.5%)

Negative predictive value 96.8% (95% CI 89.0 – 99.6%)

Table 6: Comparison of patients with low-risk (≤ 3) and high-risk (≥ 4) AMUSE score against composite outcome in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

	Composite outcome (+)	Composite outcome (-)
AMUSE score ≤ 3	2	49
AMUSE score ≥ 4	12	41

Sensitivity 85.7% (95% CI 57.2 – 98.2%)

Specificity 54.4% (95% CI 43.6 – 65.0%)

Positive predictive value 22.6% (95% CI 12.3 – 36.2%)

Negative predictive value 96.1% (95% CI 86.5 – 99.5%)

Table 7: Comparison of emergency physician-performed against radiology-performed ultrasound results in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=64)

Bedside ultrasound	Radiology US (+)	Radiology US (-)
Positive	11	4
Negative	1	44
Indeterminate	0	4

Excluding indeterminate results:

Sensitivity 91.7% (95% CI 61.5 – 99.8%)

Specificity 91.7% (95% CI 80.0 – 97.7%)

Positive predictive value 73.3% (95% CI 44.9 – 92.2%)

Negative predictive value 97.8% (95% CI 88.2 – 99.9%)

Table 8: Patient and operator characteristics of the false negative and false positives scans

Error type	Age	Sex	Status of operator	Experience level	Rated difficulty
False positive	34	Female	Staff	Inexperienced	4
False positive	75	Female	Staff	Inexperienced	1
False positive	76	Female	Staff	More experienced	2
False positive	41	Male	Staff	Inexperienced	3
False negative	85	Female	Staff	Inexperienced	2

Table 9: Comparison of determinate bedside ultrasound result versus 90-day outcome in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=94)

	90 day outcome (+)	90 day outcome (-)
Bedside ultrasound (+)	11	4
Bedside ultrasound (-)	3	76

Sensitivity 78.6% (95% CI 49.2 – 95.3%)

Specificity 95.0% (95% CI 87.7 – 98.6%)

Positive predictive value 73.3% (95% CI 44.9 – 92.2%)

Negative predictive value 96.2% (95% CI 89.3 – 99.2%)

Table 10: Univariate associations in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis between predictive elements and 90-day outcome (N=103)

	Composite outcome (+) (%) (n=14)	Composite outcome (-) (%) (n=89)	P-value
Elements of Wells score			
Previous DVT	1 (7.1)	0 (0.0)	0.14
Active cancer (treatment ongoing or within 6 months of palliative)	1 (7.1)	6 (6.7)	1.00
Paralysis, paresis or recent plaster immobilization of the lower extremities	0 (0.0)	4 (4.5)	1.00
Recently bedridden >3 days, or major surgery, within 4 weeks	2 (14.3)	7 (7.9)	0.35
Localised tenderness along the distribution of the deep venous system	9 (64.3)	34 (38.2)	0.07
Entire leg swollen	10 (71.4)	18 (20.2)	<0.0001
Calf swelling 3cm> asymptomatic side (measured 10cm below tibial tuberosity)	7 (50.0)	23 (25.8)	0.11
Pitting edema confined to the symptomatic leg	11 (78.6)	33 (37.1)	<0.01
Collateral superficial veins (non-varicose)	2 (14.3)	11 (12.4)	1.00
Alternative diagnosis as likely or greater than that of DVT	2 (14.3)	49 (55.1)	<0.01
Additional elements of AMUSE score			
Use of hormonal contraception N=103	0 (0.0)	6 (6.7)	1.00
Absence of leg trauma N=103	12 (85.7)	72 (80.9)	1.00
Investigations			
D-dimer result $\geq 300 \mu\text{g/L}$ N=100	11 (78.6)	36 (40.4)	0.01
Bedside US result (+) N=94	11 (78.6)	4 (4.5)	<0.0001
Bedside US result (+): indeterminates as positives	11 (78.6)	14 (15.7)	<0.0001
Bedside US result (+): indeterminates as negatives	11 (78.6)	4 (4.5)	<0.0001

Table 11: Multivariate associations in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis between predictive elements and 90-day outcome - maximum likelihood estimates

