Improving the diagnostic workup of deep vein thrombosis

FINDINGS FROM THE RI-SCHEDULE STUDY

Doctoral dissertation

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Oslo, February 2022

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List of included publications

Paper I. Fronas SG, Wik HS, Dahm AEA, Jorgensen CT, Gleditsch J, Raouf N, et al. Safety of D-dimer testing as a stand-alone test for the exclusion of deep vein thrombosis as compared with other strategies. *J Thromb Haemost. 2018;16(12):2471-81.*

Paper II. Fronas SG, Dahm AEA, Wik HS, Jørgensen CT, Gleditsch J, Raouf N, et al. Safety and feasibility of rivaroxaban in deferred workup of patients with suspected deep vein thrombosis. *Blood Adv. 2020;4(11):2468-76.*

Paper III. Fronas SG, Jørgensen CT, Dahm AEA, Wik HS, Gleditsch J, Raouf N, et al. Safety of a strategy combining D-dimer testing and whole-leg ultrasonography to rule out deep vein thrombosis. *Blood Adv. 2020;4(20):5002-10.*

Abbreviations

DVT	Deep vein thrombosis
VTE	Venous thromboembolism
PE	Pulmonary embolism
CUS	Compression ultrasonography
ELISA	Enzyme-linked immunosorbent assay
ELFA	Enzyme-linked fluorescent assay
C-PTP	Clinical pretest probability
CI	Confidence interval
VKA	Vitamin K antagonist
LMWH	Low-molecular-weight heparin
DOAC	Direct oral anticoagulant

Thesis summary (Norwegian)

Formålet med diagnostikken av dyp venetrombose (DVT) er å diagnostisere og behandle DVT som bør behandles, og å avstå fra videre utredning av pasienter som enten ikke har DVT, eller som har DVT som ikke er behandlingskrevende. Gjennom de siste tiårene har det vært store fremskritt i håndteringen av pasienter med spørsmål om DVT. Likevel gjenstår flere områder med potensiale for forbedring.

Rivaroksaban i utredningen av dyp venetrombose («Ri-Schedule-studien») er en prospektiv studie designet for å belyse flere aspekter knyttet til håndteringen av pasienter med mulig DVT. Denne avhandlingen baserer seg på materiale fra Ri-Schedule-studien, og har to overordnede bidrag til studiens formål.

Det første er å undersøke sikkerheten og gjennomførbarheten av en strategi som innebærer å gi pasientene rivaroksaban i påvente av diagnostikk (empirisk behandling), og å gjennomføre utredning på et planlagt tidspunkt i stedet for akutt. Empirisk antikoagulasjonsbehandling går ut på å behandle pasienter med mulig DVT inntil tilstanden eventuelt kan utelukkes. Planlagt utredning går ut på å utrede pasienter på et konkret avtaletidspunkt som er gunstigere for sykehuset. Resultatene våre viser at planlagt utredning er en trygg strategi. Den kan være mer praktisk for pasientene ved at den reduserer ventetid i akuttmottaket og øker forutsigbarheten ved utredning, og den kan ha organisatoriske fordeler for sykehuset.

Det andre bidraget er å undersøke en ny diagnostisk algoritme for pasienter med mulig DVT. Diagnostiske algoritmer er laget for å hjelpe klinikere i beslutningsprosessen, og består av de nødvendige, trinnvise elementene man går gjennom for å bekrefte eller avkrefte diagnosen basert på den enkelte pasients risiko. Vi fant at en ny og enklere algoritme var like sikker som eksisterende retningslinjer, og at den resulterte i færre ultralyder. Den består av færre elementer, og kan være mer brukervennlig for klinikere enn metoder som brukes i dag.

Thesis summary

The diagnostic process of deep vein thrombosis (DVT) aims to detect and treat DVT requiring treatment while avoiding unnecessary workup in patients whom either do not have DVT, or have DVT that do not require treatment. There have been several major advances in the diagnostic management of patients with suspected DVT over the last decades. Nonetheless, various areas of improvement remain.

The *Rivaroxaban for Scheduled Workup of Deep Vein Thrombosis* (the Ri-Schedule study) was a prospective outcome study designed to assess several aspects of the management of patients with suspected DVT. The aim of this thesis is to improve the workup of DVT through two main contributions elaborating on findings from the Ri-Schedule study.

The first contribution is to assess the safety and feasibility of a scheduled workup strategy which incorporated administering empiric rivaroxaban and deferring ultrasound imaging tests. Empiric anticoagulation treatment refers to treating patients with suspected DVT with anticoagulation therapy until the diagnosis can be confirmed or excluded. Deferring ultrasound imaging entails channeling patients to diagnostic workup from hospital peak to trough hours. We found that the scheduled workup strategy was safe. It may also be more convenient for patients, as well as for emergency department organization.

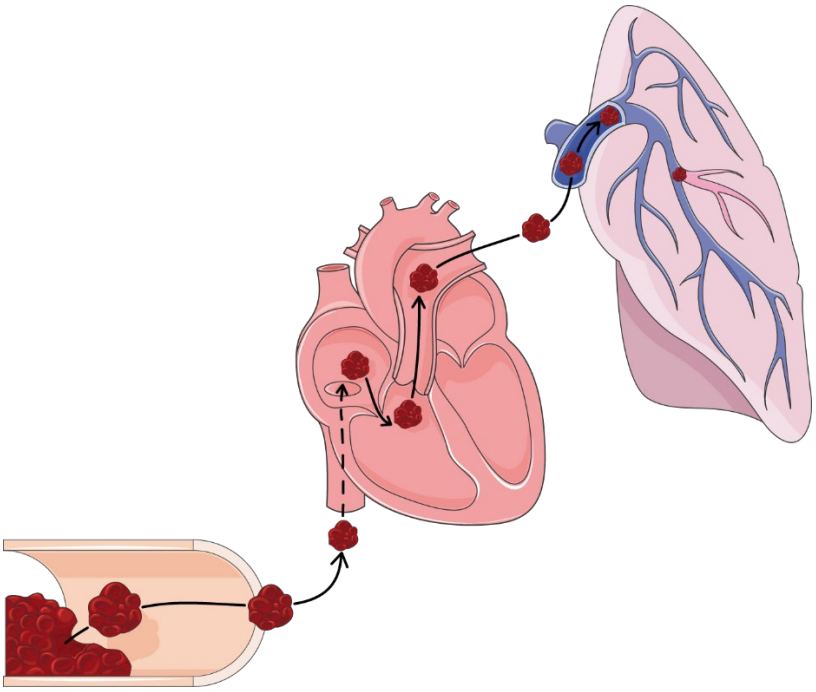
The second contribution is to assess a new diagnostic algorithm for patients with suspected DVT. Diagnostic algorithms are designed to aid clinicians in deciding how individual patients should be assessed. They consist of the necessary stepwise elements to rule in or rule out the diagnosis. We found that our suggested algorithm was as safe as existing pathways while necessitating fewer imaging tests. The new algorithm consists of fewer steps, and may be easier to implement and adhere to in clinical practice.

1. Introduction

1.1 Definitions and concepts

Thrombosis is the formation of a blood clot in the circulatory system (1). An embolism forms when a substance, such as a thrombus, travels through the circulatory system from where it originated to lodge somewhere else. Venous thromboembolism (VTE) refers to the disease entity occurring when a blood vessel is obstructed by a blood clot. VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) (2). DVT can originate anywhere in the deep venous vasculature, but the majority develop in the lower extremities. DVT in the lower extremities are stratified into proximal and distal DVT. Proximal DVT are located in the iliac, femoral or popliteal veins. Isolated distal DVT are confined to infra-popliteal veins (3), and have been found to comprise between 30-50% of lower extremity DVT (4, 5).

PE is a feared complication of DVT. Findings suggestive of PE have been demonstrated in ventilation-perfusion lung scans of 40-50% of patients with symptomatic proximal DVT without concurrent symptoms of PE (6).



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1.2 Pathophysiology and risk factors

The term hemostasis refers to the cessation of bleeding (7). In normal hemostasis, there is a balance between factors promoting coagulation and anticoagulation, i.e. the formation and breakdown of blood clots. Blood clotting is a physiological process to stop bleeding, typically precipitated in response to damage of the blood vessel. Circulating proteins, so-called coagulation factors, are activated in sequence to form a fibrin blood clot arresting the bleeding in the damaged lining of the blood vessel. The fibrinolysis system breaks down fibrin clots to prevent occlusion.

A thrombosis may form when there is an inappropriate or pathological activation of the coagulation system in response to a trigger, resulting in an obstruction of the normal blood flow.

Conditions associated with a lowered threshold for activating the coagulation system can be transient or persistent (8), minor or major triggers, and hereditary or acquired conditions. Due to their propensity for activating the coagulation system through their various mechanisms, they are risk factors for VTE (*Table 1*) (9-12).

Table 1 Examples of risk factors of venous thromboembolism		
	Transient	Persistent or permanent
Major	Major trauma, fracture, surgery (general anesthesia > 30 mins), immobilization (i.e. by plaster cast or hospitalization)	Increasing age Cancer Thrombophilia (i.e. antithrombin, protein C and protein S deficiencies, antiphospholipid antibodies)
Minor	Minor surgery (general anesthesia < 30 mins) Hospital admission Pregnancy or puerperium Prolonged travel Estrogen therapy	Thrombophilia (i.e. factor V Leiden, prothrombin 20210A variant) Obesity Various comorbidities (i.e. congestive heart failure, reduced renal function)

VTE without detectable risk factors, so-called unprovoked or idiopathic VTE, is reported to range from approximately 25-50% of all first-time cases (13).

1.3 Clinical presentation

Symptoms of lower extremity DVT are most often unilateral, and frequently include pain, swelling, and tenderness (14, 15). Clinical signs of DVT are likewise typically unilateral, with common findings of swelling and edema, warmth, tenderness, erythema, and dilated superficial veins. DVT may also be asymptomatic with no

telltale signs, and incidentally found on diagnostic imaging for unrelated reasons, or discovered in a patient presenting with PE.

Symptoms of DVT are non-specific and overlap with various other presentations (14). Common differential diagnoses include fractures, muscle pain or injuries, Baker cyst, hematomas, local infections, and edema from other causes. Due to its non-specific presentation and the potential fatal complication of PE, DVT poses a challenge for diagnosis.

1.4 Epidemiology and disease burden

VTE is a relatively common disease entity - reportedly the third most common cardiovascular syndrome after myocardial infarction and stroke (16).

The incidence rate among people of European ancestry is reported to be 1 to 1.8 cases per 1000 person-years (17, 18), of which approximately two thirds are DVT (13, 16, 19-21). Additionally, the undiagnosed or misdiagnosed VTE events or deaths increase this figure (19). Females are at a higher risk of VTE up to 40-50 years of age, whereas males are at a higher risk as older adults (17, 22). The incidence of VTE increases substantially with age in both sexes (*Figure 2*), and for both DVT and PE (*Figure 3*).

Figure 2 Annual incidence of venous thromboembolism by age and sex (17)

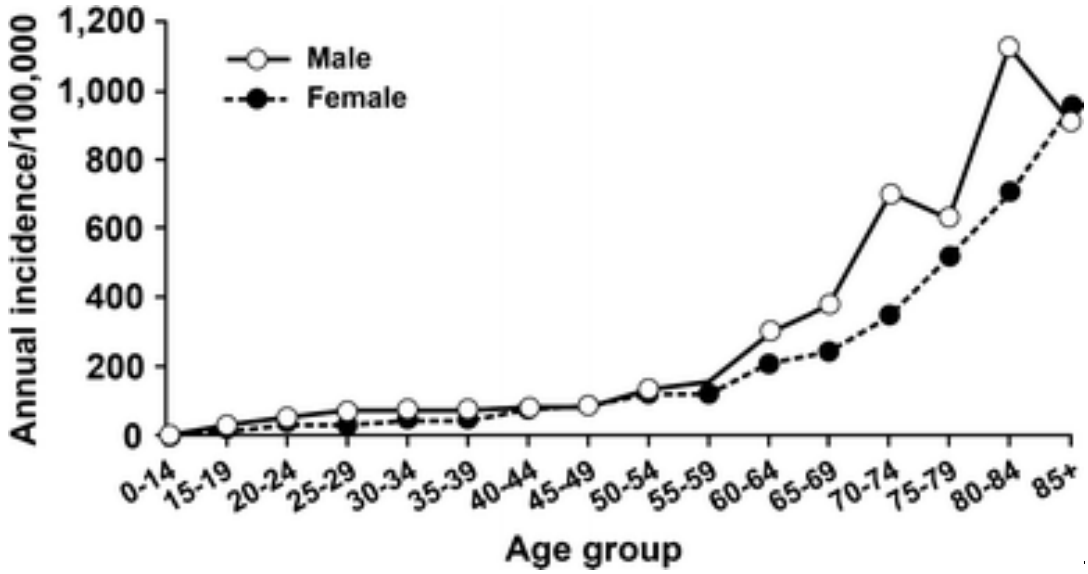


Figure 3 Annual incidence of all venous thromboembolism (17)