Parameter	DF	Beta coefficient	Standard Error	Wald Chi-Square	Pr > ChiSq	Odds ratio estimate	95% CI
Intercept	1	-3.1640	0.5894	28.8167	<.0001		
Bedside scan positive for DVT	1	4.1754	0.8926	25.3297	<.0001	65.1	12.8 – 330.8

Figure 1: Risk factors for development of deep vein thrombosis

History of venous thromboembolism	Age >45
Major surgery	Smoking
Trauma	Medical comorbidities: Congestive
Immobility: Travel, paralysis, hospital or nursing home resident	heart failure, chronic obstructive pulmonary disease, stroke
Cancer	Obesity
Increased estrogen states: Pregnancy or puerperium, oral contraceptive pills, hormonal therapy	Inherited coagulopathy: Factor V Leiden mutation, antithrombin III deficiency, protein C deficiency, protein S deficiency,
Indwelling central venous access devices	dysfibrinogenemia

Figure 2: Number of bedside scans by difficulty category of cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

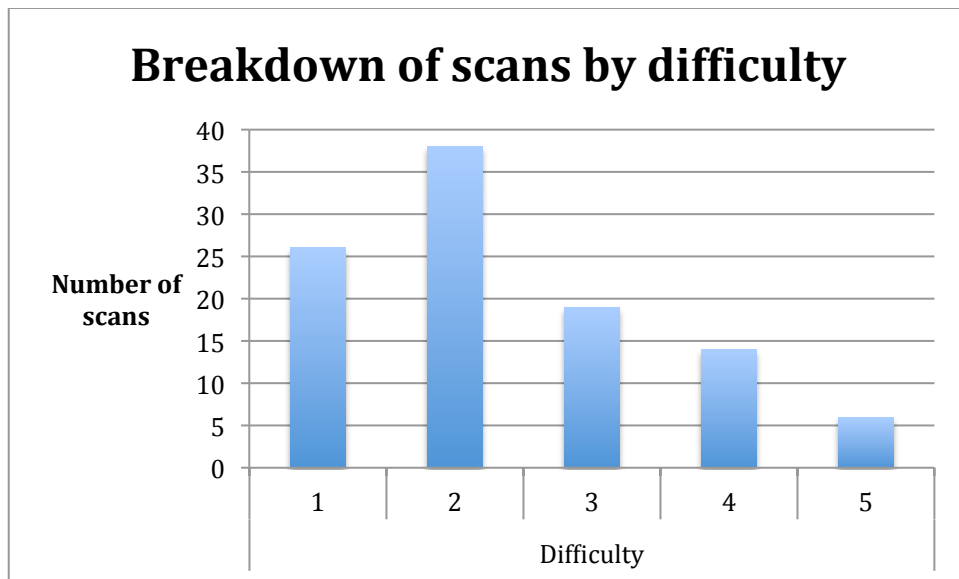


Figure 3: Proposed patient flow diagram

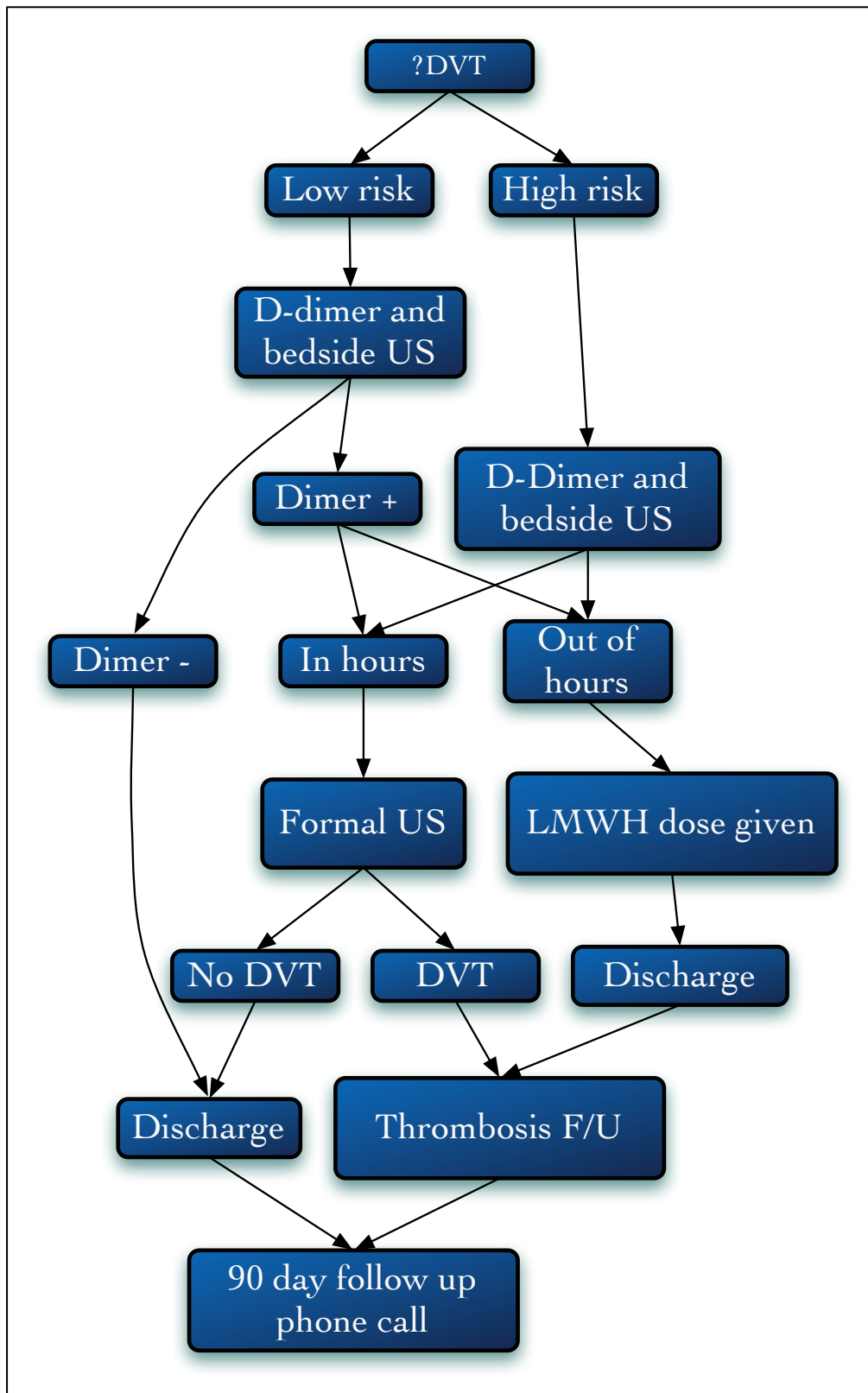


Figure 4: Number of bedside scans performed by physician in the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)

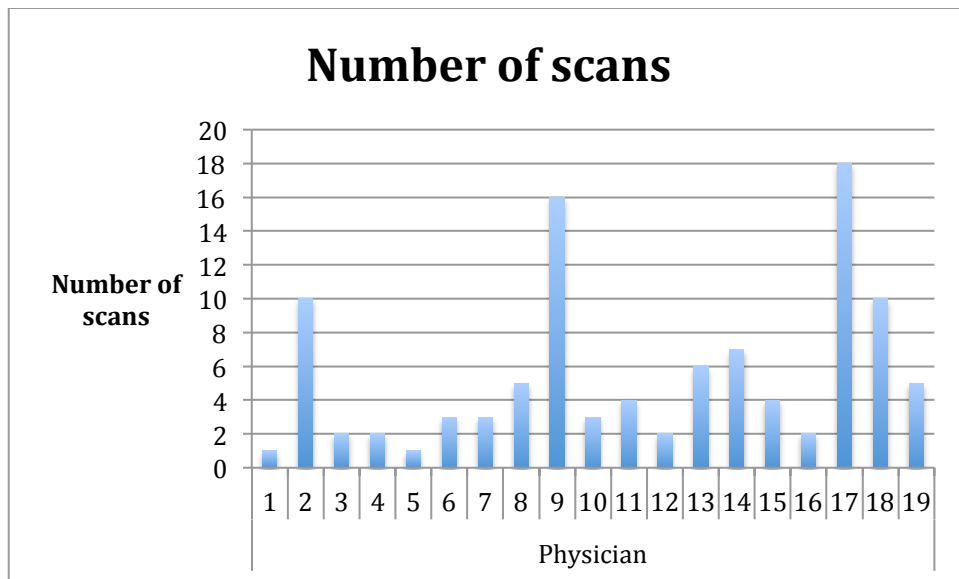
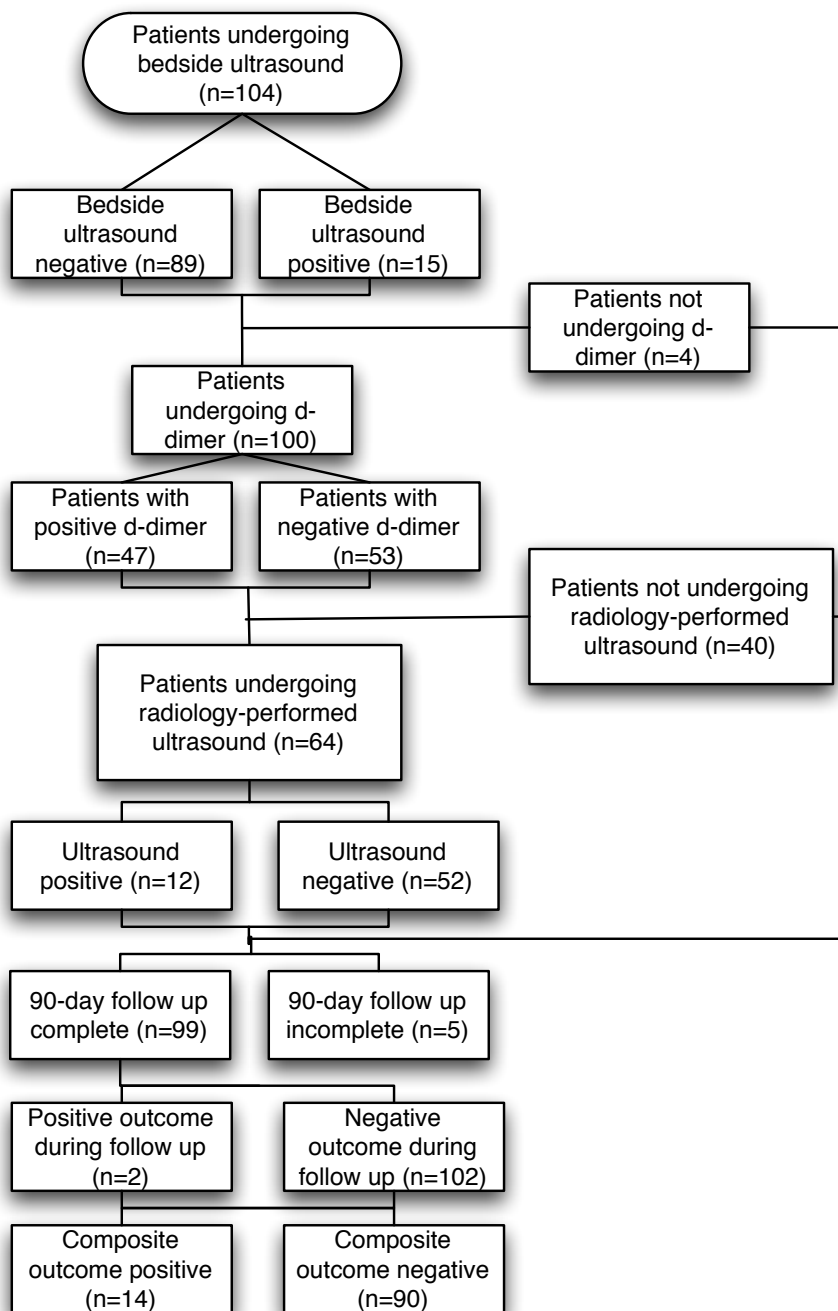