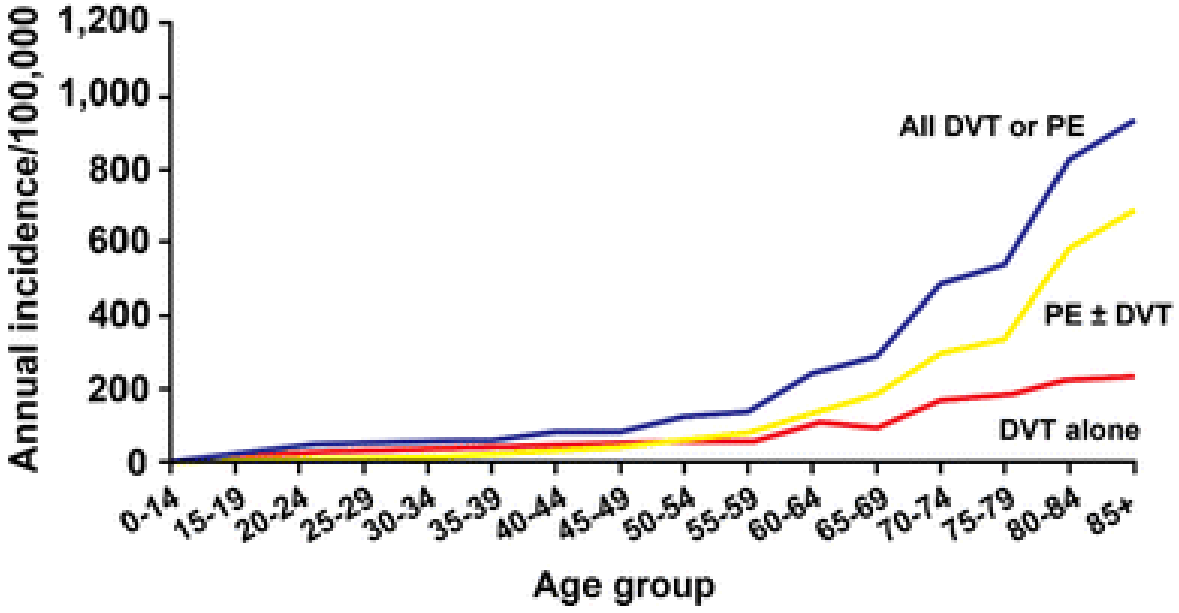


Figure 2 and Figure 3 are reprinted from Heit, J.A., Spencer, F.A. & White, R.H. The epidemiology of venous thromboembolism. J Thromb Thrombolysis 41, 3–14 (2016), https://doi.org/10.1007/s11239-015-1311-6 by Springer Nature at Springer.com. Copyright © 2016, The Author(s). The article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Patients with VTE run a substantial risk of recurrence after the treatment period has ended. Recurrence within 10 years after an initial, unprovoked VTE event affects 20-40% of patients (23-25). The American College of Chest Physicians summarized the evidence of recurrence according to risk factors, estimating that patients with provoked VTE have an approximately 3-15% chance of recurrence at 5 years depending on the severity of the risk factor, whereas patients with unprovoked VTE have an estimated 30% chance of recurrence at 5 years (12).

Patients with VTE are at risk of developing secondary complications. In addition to recurrent VTE, they may develop other conditions, such as the post-thrombotic syndrome (affecting 20-50% of patients after DVT) (26), various manifestations and degrees of severity of the post-PE syndrome (affecting up to 50% of patients with previous PE) (27), as well as diminished health-related quality of life (28).

Recent data suggest there has been an increase in the prevalence of VTE (29), as well as an increase in hospitalizations and mortality rate from PE, particularly over the past decade (30, 31). Whether these observations can be attributed to an increasing incidence and/or case fatality rate, and/or increased awareness and diagnostic improvements remain unknown. Raskob et al found that VTE associated with hospital admissions was the chief cause of lost disability-adjusted life-years in low- and middle-income countries, and the second leading cause in high-income countries (32). A 2016 study estimated the total annual cost of VTE in the US to range between $13.5-69.3 billion, depending on incidence rates and cost input (33). Barco et al calculated the total annual expenses for VTE in the EU-28 countries to €1.5-13.2 billion (34).

Summarized, VTE has a significant impact both on individual health, as well as on global morbidity and mortality. Research initiatives furthering our understanding of the various aspects of the disease entity are required.

1.5 The development of the diagnostic workup of DVT

1.5.1 Diagnostic imaging

When the possibility of diagnostic imaging emerged, there was a shift from treating suspected DVT to confirmed DVT. Contrast venography was developed in the 1920s, but was not standardized or widely used until the 1970s (35). It has since become the criterion standard for the diagnosis of DVT (36). A negative venography examination is associated with a low rate of VTE events during three months of follow-up; 1.3% (95% CI, 0.2%–4.4%) (37). This three-month VTE rate has since become the reference standard for diagnosing DVT against which new diagnostic tests or algorithms are judged (36). Other less invasive imaging modalities have been explored as alternatives to venography, including pletysmography techniques and ^{125}I-fibrinogen leg scanning (38, 39). However, their weaknesses as diagnostic tests limited their clinical usefulness (40), as they were relatively complex tests, and insensitive to distal or non-occlusive clots.

Compression ultrasonography (CUS) was explored as another imaging option throughout the 1980s, and gradually replaced venography as the primary diagnostic method after its introduction to DVT diagnostics (41). Being quick, non-invasive and accurate, the method greatly improved the availability and feasibility of imaging in suspected DVT (42). The two main CUS modalities are proximal CUS, scanning the femoral and popliteal veins and typically repeated within a week, and whole-leg CUS, extending the examination to the veins of the calf. In their 2020 systematic review and meta-analysis (43), Bhatt et al found pooled estimates for sensitivity and specificity of proximal CUS of 90.1% (95% CI 86.5-92.8) and 98.5% (95% CI, 97.6-99.1), respectively. For whole-leg CUS, the pooled sensitivity was 94.0% (95% CI, 91.3-95.9), with pooled specificity of 97.3% (95% CI, 94.8-98.6). For serial CUS pooled sensitivity and specificity were 97.9% (95% CI, 96.0-98.9) and 99.8% (95% CI, 99.3-99.9), respectively. Another 2020 systematic review and meta-analysis of diagnostic accuracy studies or management strategies applying at least one of three CUS modalities included 21,250 patients from 40 studies. The authors found a low

three-month VTE rate for both single proximal CUS (1.4%, 95% CI 0.83-2.5), repeat proximal CUS (1.9%, 95% CI 1.4-2.5), and whole-leg CUS (1.0%, 95% CI 0.6-1.6) (44).

1.5.2 Clinical prediction rules

As previously mentioned, symptoms of DVT are notoriously non-specific and overlap with several other disease entities. Even though non-invasive imaging facilitated a smoother diagnostic process, earlier workup typically entailed imaging all patients with suspected DVT. However, less than 25% of referred patients are typically found to have DVT (45-49). Consequently, there was a need for better selection of patients to undergo imaging.

Clinical prediction rules are a set of common signs and symptoms of DVT used to stratify patients into risk groups based on their likelihood of DVT. Structured assessment using clinical items in the diagnostic process was described in studies from the late 1970s without convincing results (50). In 1995, Wells and colleagues developed a model consisting of 12 common findings in patients with DVT to divide patients with suspected DVT into low-, moderate- and high-probability subgroups (15). In a prospective evaluation of 529 patients, 85% of patients in the high-probability group had DVT, whereas 33% and 5% in the moderate- and low-probability categories had DVT, respectively. Hence, the findings suggested that common manifestations of DVT could be used to interpret the likelihood of the patient having the condition. The model was simplified and used in a 1997 prospective management strategy to obviate the need for serial CUS in low-risk patients in a time where one-week repeat testing was recommended in patients with an initial negative imaging test (46). The model was modified in 2003 when the same collaborators demonstrated that CUS could be avoided altogether in low-risk patients without compromising safety, provided they had a negative D-dimer result (51).

The 1997 three-level and the 2003 two-level Wells clinical prediction rules are depicted below in *Table 2*, with the most significant changes to the modified, two-level score shown in italics.

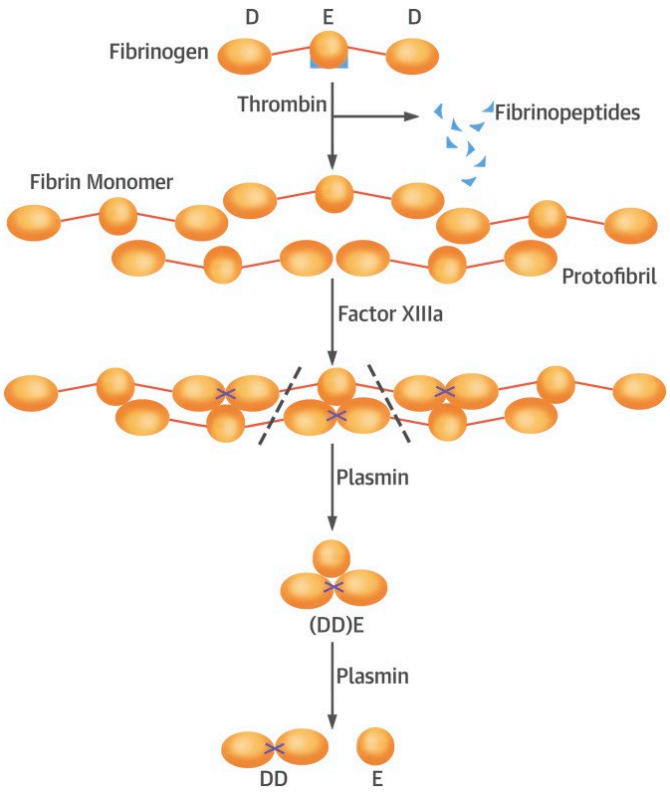
Several clinical prediction rules have since been validated (52-55), often targeting areas of improvement in other scores or developed for specific subgroups, such as primary care or hospitalized patients (56-58). While no prediction rule has been deemed superior to others, the Wells score is perhaps the most validated and used score among clinicians (59-62). An overview of some of the prediction rules initially developed in outpatient populations are outlined in *Table 2*.

Table 2 Clinical prediction rules for the workup of suspected deep vein thrombosis						
Prediction rule	Three-level Wells (46)	Two-level Wells (51)	Hamilton (54)	Kahn (52)	Constans (53)	I-DVT (55)
Items	Active cancer **1** Paralysis/paresis/plaster immobilization **1** Bedridden > 3 days/major surgery **1** Localized deep vein tenderness **1** Entire leg swelling **1** Unilateral calf > 3 cm **1** Pitting edema **1** Collateral superficial veins **1** Alternative diagnosis more likely **-2** ***HIGH PROBABILITY ≥ 3 POINTS*** ***MODERATE PROBABILITY 1-2 POINTS*** ***LOW PROBABILITY < 1 POINTS***	Active cancer **1** Paralysis/ paresis/plaster immobilization **1** Bedridden ≥ 3 days/major surgery **1** Localized deep vein tenderness **1** Entire leg swelling **1** Unilateral calf ≥ 3 cm **1** Pitting edema **1** Collateral superficial veins **1** Previous DVT ***1*** Alternative diagnosis at least as likely **-2** ***DVT LIKELY ≥ 2 POINTS*** ***DVT UNLIKELY < 2 POINTS***	Plaster immobilization of lower limb **2** Active cancer **2** Strong clinical suspicion and no other diagnostic possibilities **2** Recent bed rest or surgery **1** Male sex **1** Calf circumf. >3 cm larger on affected side **1** Erythema **1** ***DVT LIKELY IF ≥ 3 POINTS*** ***DVT UNLIKELY IF < 3 POINTS***	Male sex Orthopedic surgery (last 6 months) Superficial vein dilatation Local warmth ***HIGH PROBABILITY ≥ 3 PREDICTORS*** ***MODERATE PROBABILITY 1-2 PREDICTORS*** ***LOW PROBABILITY 0 PREDICTORS***	Male sex **1** Paralysis or immobilization of lower limb **1** Confinement to bed for > 3 days **1** Lower limb enlargement **1** Unilateral lower limb pain **1** Other diagnosis at least as plausible **-1**	Immobilization (≥ 3 days and/or major surgery < 4 weeks) Difference in calf circumference ≥ 3 cm compared to asymptomatic leg Past VTE Active cancer ***DVT UNLIKELY IF PATIENT SCORES 0 ITEMS***

1.5.3 D-dimer

Coagulation factors are sequentially activated to form a fibrin clot in response to various triggers. When activated, coagulation factor II thrombin in turn acts on several other components of the coagulation cascade, including fibrinogen and factor XIII (63). The conversion of soluble fibrinogen to fibrin results in adhesion of fibrin monomers which subsequently form covalent bonds, stabilizing the fibrin clot through the activation of factor XIII. Plasmin counteracts these mechanisms by cleaving fibrin at specific sites, releasing fibrinogen degradation products containing the D-dimer epitope. D-dimer levels rise in any condition where there is increased coagulation and fibrinolytic activity (64), such as in VTE.