Figure 5: Patient flow diagram for the cohort undergoing bedside ultrasound to exclude lower-limb deep vein thrombosis (N=104)



References

- (1) Fields JM, Goyal M. Venothromboembolism. *Emerg Med Clin North Am* 2008 Aug;26(3):649-83, viii.
- (2) Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis* 2009 Nov;28(4):465-476.
- (3) Appelman PT, De Jong TE, Lampmann LE. Deep venous thrombosis of the leg: US findings. *Radiology* 1987 Jun;163(3):743-746.
- (4) Cronan JJ. Venous thromboembolic disease: the role of US. *Radiology* 1993 Mar;186(3):619-630.
- (5) Vaccaro JP, Cronan JJ, Dorfman GS. Outcome analysis of patients with normal compression US examinations. *Radiology* 1990 Jun;175(3):645-649.
- (6) Murphy TP, Cronan JJ. Evolution of deep venous thrombosis: a prospective evaluation with US. *Radiology* 1990 Nov;177(2):543-548.
- (7) Righini M, Bounameaux H. Venous Thrombosis: Risk Factors and Management. *Herz* 2007;32(1):27-34.
- (8) Tan M, van Rooden CJ, Westerbeek RE, Huisman MV. Diagnostic management of clinically suspected acute deep vein thrombosis. *Br J Haematol* 2009 Aug;146(4):347-360.
- (9) Trottier SJ, Todi S, Veremakis C. Validation of an inexpensive B-mode ultrasound device for detection of deep vein thrombosis. *Chest* 1996 Dec;110(6):1547-1550.
- (10) White RH. The epidemiology of venous thromboembolism. *Circulation* 2003 Jun 17;107(23 Suppl 1):I4-8.
- (11) Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007 Apr;44(2):62-69.
- (12) Righini M, Le Gal G, Aujesky D, Roy PM, Sanchez O, Verschuren F, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet* 2008 Apr 19;371(9621):1343-1352.
- (13) Turkstra F, Kuijter PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. *Ann Intern Med* 1997 May 15;126(10):775-781.
- (14) Anderson FA, Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991 May;151(5):933-938.
- (15) Kline JA, Webb WB, Jones AE, Hernandez-Nino J. Impact of a rapid rule-out protocol for pulmonary embolism on the rate of screening, missed cases, and pulmonary vascular imaging in an urban US emergency department. *Ann Emerg Med* 2004 Nov;44(5):490-502.
- (16) Barnes RW, Wu KK, Hoak JC. Fallibility of the clinical diagnosis of venous thrombosis. *JAMA* 1975 Nov 10;234(6):605-607.
- (17) Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003 Sep 25;349(13):1227-1235.