Figure 4 Formation of D-dimer (65)



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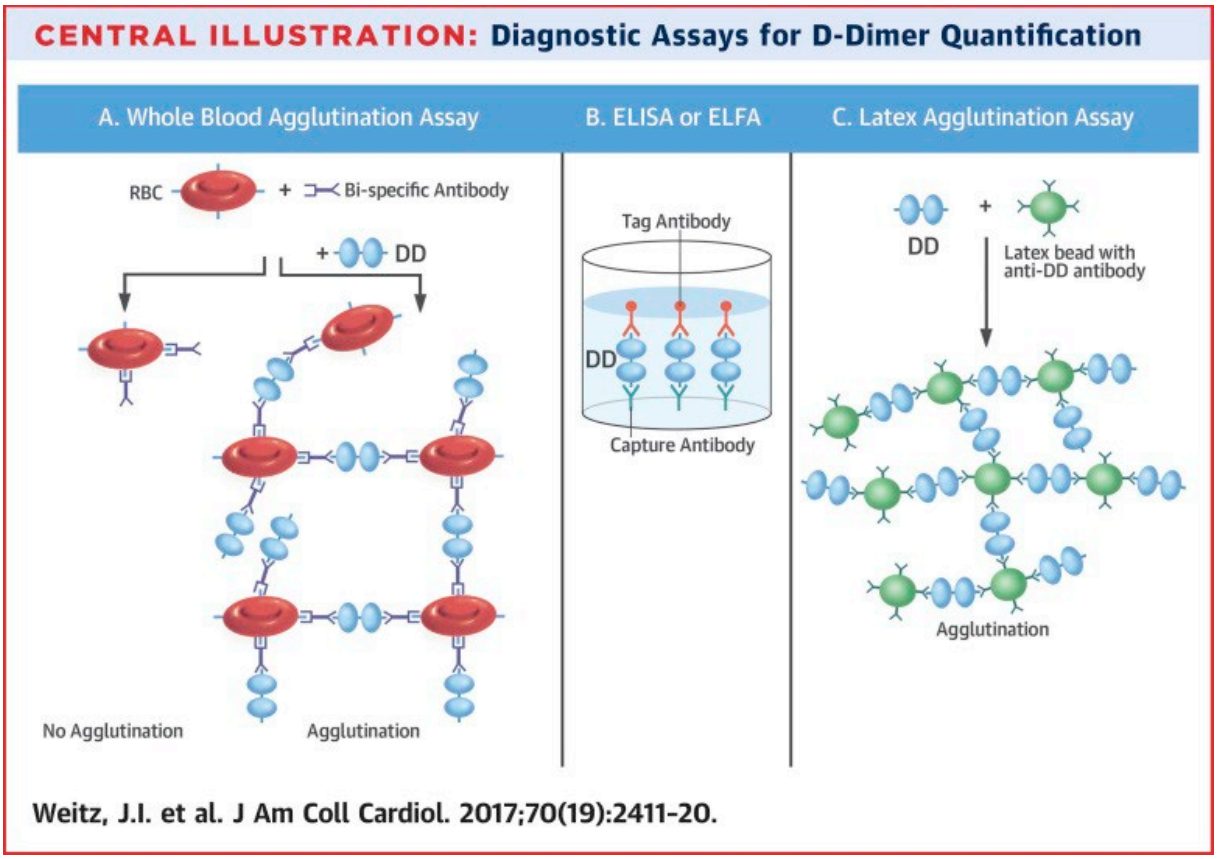
D-dimer fragments can be detected and measured by monoclonal antibodies, a technique developed in the 1980s (66, 67). In the years following the development of the technique, D-dimer was found to have favorable diagnostic properties for VTE, such as high sensitivity and negative predictive value (64). In other words, if the patient has VTE, D-dimer will most likely be elevated, or positive. If D-dimer is normal, or negative, the patient is unlikely to have VTE. The incorporation of D-dimer into the assessment of patients suspected of having VTE greatly improved the diagnostic management of these patients.

D-dimer assays can be broadly categorized into three main types based on the methods of detection; whole-blood agglutination assays, enzyme-linked

immunosorbent (ELISA) or immunofluorescent (ELFA) assays, and latex agglutination assays (65).

Figure 5 D-dimer assays (65)



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Latex agglutination assays seem to be the most commonly used method in Europe (68). Latex agglutination and ELISA/ELFA methods are known to be high-sensitivity assays, owing to their high likelihood of being positive if the patient has DVT, and are the assays primarily used in VTE diagnosis today. Their sensitivity is around 95% compared to 85% of the moderately sensitive whole-blood agglutination assays, with the trade-off of lower specificity (approximately 50% and 70%, respectively) (63, 69). A recent systematic review and meta-analysis saw a higher yield in

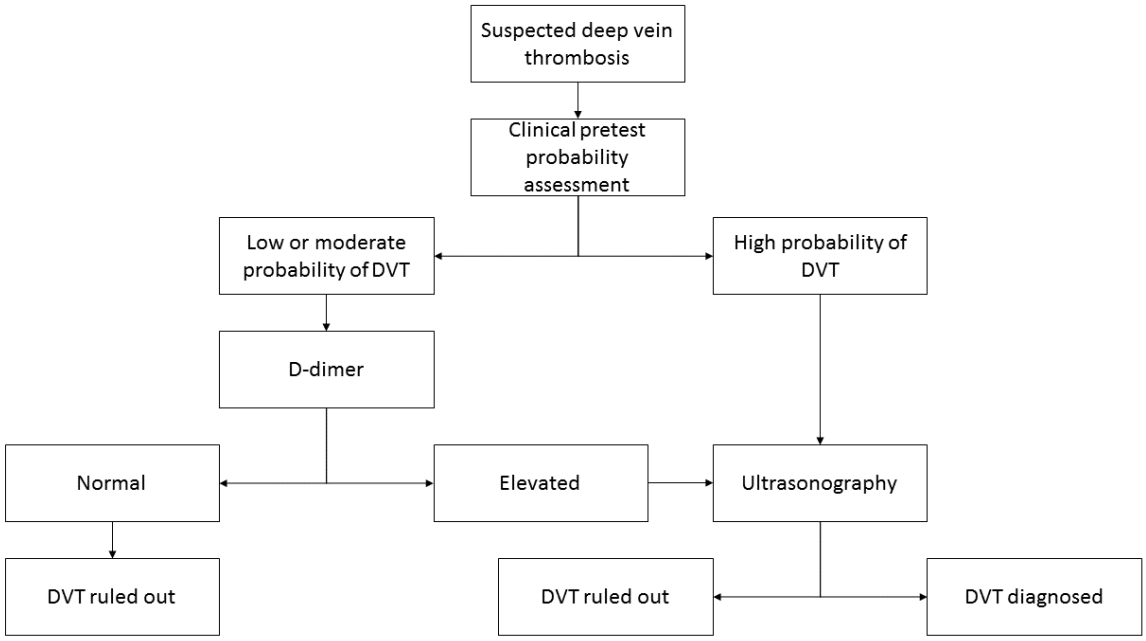
sensitivity at the cost of lower specificity for the high-sensitivity assays, with pooled estimates of 96.1% (95% CI, 92.6-98.0) and 35.7% (95% CI, 29.5-42.4), respectively (43).

Notably, D-dimer does not represent one defined analyte, and standardization has proven challenging (64, 70). D-dimer assays vary according to which D-dimer epitopes the various antibodies detect, as well as instrumentation procedures (63, 71). There are different cut-offs for the various methods (72), and consequently, results from one assay cannot necessarily be extrapolated to another (64). Instead, clinicians should interpret the results according to the test characteristics of the assay available in their individual centers. Moreover, the D-dimer cut-off used in management strategies should not be regarded as a threshold for a reference interval in a population without VTE (64). Rather, clinicians operate with an accepted threshold for when diagnostic imaging should be performed that is sufficiently low to maintain the high sensitivity. As such, the primary strength of D-dimer as a diagnostic test is its capacity for ruling out VTE with a high degree of certainty (60, 73).

1.5.4 The current workup of DVT – diagnostic algorithms and recent developments

The development of clinical prediction rules, D-dimer detection methods, and imaging techniques allowed for an increasingly targeted diagnostic approach. As previously mentioned, Wells and colleagues began to incorporate their clinical prediction rule and later D-dimer into the decision-making process of selecting which patients did and did not require diagnostic imaging from 1995 onward (15, 46, 51). Their efforts contributed to reducing the number of imaging tests required, thus sparing both patients and referral centers from unnecessary examinations. Later, several algorithms incorporating various prediction rules, D-dimer assays, and CUS modalities have been evaluated, paving way for the currently endorsed diagnostic pathway (36, 74-76), depicted below in *Figure 6*.

Figure 6 The diagnostic workup of DVT



The diagnostic pathway generally consists of the same elements. However, depending on guideline and local practice, there are minor variations in the methods used for assessing clinical pretest probability (C-PTP) and likelihood stratification, favored imaging technique, and variations depending on whether there is suspected first or recurrent DVT. The general outline starts with assessing C-PTP. Patients with high C-PTP are considered likely to have DVT, and are referred directly for whole-leg or proximal CUS (36, 74-76). If whole-leg CUS is chosen, one negative examination generally rules out DVT. Patients with negative proximal CUS require negative D-dimer or repeat proximal or whole-leg CUS to rule out DVT. For patients with perceived non-high C-PTP, CUS is only required if there is a positive D-dimer. Adhering to one of these strategies to exclude DVT, based on normal findings on CUS or otherwise negative D-dimer, is associated with a low three-month VTE rate which is deemed acceptable; ranging between 0.4%-2.0% (46, 49,

51, 55, 77-80), with an upper limit of the 95% confidence interval (CI) of mainly ≤2.2%. Furthermore, they allow for ruling out DVT in approximately 30% of outpatients without CUS referral (62). These are patients who are both deemed unlikely to have DVT based on C-PTP assessment, and who have negative D-dimer.

However, the high sensitivity and negative predictive value of D-dimer come at the cost of lower specificity, particularly in certain subgroups. D-dimer levels have been shown to increase with increasing age, reducing the specificity of D-dimer in an older population. Therefore, an age-adjusted threshold for positivity has been suggested. Although various cut-offs have been explored, it is typically defined as the patient's age multiplied by 0.01 mg/L for patients 50 years or older (81). In a recent individual patient data meta-analysis by Parpia et al consisting of 2554 patients with suspected DVT, the age-adjusted threshold increased the specificity of D-dimer by 9.5% (95% 1.0-18.0), from 45.2% to 54.7% (48). There is extensive literature supporting the use of an age-adjusted threshold in DVT management (82-87), although critical voices have been raised (88). However, due to the lack of prospective evidence directly comparing the age-adjusted threshold to the regular D-dimer threshold, adjusting D-dimer according to age is generally not incorporated into recent guidelines (74, 76), although the 2020 National Institute for Health and Care Excellence guideline suggests considering it for people aged over 50 (75).

Similarly, an alternative threshold has been suggested according to the perceived C-PTP for DVT. The C-PTP-adjusted strategy uses a cut-off that is twice as high in patients with a low C-PTP for DVT (e.g. 1.0 mg/L) compared to patients with moderate C-PTP (e.g. 0.5 mg/L) (49). This strategy has been found to reduce the proportion of required CUS by 7.6% (95% CI 2.9-12.2) without adversely affecting the three-month VTE rate in patients who are deemed not to have DVT according to the strategy. In the abovementioned meta-analysis, Parpia et al compared the two strategies, and found that they both had a high and comparable negative predictive value of 99.8%. Furthermore, the difference between the pooled specificity of the C-PTP-adjusted strategy (57.3%) and the age-adjusted strategy (54.7%) was 2.6%

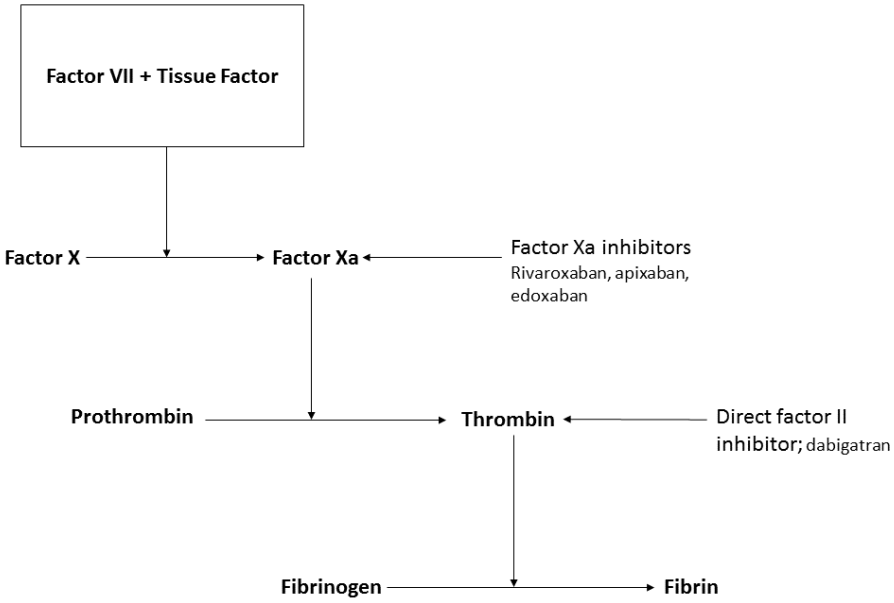
(95% CI: −7.7, 12.8). The C-PTP-adjusted strategy (49.4%) yielded a slightly higher proportion of negative D-dimer results compared with the age-adjusted approach (47.4%), with a difference of 1.9% (95% CI: −0.1, 3.9). As such, the authors concluded that both strategies have a similar utility and safety profile. As with age-adjusted D-dimer thresholds, C-PTP-adjusted D-dimer is currently not widely applied clinically. The C-PTP-adjusted threshold was recently incorporated into a simplified diagnostic algorithm for the management of patients with suspected DVT (89). In addition to D-dimer, the rule incorporates two elements based on the Wells score; calf swelling and DVT being the most likely diagnosis. According to the rule, a D-dimer of <1.0 mg/L rules out DVT without requiring CUS in patients without any of the two elements. For patients fulfilling at least one of the items, a D-dimer level of <0.5 mg/L is necessary to rule out DVT without CUS. The strategy is pending prospective validation.

1.5.5 Developments in DVT treatment

Anticoagulation therapy is the treatment of DVT, and targets various components of the coagulation system. This in turn prevents the thrombus from developing further while facilitating breakdown of the clot. The main goal of treating VTE is to prevent mortality, as well as advancement or recurrence of the thrombus (90). Patients are routinely treated for three to six months following the event (76, 90, 91).

Heparin, followed by vitamin K antagonists (VKAs), and decades later low-molecular-weight-heparin (LMWH) and heparin oligosaccharides, were applied clinically from the 1920s and over the following decades (92, 93). Heparin and its derivatives potentiate antithrombin III, which in turn inactivates several coagulation factors, such as thrombin and factor Xa.

Figure 7 Mechanism of action of direct oral anticoagulants



FIIa and FXa inhibitors, termed direct oral anticoagulants (DOACs), have gained popularity since their introduction from 2010 onward (94-97). The commercially available DOACs with VTE treatment and prophylaxis among their indications, include dabigatran, rivaroxaban, apixaban, and edoxaban. Dabigatran is a direct factor II inhibitor whilst the remainder exert their action by affecting factor Xa. Compared with LMWH followed by VKA, DOACs are non-inferior in terms of avoiding recurrent VTE (relative risk 0.90, 95% CI 0.77-1.06) with a reduced risk of major bleeding (relative risk 0.61, 95% CI 0.45-0.83) (98). Other benefits of DOACs include ease of use, apparent relatively predictable pharmacokinetics without required monitoring, and a wide therapeutic window. DOACs have caused a paradigm shift in the treatment of VTE over the past decade, and they are now endorsed as first-line therapy (75, 76, 91, 99).

There are several unresolved issues with VTE treatment and prevention. One is whether or not to administer anticoagulation therapy for suspected DVT before the diagnosis can be established or ruled out. No studies have assessed the outcomes of giving versus withholding so-called empiric or interim anticoagulation

in this patient group. This comes into question when the diagnostic workup is expected to be delayed, as is often the case for DVT patients without suspicion of concurrent PE. These patients are typically not acutely ill compared to many of their emergency department cohorts, and may thus be subject to prolonged waiting in periods of compromised staff or equipment resources during center peak hours or off-hours. When the workup is expected to be delayed, empiric anticoagulation could theoretically reduce the risk of adverse outcomes in patients later diagnosed with DVT. However, it would also put patients later found not to have DVT at a risk of bleeding, albeit low.

The American College of Chest Physicians suggests empiric treatment with LMWH if the workup is prolonged and the patient has no major risk factors for bleeding (Grade 2C level of recommendation) (90). Prompt administration of LMWH is recommended in patients with a high C-PTP. Furthermore, they suggest LMWH for patients with moderate or low C-PTP if workup exceeds 4 and 24 hours, respectively. The National Institute for Health and Care Excellence suggests empiric anticoagulation if the patient is considered likely to have DVT and the workup cannot be completed within 4 hours (75). Several studies have demonstrated the safety of deferred workup until center on-hours with LMWH or unfractionated heparin (100-106). Deferred workup may in turn avoid compromising resources that around-the-clock referrals may entail. Additionally, one retrospective chart review assessed the safety of DOACs versus LMWH in the prediagnostic phase in 173 outpatients with suspected VTE (107). The authors found no major bleeding events in the 95 outpatients given a DOAC, nor in the 78 patients given LMWH before diagnostic testing, although two patients receiving a DOAC reported a clinically significant non-major bleeding incident. Despite the scarce literature examining DOACs in the prediagnostic setting, observational data suggest that they are used relatively frequently. A recent article describing anticoagulation therapy patterns in the approximately 10,000 patients included in the global GARFIELD-VTE registry

demonstrated that 13.4% of patients had started anticoagulation therapy before the diagnosis was confirmed (108).

2. Study rationale for the Ri-Schedule study

To our knowledge, no prospective studies have assessed the safety of empiric anticoagulation and of deferred workup with DOACs. This topic should be examined further before increasingly being adopted into clinical practice.

As for diagnostic algorithms, they have undoubtedly allowed for major progress in the management of patients with suspected DVT by enabling the transition from imaging all outpatients to imaging only select patients. Besides the obvious benefit of being less resource-demanding, other potential benefits include decreasing false positive findings or clinically insignificant DVT, sparing patients the risk of side effects, as well as the inconvenience and cost of unnecessary anticoagulation therapy for patients and society.

However, from our clinical experience we observed that the algorithms were not necessarily adhered to or used correctly. For instance, we observed that D-dimer and other laboratory tests had often been obtained and were available before an emergency physician had evaluated and performed C-PTP assessment of the patient. This refutes the original purpose of such an assessment, which would stratify patients either to direct CUS referral, or to await D-dimer results. We observed that this would particularly occur during peak hours in the Emergency Department, when staff likely prioritized attending other patients until laboratory results could offer guidance on further management, thereby saving time. We hypothesized that a negative stand-alone D-dimer could prove safe in ruling out the condition in an outpatient population referred for suspected DVT, and it would also be a smoother alignment with clinical practice. Moreover, performing a single whole-leg CUS irrespective of C-PTP could reduce the number of required visits and simplify the workup, which in turn could increase adherence and clinical utility of the algorithm.

Therefore, we developed a study which aimed to enroll all consecutive outpatients referred with suspected DVT to examine these topics.

3. Aims

The overall aim of the thesis was to improve the diagnostic workup of DVT. This would be achieved through the following specific aims:

1. To assess and compare the safety and efficiency of using D-dimer as a stand-alone test for ruling out DVT with the safety and efficiency of other diagnostic strategies. This aim was assessed in Paper 1.
2. To assess the safety and feasibility of deferring DVT workup for up to 24 hours by using empiric rivaroxaban. This aim was assessed in Paper II.
3. To assess the safety of a new diagnostic strategy for DVT workup incorporating stand-alone D-dimer and single, whole-leg CUS. This aim was assessed in Paper III.

4. Materials and methods

4.1 Study population and design

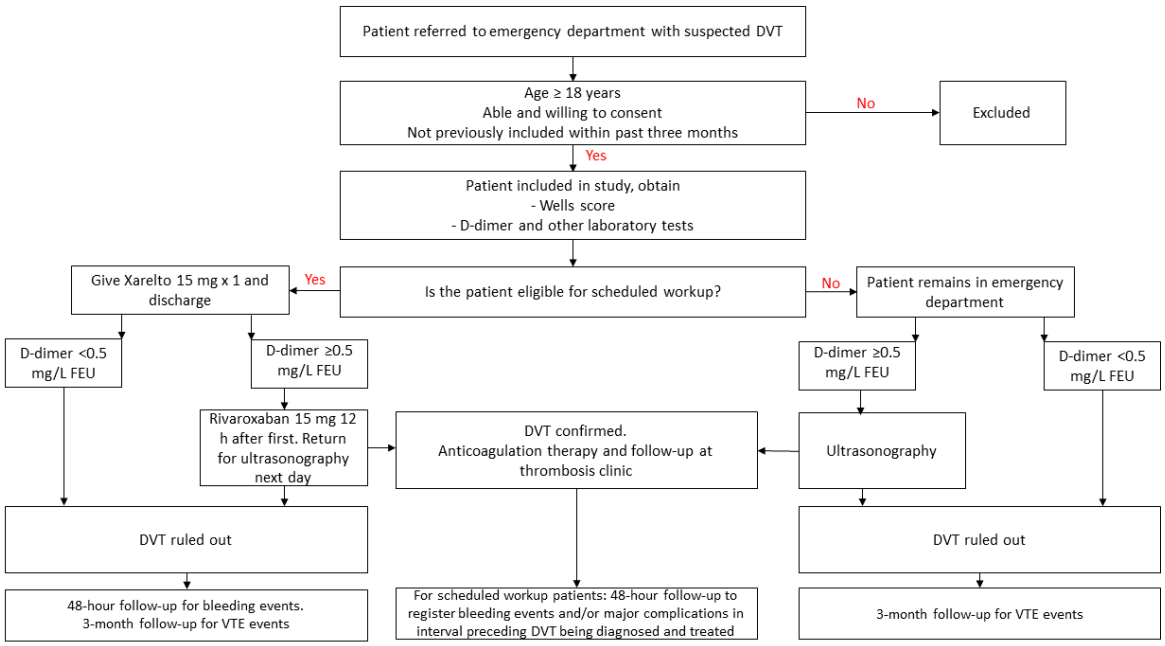
The thesis is based on material from the *Rivaroxaban for Scheduled Workup of Deep Vein Thrombosis study* (the Ri-Schedule study).

The Ri-Schedule study was a single-center, prospective management outcome trial conducted at Østfold Hospital, Norway, between February 2015, and November, 2018. The hospital is the primary referral center for approximately 300,000 patients in its proximity. Consecutive outpatients referred from primary care centers to the Emergency Department at the hospital were considered for inclusion. Inclusion criteria were ≥18 years of age, and referral for suspected first or recurrent lower extremity DVT. We excluded patients who were unwilling or unable to provide written consent, or who had been included in the study within the three months prior.

For the endpoint analyses of Paper I, we excluded patients who had been prescribed anticoagulation therapy for other reasons than VTE during a follow-up period of three months. In Paper III, the following patients were excluded from endpoint analyses: patients lacking D-dimer results at baseline, who had been prescribed anticoagulation for other reasons than VTE during follow-up, as well as patients who were on regular anticoagulation prescription for any reason at inclusion.

4.2 Study procedures

Figure 8 Flowchart of the Ri-Schedule study



The study outline is depicted in *Figure 8*. Consecutive outpatients were included if they fulfilled all inclusion criteria and no exclusion criteria, mainly by designated study personnel working in the Emergency Department. After inclusion, patients were assessed for management according to scheduled workup with empiric rivaroxaban and deferred CUS by using the list of exclusion criteria outlined in *Table 3*.

Table 3 Exclusion criteria for scheduled workup
Factors with a higher risk of adverse effects of rivaroxaban
Concomittant anticoagulation[1]
Suspected active or recent bleeding
Major risk factors for bleeding[2]
Active cancer or chemotherapy within the past six months
Pregnancy or lactation
Hemoglobin < 11 g/dL or thrombocytes < $100x10^9$/L
GFR < 45 mL/min
Liver disease with coagulopathy or other bleeding risk
Concomittant medications possibly interacting with rivaroxaban
Conditions or situations in which scheduled workup is deemed inappropriate
Suspicion of concurrent pulmonary embolism
Comorbidities necessitating admission
Suspected ischemia or eligibility for thrombolysis
Physician considers discharge unsafe
Patient objects to discharge
Logistical challenges
Workup can be completed within two hours
[1] Regular prescription or empiric anticoagulation for suspected DVT
[2] Current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

Study personnel obtained point-of-care results for pregnancy status for eligible women, as well as creatinine and hemoglobin levels for all patients. Patients who were not eligible for scheduled workup remained in the Emergency Department until DVT had been confirmed or ruled out. Although they were not managed according to scheduled workup, they were analyzed for the other endpoints. The next step for these patients was obtaining standard blood admission samples including D-dimer, and assessing Wells score for later analyses before D-dimer results were available. Wells score was assessed primarily by study personnel, or otherwise an emergency department physician not affiliated with the study. The results of the score were explicitly stated to not guide further management. D-dimer was analyzed by the immuno-turbidometric method of STA®-Liatest® D-Di Plus (Stago Diagnostics, Asnieres, France) on the STA-R Evolution Analyzer. D-dimer levels of <0.5 mg/L fibrinogen-equivalent units were considered negative, and in

this case patients were not referred for CUS. They were instead discharged either immediately, or otherwise after completing other diagnostic considerations when warranted. Patients were instructed to follow up with their family doctor if deemed necessary. D-dimer of ≥0.5 mg/L was considered positive, and led to referral for whole-leg CUS in the adjacent radiology department.

All veins were assessed for compressibility. The diagnostic criterion for DVT was non-compressibility of the vein (109), or otherwise a gray-scale visualization of the thrombus for first, recurrent contralateral, or for recurrent ipsilateral DVT where the thrombus had since been resorbed. Recurrent ipsilateral DVT was defined as non-compressibility, or visualization of, the thrombus in a venous segment not affected in the reference CUS, or non-compressibility of a new area (110). The final diagnosis was based on this CUS examination. Consequently, we considered DVT as being ruled out in patients who either had normal D-dimer, or otherwise a normal CUS examination. Patients diagnosed with DVT were prescribed anticoagulation therapy, and were referred for outpatient follow-up at the thrombosis clinic.

For patients managed according to scheduled workup, Wells score and standard admission blood samples were similarly obtained as the initial step after inclusion. Patients were subsequently given one tablet of rivaroxaban 15 mg and discharged with another tablet of rivaroxaban 15 mg for a maximum of two consumed tablets within 24 hours. When D-dimer results were available, study personnel contacted patients by phone. DVT was considered ruled out in patients with negative D-dimer, and no further workup was done. Patients were instructed not to take the second tablet of rivaroxaban, and to follow up with their family doctor for further diagnostic considerations. Patients with positive D-dimer were scheduled for an appointment for whole-leg CUS the next day and within 24 hours of enrollment.

Study personnel contacted patients who had been managed according to scheduled workup by phone 48 hours after taking the last tablet of rivaroxaban to

assess for bleeding events. The 48-hour range was chosen based on the estimated time needed to eliminate the drug (111). In cases where VTE had been diagnosed, study personnel determined whether patients had experienced bleeding or major complications in the interval between inclusion and the diagnosis being confirmed. This interval was chosen as we wanted to assess complications occurring in the prediagnostic phase, and complications from VTE or its therapy was outside the scope of the study.

All patients in whom DVT had been considered ruled out at the baseline visit, either by negative D-dimer or negative CUS and regardless of whether or not they had been managed according to scheduled workup, were followed up by phone three months after inclusion. Study personnel assessed whether the patients had since been diagnosed with VTE or had started on anticoagulation therapy for other reasons during this period.