- (18) Vaccaro P, Van Aman M, Miller S, Fachman J, Smead WL. Shortcomings of physical examination and impedance plethysmography in the diagnosis of lower extremity deep venous thrombosis. *Angiology* 1987 Mar;38(3):232-235.
- (19) Locker T, Goodacre S, Sampson F, Webster A, Sutton AJ. Meta-analysis of plethysmography and rheography in the diagnosis of deep vein thrombosis. *Emerg Med J* 2006 Aug;23(8):630-635.
- (20) Bernardi E, Prandoni P, Lensing AW, Agnelli G, Guazzaloca G, Scannapieco G, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. *BMJ* 1998 Oct 17;317(7165):1037-1040.
- (21) Tick LW, Ton E, van Voorthuizen T, Hovens MM, Leeuwenburgh I, Lobatto S, et al. Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography, and D-dimer test. *Am J Med* 2002 Dec 1;113(8):630-635.
- (22) Heijboer H, Buller HR, Lensing AW, Turpie AG, Colly LP, ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med* 1993 Nov 4;329(19):1365-1369.
- (23) Lensing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989 Feb 9;320(6):342-345.
- (24) Cogo A, Lensing AW, Koopman MM, Piovella F, Siragusa S, Wells PS, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ* 1998 Jan 3;316(7124):17-20.
- (25) Birdwell BG, Raskob GE, Whitsett TL, Durica SS, Comp PC, George JN, et al. Predictive value of compression ultrasonography for deep vein thrombosis in symptomatic outpatients: clinical implications of the site of vein noncompressibility. *Arch Intern Med* 2000 Feb 14;160(3):309-313.
- (26) Kraaijenhagen RA, Piovella F, Bernardi E, Verlato F, Beckers EA, Koopman MM, et al. Simplification of the diagnostic management of suspected deep vein thrombosis. *Arch Intern Med* 2002 Apr 22;162(8):907-911.
- (27) Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. *Arch Intern Med* 2002 Apr 8;162(7):747-756.
- (28) Hager K, Platt D. Fibrin degeneration product concentrations (D-dimers) in the course of ageing. *Gerontology* 1995;41(3):159-165.
- (29) Kruskal JB, Commerford PJ, Franks JJ, Kirsch RE. Fibrin and fibrinogen-related antigens in patients with stable and unstable coronary artery disease. *N Engl J Med* 1987 Nov 26;317(22):1361-1365.
- (30) Gustafsson C, Blomback M, Britton M, Hamsten A, Svensson J. Coagulation factors and the increased risk of stroke in nonvalvular atrial fibrillation. *Stroke* 1990 Jan;21(1):47-51.
- (31) Becker DM, Philbrick JT, Bachhuber TL, Humphries JE. D-dimer testing and acute venous thromboembolism. A shortcut to accurate diagnosis? *Arch Intern Med* 1996 May 13;156(9):939-946.
- (32) Giroud M, Dutrillaux F, Lemesle M, Volot F, Lorenzini JL, Becker F, et al. Coagulation abnormalities in lacunar and cortical ischemic stroke are quite different. *Neurol Res* 1998 Jan;20(1):15-18.

- (33) Blumenberg RM, Barton E, Gelfand ML, Skudder P, Brennan J. Occult deep venous thrombosis complicating superficial thrombophlebitis. *J Vasc Surg* 1998 Feb;27(2):338-343.
- (34) Scarvelis D, Wells PS. Diagnosis and treatment of deep-vein thrombosis. *CMAJ* 2006 Oct 24;175(9):1087-1092.
- (35) Kearon C. Long-term management of patients after venous thromboembolism. *Circulation* 2004 Aug 31;110(9 Suppl 1):I10-8.
- (36) Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic Therapy for Venous Thromboembolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008 06/02:454-545.
- (37) Imberti D, Ageno W, Dentali F, Giorgi Pierfranceschi M, Croci E, Garcia D. Management of primary care patients with suspected deep vein thrombosis: use of a therapeutic dose of low-molecular-weight heparin to avoid urgent ultrasonographic evaluation. *J Thromb Haemost* 2006 May;4(5):1037-1041.
- (38) Anderson DR, Wells PS, Stiell I, MacLeod B, Simms M, Gray L, et al. Thrombosis in the emergency department: use of a clinical diagnosis model to safely avoid the need for urgent radiological investigation. *Arch Intern Med* 1999 Mar 8;159(5):477-482.
- (39) Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al. Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two centre paired-design prospective trial. *Thromb Haemost* 1995 Dec;74(6):1423-1427.
- (40) Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997 Dec 20-27;350(9094):1795-1798.
- (41) Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA* 2006 Jan 11;295(2):199-207.
- (42) Blaivas M, Lambert MJ, Harwood RA, Wood JP, Konicki J. Lower-extremity Doppler for deep venous thrombosis--can emergency physicians be accurate and fast? *Acad Emerg Med* 2000 Feb;7(2):120-126.
- (43) Jang T, Docherty M, Aubin C, Polites G. Resident-performed compression ultrasonography for the detection of proximal deep vein thrombosis: fast and accurate. *Acad Emerg Med* 2004 Mar;11(3):319-322.
- (44) Magazzini S, Vanni S, Toccafondi S, Paladini B, Zanobetti M, Giannazzo G, et al. Duplex ultrasound in the emergency department for the diagnostic management of clinically suspected deep vein thrombosis. *Acad Emerg Med* 2007 Mar;14(3):216-220.
- (45) Pezzullo JA, Perkins AB, Cronan JJ. Symptomatic deep vein thrombosis: diagnosis with limited compression US. *Radiology* 1996 January 01;198(1):67-70.
- (46) Frederick MG, Hertzberg BS, Kliever MA, Paulson EK, Bowie JD, Lalouche KJ, et al. Can the US examination for lower extremity deep venous thrombosis be abbreviated? A prospective study of 755 examinations. *Radiology* 1996 April 01;199(1):45-47.
- (47) McQueen AS, Elliott ST, Keir MJ. Ultrasonography for suspected deep vein thrombosis: how useful is single-point augmentation? *Clin Radiol* 2009 Feb;64(2):148-155.

- (48) Frazee BW, Snoey ER, Levitt A. Emergency Department compression ultrasound to diagnose proximal deep vein thrombosis. *J Emerg Med* 2001 Feb;20(2):107-112.
- (49) Theodoro D, Blaivas M, Duggal S, Snyder G, Lucas M. Real-time B-mode ultrasound in the ED saves time in the diagnosis of deep vein thrombosis (DVT). *Am J Emerg Med* 2004 May;22(3):197-200.
- (50) Jacoby J, Cesta M, Axelband J, Melanson S, Heller M, Reed J. Can emergency medicine residents detect acute deep venous thrombosis with a limited, two-site ultrasound examination? *J Emerg Med* 2007 Feb;32(2):197-200.
- (51) Burnside PR, Brown MD, Kline JA. Systematic Review of Emergency Physician–performed Ultrasonography for Lower-Extremity Deep Vein Thrombosis. *Acad Emerg Med* 2008;15(6):493-498.
- (52) Kline JA, O'Malley PM, Tayal VS, Snead GR, Mitchell AM. Emergency Clinician–Performed Compression Ultrasonography for Deep Venous Thrombosis of the Lower Extremity. *Ann Emerg Med* 2008 10;52(4):437-445.
- (53) Bernardi E, Camporese G, Buller HR, Siragusa S, Imberti D, Berchio A, et al. Serial 2-Point Ultrasonography Plus D-Dimer vs Whole-Leg Color-Coded Doppler Ultrasonography for Diagnosing Suspected Symptomatic Deep Vein Thrombosis: A Randomized Controlled Trial. *JAMA* 2008 October 8;300(14):1653-1659.
- (54) Goodacre S, Sutton AJ, Sampson FC. Meta-analysis: The value of clinical assessment in the diagnosis of deep venous thrombosis. *Ann Intern Med* 2005 Jul 19;143(2):129-139.
- (55) Anand SS, Wells PS, Hunt D, Brill-Edwards P, Cook D, Ginsberg JS. Does this patient have deep vein thrombosis? *JAMA* 1998 Apr 8;279(14):1094-1099.
- (56) Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. *Ann Intern Med* 2005 Jul 19;143(2):100-107.
- (57) Buller HR, Ten Cate-Hoek AJ, Hoes AW, Joore MA, Moons KG, Oudega R, et al. Safely ruling out deep venous thrombosis in primary care. *Ann Intern Med* 2009 Feb 17;150(4):229-235.
- (58) Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost* 2005 Jul;94(1):200-205.
- (59) Stiell IG, Wells GA, Vandemheen KL, Clement CM, Lesiuk H, De Maio VJ, et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. *JAMA* 2001 Oct 17;286(15):1841-1848.
- (60) Stiell IG, Wells GA, Vandemheen K, Clement C, Lesiuk H, Laupacis A, et al. The Canadian CT Head Rule for patients with minor head injury. *Lancet* 2001 May 5;357(9266):1391-1396.
- (61) van der Velde EF, Toll DB, Ten Cate-Hoek AJ, Oudega R, Stoffers HE, Bossuyt PM, et al. Comparing the diagnostic performance of 2 clinical decision rules to rule out deep vein thrombosis in primary care patients. *Ann Fam Med* 2011 Jan-Feb;9(1):31-36.
- (62) Emergency Ultrasound Guidelines. *Ann Emerg Med* 2009 200904;53(4):550-570.
- (63) Abstracts of the Society for Academic Emergency Medicine 2005 Annual Meeting. May 22-25, 2005, New York City, New York, USA. *Acad Emerg Med* 2005;12(5 Suppl 1):7.