4.3 Study endpoints

4.3.1 Paper I

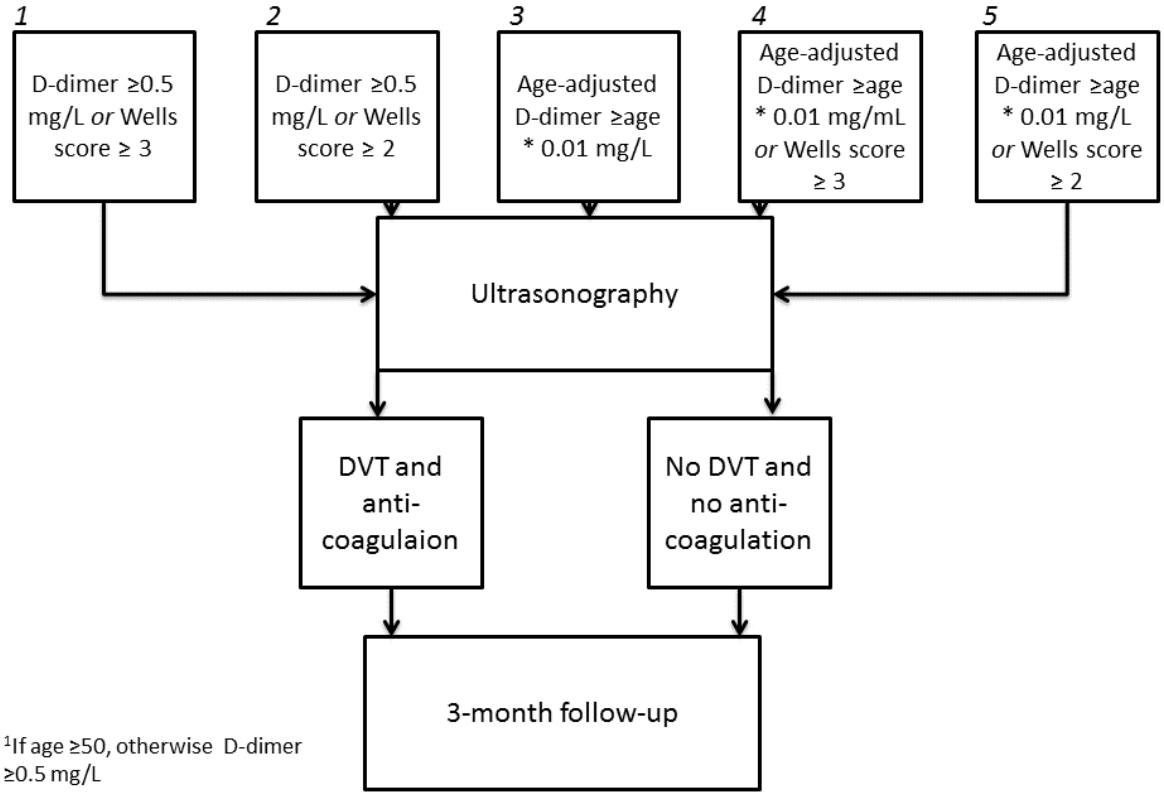
The primary endpoints of Paper I were

i) the failure rate of stand-alone D-dimer. Failure rate was defined as the proportion of all patients with negative D-dimer at baseline who had been diagnosed with VTE or had died, possibly from VTE, at three months of follow-up (*n* patients with negative D-dimer and diagnosed with VTE at baseline or within follow-up, or who had died from VTE during follow-up/all patients with negative D-dimer).

ii) the efficiency of stand-alone D-dimer. Efficiency was defined as the proportion of patients requiring CUS according to the strategy out of all patients (*n* patients with positive D-dimer/all patients).

The secondary endpoints were the failure rate and efficiency of five diagnostic strategies (*Figure 9*), and the diagnostic performance of the five strategies in addition to stand-alone D-dimer.

Figure 9 Diagnostic workup of DVT according to various strategies



Only the stand-alone D-dimer strategy was assessed prospectively, whereas performance of the five remaining strategies was assessed retrospectively. Consequently, to determine performance of the five strategies in retrospective comparison, we used the criteria that would have led to a referral for CUS according to each strategy as depicted. If the patient did not meet the criteria for CUS as defined by each strategy, we considered that they would not have been referred for CUS, and would have remained untreated at baseline.

Failure rate was likewise defined as the proportion of patients in whom DVT was considered ruled out according to each strategy, but who were nonetheless diagnosed with VTE either at baseline or during follow-up. Efficiency was likewise defined as the proportion of all patients requiring CUS according to the strategies out of all patients.

Diagnostic performance was expressed by sensitivity (proportion of patients with DVT who required CUS according to the criteria of each strategy), specificity (proportion of patients without DVT who did not require CUS according to each strategy), negative predictive value (proportion of patients without DVT among patients who did not require CUS according to each strategy), positive predictive value (proportion of patients with DVT among patients who required CUS according to each strategy), positive likelihood ratio (the probability that a patient with DVT required CUS according to each strategy divided by the probability that a patient without DVT required CUS according to each strategy), and negative likelihood ratio (the probability that a patient with DVT did not require CUS according to each strategy divided by the probability that a patient without DVT did not require CUS according to each strategy).

4.3.2 Paper II

The primary endpoint of Paper II was the proportion of patients in whom DVT had been considered excluded who experienced a major bleeding event within 48 hours after consuming the last tablet of rivaroxaban, or otherwise until DVT had been confirmed and anticoagulation therapy consequently had been continued. Bleeding events were classified as stated by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (112). According to this definition, major bleeding is 'fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 or more units of whole blood or red cells'.

The secondary safety endpoints were the proportion of clinically significant non-major or minor bleeding events, and major complications while awaiting CUS. Clinically significant non-major bleeding according to the definition of the Subcommittee on Control of Anticoagulation is a bleeding event not fulfilling the

criteria for major bleeding, but associated with an increased level of care through face to face evaluation, medical intervention or admission to hospital (113).

Major complications were defined as progressive DVT symptoms or signs, or a clinical picture consistent with PE (*n* patients with major complications/*N* patients diagnosed with VTE). This would be any of the following criteria occurring: hemodynamic instability, worsening of vital signs (increased respiratory rate or resting pulse after 15 minutes of rest, lowered resting systolic blood pressure or oxygen saturation by more than 20% compared to baseline), increased leg circumference by more than 10% from baseline, and/or progressive symptoms until VTE had been diagnosed.

The secondary feasibility endpoint was the proportion of patients who were managed according to scheduled workup out of all patients.

All potential outcome events were adjudicated by an independent committee.

4.3.3 Paper III

In Paper III, the primary endpoint of failure rate of the strategy was defined as the proportion of patients with negative D-dimer or normal whole-leg CUS who went on to develop VTE, or died possibly from VTE, within the follow-up period out of all patients in whom DVT had been ruled out.

The secondary safety endpoints were

i) the failure rate of stand-alone D-dimer, i.e. the proportion of patients with negative D-dimer at baseline who had been diagnosed with VTE or died possibly from VTE during follow-up out of all patients with negative D-dime at baseline, and ii) the failure rate of whole-leg CUS, i.e. the proportion of patients with normal CUS at baseline who had been diagnosed with VTE or died possibly from VTE during follow-up out of all patients with normal CUS at baseline.

The feasibility endpoint of adherence was expressed as the proportion out of all patients managed according to the suggested strategy.

All potential outcome events were adjudicated by an independent committee.

4.4 Statistical analyses

4.4.1 Reporting results

The software used was the IBM® SPSS® Statistics Software, Version 25 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed in numbers and proportions. Continuous variables were expressed by median with interquartile range when not normally distributed, and by mean with standard deviation when normally distributed.

Safety, feasibility and efficiency endpoints were all expressed as proportions in descriptive summary percentages and 95% CIs, calculated by Clopper-Pearson exact method (114).

Diagnostic properties were calculated using OpenEpi statistical software, Version 3.01, Atlanta, GA, USA, and the Wilson method for calculating binomial 95% CI.

4.4.2 Sample size

The analyses described in Paper I were not planned when the Ri-Schedule study was designed, and as such there was no predefined sample size calculation. We decided to conduct an interim analysis when approximately 50% of the patients had been enrolled to compare the safety and feasibility of the stand-alone versus the age-adjusted D-dimer cut-offs to evaluate which of the two cut-offs to proceed with as routine practice for the emergency department. Based on previous prevalence data from the hospital we expected negative D-dimer in 24-32% of patients (115), necessitating an estimated approximately 300 patients in whom DVT was ruled out based on a negative D-dimer in the interim study population which by then was approaching 1000 patients. A post-hoc power calculation showed that a sample size of 306 patients would be needed to detect an incidence rate of the primary outcome of <2% with a power of 80% at a 5% significance level.

For Paper II, we based the expected occurrence of major bleeding events on the number of patients included in studies reporting major bleeding rates with LMWH (100-102, 104). A total of 729 patients were included in these studies, and no major bleeding events occurred. This resulted in an observed major bleeding rate of 0% with a 95% CI of 0-0.6%. We assumed a frequency of major bleeding events with rivaroxaban at ≤0.2% with a one-sided 95% confidence limit of <0.8%. These assumptions, a significance level of 5% and a power of 80% (beta=20%) resulted in an estimated sample size of 620 patients.

For the primary endpoint of failure rate of the strategy assessed in Paper III, we would accept a point estimate of 2% with an upper limit of the 95% CI of 4%. This was similar to and based on the rate of symptomatic VTE after a negative venography (1.3%; 95% CI, 0.2%–4.4). As previously mentioned, this is the currently endorsed safety standard for diagnostic management studies of DVT (36, 37). At least 500 patients with negative workup according to the strategy were required for a power of 80% at a 5% significance level. However, more patients could be included if it were necessary to meet the sample size requirements of Paper II.

4.5 Permissions, approvals and study conduct

The Ri-Schedule study was approved by the South-Eastern Regional Committee for Medical and Health Research Ethics (REK) in January 2015, with reference number 2014/377. All later amendments to the protocol were likewise approved by REK in August 2015, March 2017, and August 2017. Among the amendments were minor adjustments to the criteria for scheduled workup, adjustments of sample size, as well as comparison of fixed versus age-adjusted D-dimer as an objective. The study was approved by the Norwegian Medicines Agency on January 6th 2015, EudraCT number 2013-005484-11. The study was registered at ClinicalTrials.gov with identifier NCT02486445.

A study-specific electronic case report form was created, and the data was regularly monitored for accuracy and completeness to ensure internal quality

control. Study documents were archived securely. Electronic case report forms and database were stored in a secured server at Østfold Hospital, and will be archived for 15 years after completion of the study before termination. The following committees were appointed with tasks in parentheses to ensure the integrity of the study conduct: a safety and monitoring committee (tasked with safety aspects of rivaroxaban, including reviewing outcomes and terminating the study if deemed necessary), an adjudication committee (adjudicate outcomes of the study), an executive committee (ensuring day-to-day study conduct), and a steering committee (with the overall scientific responsibility of the study).

The researchers adhered to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and the International Conference on Harmonization – Good Clinical Practice Guideline.

5. Main results

5.1 Paper I

In Paper I, we found that stand-alone D-dimer safely and efficiently ruled out DVT in our outpatient population. One of the 298 patients with negative D-dimer was diagnosed with DVT at baseline, resulting in a failure rate of 0.3% (95% CI 0.1-1.9%). Diagnostic properties are summarized in *Table 4*. Of the 913 included patients, 615 (67.4%, 95% CI 64.3-70.3) had positive D-dimer, thereby requiring CUS according to the strategy. Adding the modified, two-level Wells score would have detected the one patient missed in the stand-alone D-dimer strategy (as the patient had a Wells score of 2), but would have required 9.5% (95% CI 5.4-13.6) additional CUS examinations. Two of the strategies required less CUS examinations than stand-alone D-dimer. Stand-alone age-adjusted D-dimer would have required 8.8% less CUS examinations (95% CI -13.2 to -4.4) at the cost of a failure rate of 1.6% (95% CI 0.7-3.4). Adding the original, three-level Wells score to the age-adjusted D-dimer yielded 5.1% fewer CUS examinations (95% CI from -9.5 to -0.7) at the expense of a failure rate of 1.5% (95% CI 0.6-3.4).

Table 4 Diagnostic performance of different strategies (n = 913)						
	Fixed D-dimer			Age-adjusted D-dimer		
		or Wells score ≥ 3	*or* Wells score ≥ 2		*or* Wells score ≥ 3	or Wells score ≥ 2
Sensitivity						
TP/(TP + FN)	175/176	175/176	176/176	170/176	171/176	175/176
Estimate, %	**99.4**	**99.4**	**100**	**96.6**	**97.2**	**99.4**
95 % CI	96.9-99.9	96.9-99.9	97.9-100	92.8-98.4	93.5-98.8	96.9-99.9
Specificity						
TN/(TN + FP)	297/737	270/737	211/737	372/737	339/737	253/737
Estimate, %	**40.3**	**36.6**	**28.6**	**50.5**	**46.0**	**34.3**
95 % CI	36.8-43.9	33.2-40.2	25.5-32.0	46.9-54.1	42.4-49.6	31.0-37.8
Negative predictive value						
TN/TN + FN	297/298	270/271	211/211	372/378	339/344	253/254
Estimate, %	**99.7**	**99.6**	**100**	**98.4**	**98.5**	**99.6**
95 % CI	98.1-99.9	97.9-99.9	98.2-100.0	96.6-99.3	96.6-99.4	97.8-99.9
VTE at 3-month follow-up[1]						
FN/FN + TN	1/298	1/271	0/211	6/378	5/344	1/254
Estimate, %	0.3	0.4	0.0	1.6	1.5	0.4
95 % CI	0.1-1.9	0.1-2.1	0.0-1.8	0.7-3.4	0.6-3.4	0.1-2.2
Required ultrasonographies[2]						
TP + FP/TP + FN + FP + TN	615/913	642/913	702/913	535/913	569/913	659/913
Estimate, %	**67.4**	**70.3**	**76.9**	**58.6**	**62.3**	**72.2**
95 % CI	64.3-70.3	67.3-73.2	74.1-79.5	55.4-61.8	59.1-65.4	69.2-75.0

CI, confidence interval; TP, true positive; TN, true negative; FP, false positive; FN, false negative; VTE, venous thromboembolism

[1] In patients with negative diagnostic work-up at baseline

[2] According to the criteria warranting ultrasonography in each strategy

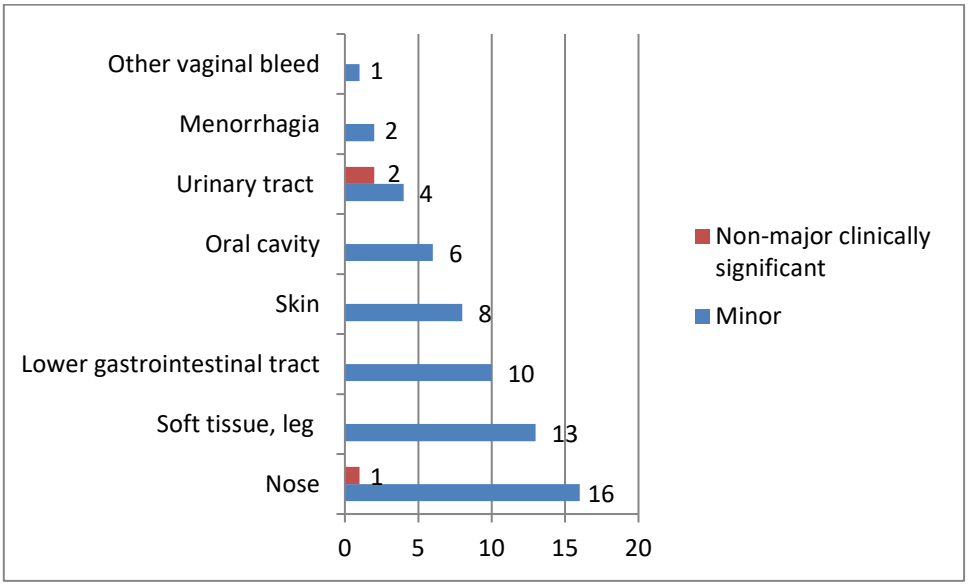
5.2 Paper II

In Paper II, we found that it was safe to defer CUS for up to 24 hours with empiric rivaroxaban in scheduled workup. Outcomes are summarized in *Table 5*. Origin and number of bleeding events are shown in *Figure 10*.

Table 5 Primary and secondary outcomes	n (%)	95 % CI
Safety, bleeding events		
Major	0	<0.4
Clinically relevant non-major	3 (0.5)	0.1-1.4
Minor	60 (9.6)	7.4-12.2
Major complications[1]	0	0.0-0.6
Feasibility		
Patients included in the study	624 (37.7)	35.4-40.1

[1]Worsening of symptoms, development of symptoms or signs of pulmonary embolism between inclusion and diagnosis of venous thromboembolism

Figure 10 Origin and number of bleeding events



One thousand twenty-nine patients of the 1653 included patients (62.3%, 95% CI 59.9-64.6) could not be managed according to scheduled workup (*Table 6*). The most common exclusion criterion was having received empiric anticoagulation in primary care before referral to the emergency department. This applied to 328 patients (19.8%, 95% CI 17.9-21.9), 245 of whom had this as their only exclusion criterion (14.8%, 95% CI 13.1-16.6).

Table 6 Exclusion criteria for scheduled workup in eligible patients (n = 1653)	n (%) with criterion	n (%) with only criterion
Anticoagulation[1]	447 (27.0)	329 (19.9)
Empiric anticoagulation treatment in primary care before referral	*328 (19.8)*	*245 (14.8)*
Regular prescription of anticoagulation treatment	*129 (7.8)*	*76 (4.6)*
Both empiric and regular use of anticoagulation treatment	*10 (0.6)*	*8 (0.5)*
Patient objects discharge	192 (11.6)	117 (7.1)
Physician deems discharge unsafe	189 (11.4)	89 (5.4)
Suspected active or recent bleeding	70 (4.2)	11 (0.7)
GFR < 45 mL/min	66 (4.0)	17 (1.0)
Active cancer or chemotherapy within the past six months	65 (3.9)	23 (1.4)
Major risk factors for bleeding	59 (3.6)	4 (0.2)
Logistical challenges for at-home observation	45 (2.7)	16 (1.0)
Work-up expected to complete within two hours	44 (2.7)	28 (1.7)
Medications possibly interacting with rivaroxaban	44 (2.7)	10 (0.6)
Hb < 11 g/dL and/or thrombocytes < $100x10^9$/L	39 (2.4)	6 (0.4)
Pregnancy or lactation	23 (1.4)	14 (0.8)
Suspected concurrent pulmonary embolism	22 (1.3)	2 (0.1)
Comorbidities necessitating admission	20 (1.2)	2 (0.1)
Suspected ischemia or eligibility for thrombolysis	4 (0.2)	0 (0)
Liver disease[2]	2 (0.1)	0 (0)

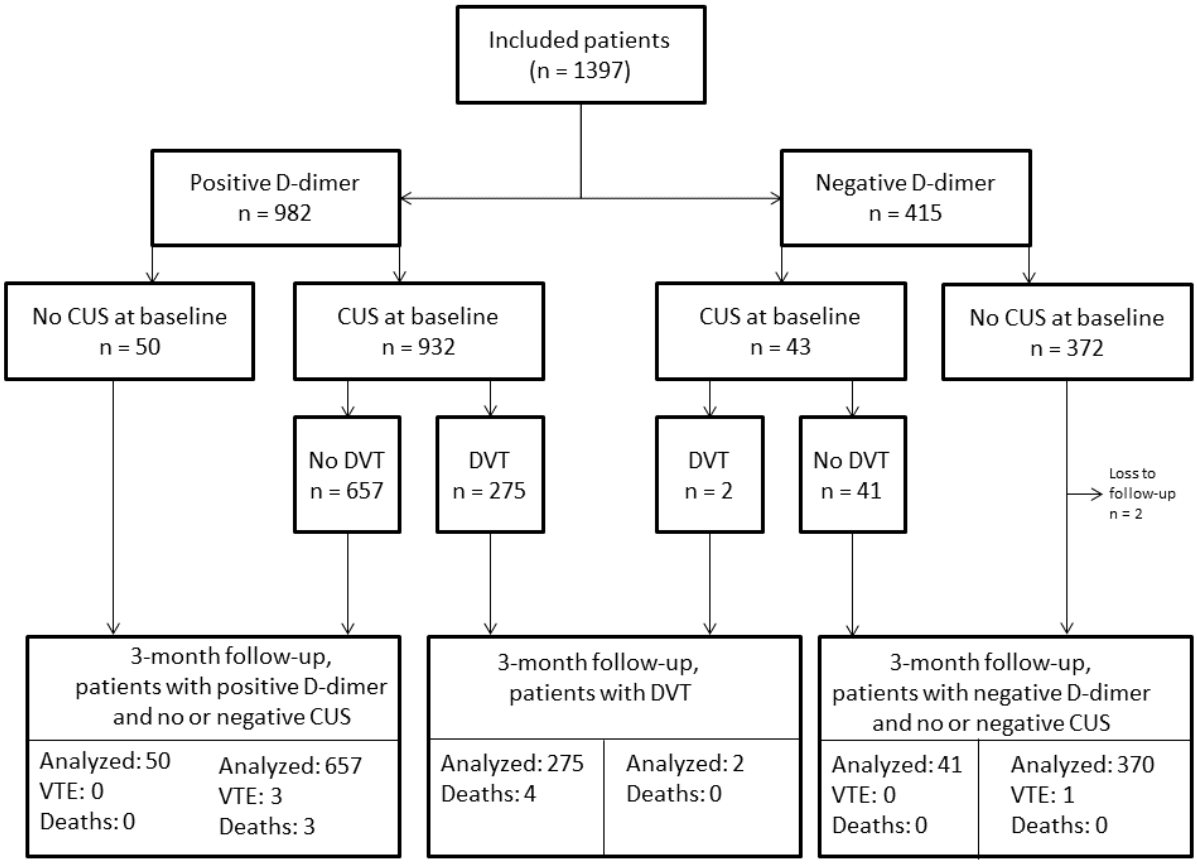
[1] Regular prescription or empiric anticoagulation for suspected DVT

[2] Associated with coagulopathy or other bleeding risk

5.3 Paper III

In Paper III, we found that ruling out DVT in patients with negative D-dimer or otherwise one negative whole-leg CUS is a safe strategy. Study flow and endpoints are depicted below (*Figure 11*). Six of 1113 patients who had negative D-dimer or normal whole-leg CUS were subsequently diagnosed with DVT within three months for a failure rate of 0.5% (95% CI 0.2-1.2). Three out of 415 patients with negative D-dimer were diagnosed with DVT within three months for a failure rate of 0.7% (95% CI 0.1-2.1). Three of 698 patients with normal whole-leg CUS were diagnosed with DVT within three months for a failure rate of 0.4% (95% CI 0.1-1.3). Additionally, there were three patients with normal CUS who had died within three months of follow-up in whom VTE could not be ruled out as cause of death due to lack of an autopsy. Moreover, there were two patients with negative D-dimer who were lost to follow-up, and where it consequently cannot be determined if the patients had developed VTE. Adding these five patients to a worst-case scenario yielded an overall failure rate of 1.0% (95% CI 0.5-1.8); 1.2% (95% CI 0.4-2.8) for the D-dimer group, and 0.9% (95% CI 0.3-1.9) for the whole-leg CUS group.

Figure 11 Study flow and endpoints



CUS was not performed in 50 of the 982 patients with positive D-dimer (5.1%), and performed in 43 of the 415 patients despite negative D-dimer (10.4%). In all cases where CUS was not performed despite positive D-dimer, review of patient files revealed that the suspicion of DVT was discarded after evaluation by the emergency department physician attending. Reasons for requesting CUS despite negative D-dimer are listed below (*Table 7*).

Table 7 Reasons for requesting CUS despite negative D-dimer[1]	Total n	No DVT n	DVT n
No recorded reason in patient files	14	14	0
Strong suspicion of DVT due to specific symptoms or signs	14	12	2
Evaluate extent of suspected thrombophlebitis to determine treatment	2	2	0
Evaluate other suspected diagnosis than DVT	7	7	0
High clinical pre-test probability	4	4	0
Lack of alternative diagnosis to DVT	2	2	0
Total, n	43	41	2

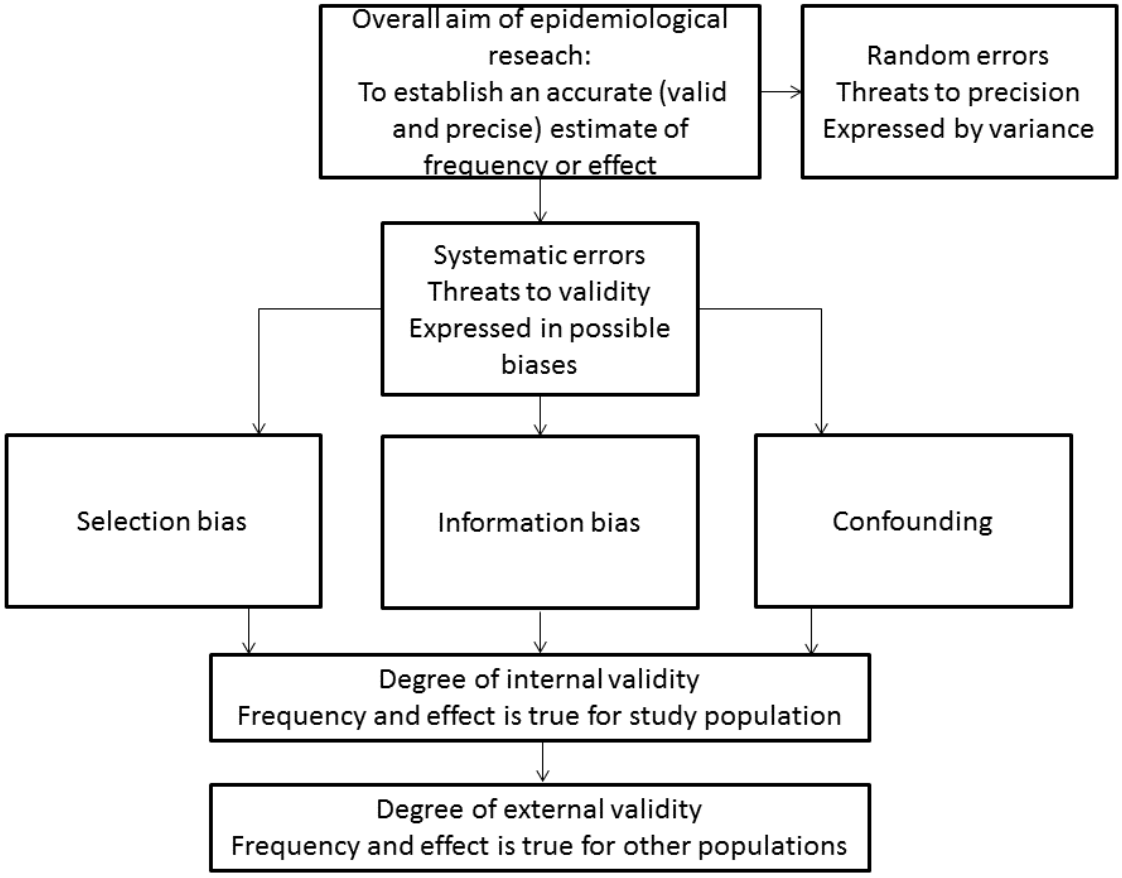
[1]As recorded in patient files

As such, 1304 of 1397 patients (93.3%, 95% CI 91.9-94.6) were managed according to protocol.

6. Methodological considerations

The overall aim of epidemiological research is to establish accurate estimates of frequency of a condition, or effect of an exposure (116). Both the degree of validity and precision in the estimates influence accuracy. A precise estimate reflects little random error. Random error is expressed by variance in the estimate and may be counteracted by including a larger sample size. An estimate with a high degree of internal validity reflects little systematic error. Systematic error are commonly known as biases, of which there exist several classifications. *Figure 12* outlines a simplified version of a common interpretation of the various threats to an accurate estimate of frequency or effect.

Figure 12 Aims for research and potential challenges to obtaining them



6.1. Study design

Epidemiological research consists of the two broad categories interventional and non-interventional trials, the latter commonly referred to as observational studies (116).

An interventional trial was the overall design of choice for the Ri-Schedule study. First, we investigated a new indication for a licensed drug and incorporated it into a scheduled workup strategy which had not previously been practiced at the hospital. As such, both components required an interventional design in order to be assessed. As for withholding CUS and treatment in patients with negative D-dimer or otherwise negative whole-leg CUS, an interventional, prospective design would more accurately depict outcomes than retrospective analysis.

The Ri-Schedule study was designed as a single-center, single-group, open label prospective management outcome trial. This entailed that all consecutive outpatients included at the study center were managed according to the same protocol provided they fulfilled all inclusion criteria and no exclusion criteria, and were followed up for a time period deemed necessary to detect potential adverse events. The main advantage of the study design was the prospective collection of data with well-established outcome measures and routines for detecting these, as well as few losses to follow-up. This likely increased the validity of our estimates, and reduced the risk of information or selection bias that could result from a retrospective design with incomplete, inaccurate or inconsistently measured data.