Appendices

Appendix 1: Case record form – Thrombosis Unit Suspected DVT Referral

Please **FAX** this complete
Form to : **761-4781**
ONLY if consult required

PATIENT'S DETAILS

Thrombosis Unit Suspected DVT Referral

Patient's Name : _____ Date ____/____/____ Time ____ h

The Clinical Model for Predicting Probability for DVT (note each finding scores a separate point)	NO	YES	If Yes SCORE
Previous DVT	<input type="radio"/>	<input type="radio"/>	1
Active Cancer (treatment ongoing or within 6 months or palliative)	<input type="radio"/>	<input type="radio"/>	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	<input type="radio"/>	<input type="radio"/>	1
Recently bedridden > 3 days, or major surgery, within 4 weeks	<input type="radio"/>	<input type="radio"/>	1
Localized tenderness along the distribution of the deep venous system	<input type="radio"/>	<input type="radio"/>	1
Entire leg swollen	<input type="radio"/>	<input type="radio"/>	1
Calf swelling 3cm > asymptomatic side (measured 10cm below tibial tuberosity)	<input type="radio"/>	<input type="radio"/>	1
Pitting edema confined to the symptomatic leg	<input type="radio"/>	<input type="radio"/>	1
Collateral superficial veins (non-varicose)	<input type="radio"/>	<input type="radio"/>	1
Alternative diagnosis as likely or greater than that of DVT	<input type="radio"/>	<input type="radio"/>	-2
Please specify alternative diagnosis _____ (see below)			
		Total	_____

NOTE: In patients with symptoms in both legs, the more symptomatic leg is used.

<p>Clinical probability calculates as follows: Total Points</p> <p>DVT Unlikely: ≤ 1 _____</p> <p>DVT Likely: 2 or more _____</p> <p>A patient with 2 or more points will require imaging</p>	<p>Alternative Diagnoses: (Please circle)</p> <table style="width: 100%; border: none;"> <tr> <td>cellulites</td> <td>heart failure</td> </tr> <tr> <td>arterial insufficiency</td> <td>arthritis</td> </tr> <tr> <td>chronic venous stasis</td> <td>post-op swelling</td> </tr> <tr> <td>musculoskeletal injury</td> <td>trauma</td> </tr> <tr> <td>pelvic obstruction</td> <td>superficial phlebitis</td> </tr> <tr> <td>ruptured Baker's cyst</td> <td></td> </tr> </table>	cellulites	heart failure	arterial insufficiency	arthritis	chronic venous stasis	post-op swelling	musculoskeletal injury	trauma	pelvic obstruction	superficial phlebitis	ruptured Baker's cyst	
cellulites	heart failure												
arterial insufficiency	arthritis												
chronic venous stasis	post-op swelling												
musculoskeletal injury	trauma												
pelvic obstruction	superficial phlebitis												
ruptured Baker's cyst													

D-Dimer ____ pos ____ neg ____ LEFT LEG RIGHT LEG

OTHER (please specify)

CBC Hb _____ plt _____ creatinine _____

Dose of Fragmin given: _____ at _____ on _____
(total units given) (time) (date)

Please call referral to: 17622 (including patient name, phone #, Hospital ID and campus).

Referring MD _____ Campus: Civic Gen Riv
(please print FULL NAME) (please circle)

Appendix 2: Case record form – DVT in the ED study



**The Ottawa
Hospital | L'Hôpital
d'Ottawa**

CASE RECORD FORM

DVT in the ED Study

CASE # _____ MRN _____

Physician: _____

ULTRASOUND

Start time (*hh:mm-24 hr clock*) : Completion time :

Result: DVT present DVT absent Indeterminate

Difficulty level: (1-5) ____ If difficult, reason: _____

Where: 1-v.easy 2-easy 3-neither easy nor difficult 4-difficult 5-v.difficult

COMMENTS:

RISK FACTORS

Use of hormonal contraception yes no

Leg trauma yes no