Randomized controlled trials are considered the gold standard for assessing the efficacy and safety of a treatment as they eliminate other systematic differences between the groups than the intervention (117, 118). However, they also crave resources and are time-demanding, they may not be feasible due to the ethical considerations of administering or withholding medication, and their external validity may be hampered due to their homogenous study population. In the Ri-Schedule study, this design would have entailed randomizing patients to either receiving rivaroxaban or LMWH, or rivaroxaban or placebo. Administering

placebo medication would be ethically questionable as the strategy entailed discharging patients and deferring workup, thereby subjecting them to a risk of VTE complications without observation and treatment. Consequently, this was not an appropriate alternative for our study.

As for randomizing patients to receiving either rivaroxaban or LMWH, the time and larger sample size required would have jeopardized our ability to conduct the study in a timely manner. An example of such a study design are non-inferiority trials, which are common when a new treatment may offer advantages over standard therapy, such as an improvement in patient satisfaction or convenience (119). With this study design, researchers aim to demonstrate that the new treatment is not unacceptably inferior to standard treatment, with efficacy and safety being common outcome measures. The efficacy of rivaroxaban for the treatment of VTE has already been demonstrated (95), and efficacy considerations in DVT treatment were beyond the aims of this study. As several studies have demonstrated the safety of prediagnostic LMWH, this aspect was not of primary concern for this study. However, randomizing patients to receiving either rivaroxaban or LMWH could have explored implications of any observed differences in bleeding rates.

For the endpoints of papers I and III, it was our opinion that we generally could assess our aims satisfactorily with a less time-demanding and resource-demanding study design than a randomized controlled trial. Prospective management trials are well established and common when assessing diagnostic tests or strategies in DVT management (74). As addressed in Chapter 1.5.4, the safety of existing management strategies has been extensively validated, and was not of primary concern for this trial. Furthermore, considering the low VTE rate found in these studies further improvements of safety would likely not be feasible.

However, particularly when addressing the efficiency of the various strategies described in Paper I, the study would have benefited from a design randomizing patients to management according to the different strategies.

Unfortunately, even if the design had been planned for in the original protocol of the trial, it would have required more patients than was feasible for the scope of the study. Therefore, we opted for what we considered the second best solution of a retrospective comparison for Paper I, and comparing the suggested strategy to existing data for the remainder of the objectives. Consequently, the findings from Paper I need prospective validation in order to definitively conclude on the optimal strategy.

Lastly, the external validity of our findings would have profited from seeking multicenter collaboration, preferably including international institutions. Conducting the study in different centers would have increased the number of participants, provided population heterogeneity, and included several D-dimer assays. By taking into account the different healthcare organization and various demographic factors that could affect our endpoints, we could have assessed the generalizability of our findings to other populations, centers and regions. In particular, we suspect this would have especially benefited the generalizability of our scheduled workup strategy. The strategy contained several subjective or organizational elements, i.e. evaluation of bleeding risk, as well as medical or logistical hindrances to scheduled workup. However, the efforts required from such an undertaking was outside the means and scope of the study, and must instead be examined in separate future trials.

6.2 Study population

The inclusion process introduced the possibility of selection bias. The implication of this bias is that any association between intervention and outcome differs between the study population and the source population of all eligible patients; i.e. the study population is not representative of the source population (116, 120). This may in turn compromise the internal validity of the study. Of the 2347 patients meeting the inclusion criteria and who were potentially eligible for the study, 694 patients (29.6%) were excluded and 1653 patients (70.4%) were included. The following

reasons were registered for why patients were excluded: lack of consent (212), time or resource constraints (152), unspecified (102), dementia diagnosis or other cognitive impairment (77), acute or chronic disease certainly or possibly affecting the ability to consent (65), language barriers (54), inability to consent because of developmental issues (15), study personnel not working at time of admission (15), and previous enrollment less than 90 days prior (2). In summary, patients were excluded either because of (a potential) inability to obtain consent for various reasons, or because of study logistics. It is possible that excluded patients had inherent differences that made them more or less susceptible to outcomes than the included study group. Notably, when study personnel did not have time to include all presenting patients, prioritizing which patients should be screened for inclusion could lead to selection bias (121). Study personnel may have prioritized the inclusion of patients deemed more likely to be eligible for scheduled workup, or patients with a lower risk of high D-dimer levels. By including consecutive outpatients we partially mitigated this issue. Indeed, in only 6.5% of screened cases did study personnel register an inability to include potentially eligible patients due to time restrictions. We believe that the remainder of eligible patients were mainly included consecutively. To support this finding is the fact that approximately 5% of the patients did not undergo CUS despite positive D-dimer because the emergency physician attending the patient regarded the risk of DVT low after renewed evaluation in the emergency department. The practice was protocol violation, and likely reflected that study personnel adhered to including all patients with a referral diagnosis of suspected DVT even when other diagnoses were more likely and of primary concern (i.e. suspected trauma or infection).

Moreover, we did not exclude the protocol violations. This applies to the patients who did not undergo CUS despite positive D-dimer (in whom there were no VTE events within three months of follow-up), as well as the patients who did undergo CUS despite negative D-dimer (in whom two DVT were detected during the baseline visit). The numbers were too few to affect our failure rates. However, the

protocol violations likely reflect clinical practice, as research suggests there is varying adherence to diagnostic algorithms.

Although the number of patients fulfilling each exclusion criterion separately was low, the 29.6% of excluded patients could affect the generalizability of our findings when extrapolating them to other emergency department outpatients. This must be taken into consideration when interpreting our findings.

6.2.1 Paper I and Paper III

The study population of these papers will be discussed together as Paper I was an interim analysis of 913 of the 1397 patients included in Paper III. Of the 1653 patients included in the study, 256 patients (15.5%) were excluded from the analyses of Paper III. They consisted of patients with missing D-dimer at inclusion (n=7), patients who had initiated anticoagulation therapy within three months of follow-up for other reasons than VTE (n=120), and patients on regular prescription of anticoagulation therapy (n=129). The latter group was only excluded from the analyses of Paper III after further discussion, but before analyses of the data.

The patients who had initiated anticoagulation therapy during follow-up for other reasons than VTE were already receiving adequate therapy and were thus unlikely to develop VTE (122). Hence, they were excluded so as to not deflate the three-month VTE rate. Importantly, 93 of the 120 patients were anticoagulated because of clinically suspected or verified isolated superficial thrombophlebitis. Eighty-eight of these were detected at the baseline visit. Additionally, 18 patients had received DVT prophylaxis during follow-up because of established risk factors (i.e. surgery), 5 patients due to atrial fibrillation, 1 patient due to myocardial infarction, and 3 for unspecified reasons.

We also excluded patients who were regularly prescribed anticoagulation therapy from the analyses of Paper III. As anticoagulation therapy may decrease D-dimer (123), the role of D-dimer in these patients warrants a separate study.

Consequently, we decided that our findings should not be extrapolated to include these patients.

6.2.2 Paper II

Of the 1653 patients included in the Ri-Schedule study, 624 (37.7%) were managed according to scheduled workup. We have elaborated on the rationale behind our relatively conservative criteria in Paper II. Briefly, stringent criteria were elected to maximize safety for patients later found to have DVT who were managed at home, and to minimize the risk of side effects from anticoagulation treatment in the estimated 80% later found not to have DVT (124). The conservative exclusion criteria may yield higher internal validity as they clearly demarcate which patients the strategy is applicable to and not. However, they may simultaneously diminish generalizability.

As such, the patients excluded from data analyses in Paper I and Paper III, as well as the patients not eligible for scheduled workup in Paper II, adversely impact the generalizability of our findings to an unselected emergency department outpatient population by excluding a substantial proportion of patients the findings could be extrapolated to.

6.3 Data acquisition

Measurement errors in information required for the estimates are known as information bias (116), and may derive from study personnel, participants, exposures and outcomes (120). Classification error depending on the values of other variables is termed differential classification, whereas classification error not depending on the values of other variables is called nondifferential misclassification (116).

6.3.1 Paper I

The estimates of failure rates, efficiency and diagnostic performance relied on D-dimer and CUS results, as well as age and Wells score for some of the strategies.

We measured D-dimer by the immuno-turbidometric method of STA®-Liatest® D-Di Plus**.** While 0.5 mg/L is commonly used as a threshold for D-dimer positivity, the levels for the different analyses vary considerably (72), and it has previously been called for different positivity thresholds according to assay (63). For some of the most commonly used methods there is high imprecision for values around 0.5 mg/L. Internal validation of the STA-Liatest at Oslo University Hospital found a coefficient of variation of 10-15% for levels around 0.5 mg/L (68). A widely used measure of relative standard deviation, the coefficient of variation expresses the precision and repeatability of an assay. These results thus suggest that D-dimer around the cut-off level varies considerably. We did not apply study-specific control measures to D-dimer, and there is the possibility that D-dimer results and therefore failure rates would have varied if we had obtained repeated tests in the same individual. However, the failure rate of stand-alone D-dimer was in the same range as seen in similar studies using clinical follow-up as outcome (125-128), and the diagnostic properties were similar to other high-sensitivity assays (69). Moreover, the fact that we withheld CUS in most patients with negative D-dimer, none of whom developed clinically significant VTE within three months, could suggest that variability of D-dimer at levels as low as 0.5 mg/L is less clinically significant. This could be supported by literature suggesting that increasing thrombus burden has been shown to be associated with higher D-dimer levels (129, 130). Ideally, several D-dimer assays should have been examined to assess generalizability. However, this was not logistically feasible for our study.

Documentation of the Wells score was complete for all patients. The Wells score is subject to possible bias, with both objective (for instance active cancer) and subjective elements (for instance whether alternative diagnoses are more likely). We do not believe that the objective elements of the score constituted important

sources of information bias as it was documented in all patients by nurses and physicians familiar with its use, documented in the electronic case report form as it was scored rather than retrospectively, and the data were later validated. Additionally, study personnel had access to the patient files for details regarding individual histories. This could reduce the risk of recall bias, for instance in the case of whether the patient had previously been diagnosed with VTE. In some instances, D-dimer results were available before the score had been obtained, in which case scoring could be prone to bias as it might influence the assessor's interpretation of C-PTP (131). Although study personnel were instructed to calculate the score before D-dimer was obtained to avoid this issue, it is plausible that D-dimer results occasionally influenced scoring. This could for instance occur when D-dimer had been obtained by others before study personnel had included the patient. As such, blinding of study personnel to D-dimer results could theoretically have resulted in a different stratification of patients into low, moderate, and high-probability subgroups. This bias could have influenced our comparison of strategies both in favor of stand-alone D-dimer, and the standard strategy incorporating Wells score. Blinding was unfortunately not feasible as study personnel required these results when deciding the next step. Multicenter collaboration with multiple assessors of Wells score could have counteracted this issue. However, as previously addressed this was not attainable, and iterates the necessity of validation studies when comparing strategies.

6.3.2 Paper II

Bleeding events and major complications were consecutively documented within the relatively short interval of 48 hours by study personnel familiar with their definitions. Furthermore, by definition these bleeding events often required hospital interventions that were recorded in patient files, thus providing study personnel with easily accessible information regarding the events. We therefore consider it unlikely that these events went unreported. We opted for follow-up at

48 hours to be a pragmatic interval based on the pharmacological properties of rivaroxaban. Nonetheless, it could be argued that 48 hours was too short of an interval to detect all bleeding events. The half-life of rivaroxaban is 4-9 hours, and up to 12 hours in elderly patients (111). Consequently, a conservative estimate would put 6.25% of the maximum concentration remaining in the body at 48 hours. While this concentration likely does not represent a major contribution to bleeding at this time, occult bleedings by definition may go well beyond 48 hours before being detected. As discussed in Paper II, this was the case for one study patient who experienced major bleeding with melena and was hospitalized 70 hours after taking rivaroxaban. While the bleeding was likely exacerbated rather than triggered by the drug, the case exemplifies why the follow-up interval could have profited from being prolonged. It is possible that some bleeding events might have gone undetected if they occurred after the end of follow-up. However, we consider this unlikely as endpoints were verified for accuracy throughout the study. As a single-center study, we had access to fairly comprehensive information regarding endpoints - in this case, whether patients were re-assessed.

The minor bleeding events reported in our study could be subject to observer/interviewer bias, for instance in how the patient was questioned or interpreted for registering events. Another pitfall could be reporting bias or participant expectation bias, as patients were well informed of potential complications, and may have had a lower threshold for reporting these.

We documented all bleeding events. Many of these were nuisance bleedings likely to have gone unreported in a side effect registry, or during regular follow-up with scheduled visits outside of a study setting. Additionally, it is likely that many of the lower extremity hematomas found during the CUS examination were present before rivaroxaban was administered, as the hematoma likely was misinterpreted as DVT by referring instances (*Figure 10*). However, as rivaroxaban was administered before the patient underwent CUS, the sequence of events cannot be established. Based on the symptoms reported by the patients, it was our impression

that there was a low threshold for reporting and registering bleeding events. However, considering that the literature suggests minor bleedings may be underreported in large clinical data trials (113), we cannot be sure whether the observed proportion of 10.1% is higher than should be expected. Nonetheless, it does serve as a reminder that for long-term use the drug may be affiliated with nuisance bleedings possibly inconveniencing patients despite the low risk of severe bleeding events.

6.3.3 Paper III

In addition to the D-dimer considerations elaborated on in Paper I being similarly applicable to this paper, some aspects of failure rate of whole-leg CUS should be addressed. The failure rate of the strategy depended on CUS results. Information bias could occur if the patients were misclassified as having or not having DVT at baseline or during follow-up. Counteractive measures in our study could have been assessing repeatability either by systematically repeating CUS, examination by two independent observers, or applying reference imaging. A recent systematic review and meta-analysis examined the accuracy of diagnostic tests for DVT, with whole-leg CUS being one of the components assessed. By using venography as reference standard in all of the studies analyzed, the authors found a pooled estimate for sensitivity of 94.0% (95% CI 91.3-95.9), for specificity of 97.3% (95% CI 94.8-98.6), a low rate of <5% of false positive and false negative examinations, as well as few inconclusive test results (43). We believe this aspect did not constitute a major issue due to the favorable diagnostic properties of CUS. Moreover, as previously addressed three-month VTE rates after negative imaging is a common practice for assessing current diagnostic management strategies (74). However, it is a precaution to acknowledge when reporting endpoints in our study.

There is a risk that the three-month VTE rate was underreported by relying on self-reporting rather than CUS at the end of follow-up. However, CUS for all

patients could have resulted in overdiagnosis by detecting and treating asymptomatic DVT with uncertain benefit, a topic insufficiently researched (132).

6.3.4 Preventive steps against bias in the Ri-Schedule study

All events classified as primary endpoints in papers II and III were adjudicated by an independent committee, thus mitigating observer bias. The one failure rate in Paper I was not adjudicated as it was an interim analysis, and how the one event was adjudicated would not have changed the conclusion. Moreover, experienced radiologists both conducted CUS as well as interpreted endpoints. The conclusions of previous baseline and follow-up CUS were not known to the adjudicators.

Blinding of the adjudicators was not possible for endpoints pertaining to bleeding events or cause of death, as these required information regarding the interventions and outcomes.

Other preventive steps included following explicit protocols for data collection, handling, and monitoring, study personnel familiar with the assessment methods, and clear, evidence and clinically practiced-based definitions of exposures and outcomes with prospective data collection in a standardized electronic case report form.

6.4 Statistical considerations

6.4.1 Choice of endpoints

The primary objective of all papers was to assess an association between an intervention and an outcome.

Efficacy is the commonly used primary endpoint in the non-inferiority trials comparing DOACs with LMWH and VKA (94-97). For Paper II, we chose safety as the primary endpoint because the efficacy of rivaroxaban for the treatment of DVT is well established as non-inferior to standard treatment, and was therefore of less concern as the patients in our study received therapeutic doses of rivaroxaban. Secondly, based on the previously reported prevalence in our study population we

expected that 80% of patients would later be found not to have DVT. As such, the safety aspect of anticoagulating healthy patients was of primary concern.

As for papers I and III, acceptable post-test probability thresholds are the benchmarks when evaluating the safety of new diagnostic tests or management strategies for VTE. As previously addressed, diagnostic strategies for VTE are currently validated in management studies through the observed VTE rate within three months in untreated patients (74). This is traditionally set at a false negative rate of 2%, and is based on the three-month VTE rate after a negative venography. As such, a post-test probability of ≤2% for a diagnostic test or algorithm is considered safe to rule out DVT.

6.4.2 Sample size calculation

The estimated sample size required to satisfactorily assess our objectives was predefined for papers II and III. They were both based on recruiting the number of patients required to demonstrate that the endpoint did or did not occur more frequently than our predefined acceptable safety thresholds. We used a power of 80% (β=20%) and a significance level of 5% for both papers, yielding an estimated sample size of 620 patients in Paper II and 500 patients in Paper III. Both these sample size preferences were ultimately met, with more patients included than predefined for Paper III as it took longer to include the 620 required patients for Paper II.

6.5 Ethical considerations

We undertook several measures to ensure quality control, as elaborated on in Chapter 4.5.

However, given that patients and healthcare providers are not equal participants in a study, there is the possibility that study participants may have felt obliged to participate. To mitigate this, we aimed to provide as neutral and

complete information as possible, including the possibility to decline or withdraw consent at a later point.

By administering rivaroxaban, we exposed patients to potentially harmful side effects. However, patients who were subsequently diagnosed with DVT had an earlier treatment start than they otherwise would have had, and empiric anticoagulation is already often given to patients with suspected DVT. We aimed to minimize the risk by thorough information regarding how and when to contact the Emergency Department in case of side effects, having a relatively low threshold for terminating the study if deemed unsafe, and applying stringent criteria for management with rivaroxaban.

Lastly, patients may experience positive effects by participating in a clinical trial. Several patients expressed the feeling of reassurance from the additional follow-up of the study, and from the low threshold for re-contacting the Emergency Department.

We considered that these precautions and the potential benefits from the study supported it being conducted.

7. Discussion of main findings

So far the historical context, current practices, recent advances, as well as some of the knowledge gaps and areas for improvement in the workup of DVT have been discussed. This chapter summarizes the contributions of our findings and their potential impact on clinical practice, as well as their limitations and areas to target for future research.

7.1 Paper I and Paper III

7.1.1 Our findings compared to the existing diagnostic algorithm

In Paper I, we found that D-dimer as a stand-alone test was comparably safe to existing diagnostic algorithms. Moreover, the strategy required fewer CUS examinations than D-dimer combined with the original or modified Wells scores (*Table 4*). In Paper III, we demonstrated the safety of a new diagnostic management strategy incorporating a single whole-leg CUS in patients with positive D-dimer and withholding imaging and anticoagulation in patients with negative D-dimer.

To our knowledge, our study is the first large prospective study to withhold imaging and anticoagulation treatment in patients with negative D-dimer regardless of C-PTP. Stand-alone D-dimer for ruling out DVT is generally perceived to be unsafe (36, 133), and there is extensive literature supporting this view (69, 134, 135). For many of these studies, there was insufficient information regarding the proportion of proximal versus distal DVT. Additionally, few studies used clinical follow-up in a prospective management design similar to ours. A strength of this design is assessing the clinical impact of withholding diagnostics and therapy, i.e. whether the DVT would persist, progress or embolize if untreated. Instead, most studies assessed D-dimer against reference imaging at inclusion either for all patients, or for perceived high-risk patients regardless of D-dimer. Rathbun et al found three-month VTE rates of 0.0% (95% CI 0-4.4) for suspected first DVT and 0.75% (95% CI 0.02-4.1) for suspected recurrent DVT when ruling out the diagnosis on the basis of negative stand-alone D-dimer in 81 and 134 patients, respectively (126, 127).

Perrier et al applied a similar design, but imaged patients with negative D-dimer as a precautionary measure (128).

As such, the main implication of our findings is that they challenge the currently held view that stand-alone D-dimer to rule out suspected DVT is unsafe. As discussed in papers I, III and Chapter 6, our study has several limitations, such as being conducted in a single center and applying one D-dimer assay. Even though we expect it can be extrapolated to other intermediate risk outpatient populations and high-sensitivity assays, validation studies are needed to examine this before the approach may be considered for general clinical practice. Nonetheless, the favorable safety profile of stand-alone D-dimer in our study may reflect certain contemporary developments. As pointed out by several others when discussing the management of suspected DVT (136, 137), prevalence and failure rate are related. The negative predictive value of a test is inversely related to prevalence. This implies that negative predictive value increases as prevalence decreases. The comparatively low DVT prevalence seen in recent studies may be associated with increased awareness of DVT and a lower threshold for workup (136). A negative D-dimer will have a higher value in these settings, particularly as high-sensitivity assays are currently recommended by guidelines. Our findings may suggest that the added precautionary measure of C-PTP assessment may be unnecessary in these overall low and intermediate risk populations. Instead, they may primarily serve to complicate the algorithm, and possibly result in more unnecessary CUS.

The study does not solve the issues inherent to this and other current diagnostic management strategies: they may not be suitable for certain high-prevalence or anticoagulated populations due to the risk of false negative tests. Likewise, they may not be appropriate for the several situations and conditions in which D-dimer is expected to be elevated with subsequent risk of false positive tests. Examples of the latter would be patients with cancer (63), inpatient or pregnant populations (138, 139). These groups are also at a higher risk of

developing DVT. Consequently, they may benefit from separate management strategies entirely.

As for selecting a CUS modality, whole-leg CUS was the preferable option for our study as we attempted to simplify the algorithm and make it applicable to the whole population regardless of C-PTP. We acknowledge that this may not be suitable or desirable for all centers. As previously mentioned, both proximal and whole-leg CUS are accepted imaging strategies. Choice of strategy is not widely consensus-based, and the practice varies according to individual preference, availability and resources, as well as the organization of imaging in individual centers. While whole-leg CUS typically requires a single examination, proximal CUS often entails repeat examination after one week, treating only DVT extending to the proximal veins by the second examination. Randomized studies comparing the two strategies found similar three-month VTE risks for whole-leg and repeat proximal CUS (77, 79), which questions the necessity to systematically detect and treat all distal DVT. A recent meta-analysis found no significant differences in the three-month VTE rates of single proximal CUS, repeat proximal CUS, and single whole-leg CUS, respectively (44). However, the DVT prevalence was lower in studies assessing single proximal CUS, which likely reflects the selection of low-risk patients to undergo a limited examination. Consequently, the populations are likely to not be comparable. As few studies have conducted direct comparisons between the strategies, recommendations mainly derive from the individual safety profile of each strategy, as well as expert opinion (44).

These uncertainties are reflected in the lack of unified recommendations by guidelines and consensus statements. The 2018 American Society of Hematology guidelines do not state their preference for one modality (74), whereas the 2012 American College of Chest Physicians guidelines advised a single proximal CUS for patients considered to have a low C-PTP, and repeat proximal or whole-leg CUS for the remainder (36). The 2020 National Institute for Health and Care Excellence guidelines suggests single or repeat proximal CUS for patients perceived to be

unlikely and likely to have DVT, respectively (75). The 2018 European Society of Cardiology joint consensus statement and others suggest whole-leg CUS over proximal CUS (76, 140).

As elaborated on in Paper III, the main advantage of conducting a single, whole-leg CUS is that the workup can be completed in one visit regardless of C-PTP. It does not require the resources of an additional visit whilst also being less time-consuming for the patient. Proximal CUS necessitates repeat testing unless the perceived C-PTP is low (36, 74). On the other hand, one proximal CUS examination takes less time and requires less skill to perform than whole-leg CUS (141, 142).

An additional advantage of whole-leg CUS is the ability to identify alternative diagnoses in up to 42% of patients (143). However, by detecting possibly insignificant distal DVT, whole-leg CUS can simultaneously result in overdiagnosis. The European Society of Cardiology, which states a preference for whole-leg CUS, suggests surveilling or treating distal DVT with a lower dose or shorter duration of anticoagulation therapy to remedy the potential for overtreatment (76).

The detection and treatment of distal DVT remain disputed (4). Guidelines suggest stratifying patients according to symptoms and risk factors for proximal extension of the thrombus (76, 90). As such, they suggest anticoagulation for patients with severe symptoms or risk factors for proximal extension, and serial CUS without anticoagulation for the remainder. However, the Grade 2C level of recommendations (weak, low-quality evidence) underscores the uncertainty regarding the optimal management of these patients. The CACTUS trial, currently the only randomized placebo-controlled trial conducted, compared 6-week LMWH therapy with placebo in patients with distal DVT who were deemed to have a low risk of recurrent VTE (144). There was no significant difference between the groups regarding progression of the DVT, but there was a significantly higher rate of clinically relevant bleeding in the group receiving anticoagulation therapy compared to placebo (risk difference 4% vs. 0%; $p = 0.0255$). However, only half of the estimated sample size was ultimately included, and the findings must be

interpreted with caution. Future advances in research clarifying which distal DVT should be treated will likely guide the selection of preferred CUS modality.

7.1.2 Our findings compared to age-adjusted and C-PTP-adjusted D-dimer strategies

As addressed in Chapter 1.5.4, a recent individual patient data meta-analysis of four studies found that the age-adjusted and C-PTP-adjusted D-dimer strategies were similarly useful (48). Both strategies had high sensitivity and negative predictive values, and necessitated a similar number of CUS examinations. Furthermore, they both had several advantages over using a fixed D-dimer cut-off: age-adjusted D-dimer increased specificity by 9.5%, and C-PTP-adjusted D-dimer increased specificity by 12.0%. Sensitivity and negative predictive value remained comparably high for all three thresholds. There was an 8.2% and 10.2% absolute decrease in required CUS examinations for age- and C-PTP-adjusted D-dimer, respectively.

In Paper I, we similarly found that age-adjusted D-dimer with the three-level Wells score necessitated 8.0% fewer CUS as compared to fixed D-dimer while increasing specificity by approximately 10% (*Table 4*). However, this came at the cost of a slightly higher three-month VTE rate. The three-month VTE rate was 0.4% (95% CI 0.1-2.1) for fixed D-dimer with the three-level Wells score, and 1.5% (95% CI 0.6-3.4) for age-adjusted D-dimer with the three-level Wells score. Stand-alone D-dimer required 5.1% more CUS compared to age-adjusted D-dimer with the three-level Wells score. However, the three-month VTE rate of the stand-alone D-dimer strategy was lower; 0.3% (95% CI 0.1-1.9). In Paper III, a retrospective comparison demonstrated that the age-adjusted and C-PTP-adjusted strategies with the three-level Wells score both necessitated approximately 4% fewer CUS than our strategy, albeit at a slightly higher three-month VTE rate. The 30-day case fatality rate of first DVT has been reported to be around 5.5-11% (22, 145). Therefore, it could be argued that a lower failure rate may be preferable when the number of required CUS examinations are similar.

Both the age-adjusted D-dimer as a stand-alone test, as well as combined with the two-level Wells score seem less clinically relevant. Age-adjusted D-dimer as a stand-alone test may have an unacceptably high failure rate, and it has primarily been assessed using the three-level Wells score.

An advantage with our strategy is that the same approach applies to the whole population, unlike the age-adjusted and C-PTP-adjusted strategies for whom only perceived low or moderate-risk patients are eligible (146). Additionally, the studies included in the above-mentioned meta-analysis all excluded patients with previous VTE. As such, the utility of the strategies in this study population, comprising 15% of patients in our material, cannot be ascertained.

Other advantages with our strategy are that it is simple, objective, and may easily be standardized. It is less dependent on physician experience than strategies incorporating clinical prediction rules. This may be advantageous in a clinical setting such as emergency departments, where there may be a high turnover of relatively inexperienced staff.

Moreover, it may counteract some of the challenges associated with current clinical prediction rules as discussed in Paper III. These include the subjective elements of some scores (61, 147), not widely validated interrater reliability (36), and incorrect use. The latter may result from knowledge of D-dimer results prior to scoring, which may in turn influence how physicians perceive the risk of DVT (131). Several studies from clinical practice show lack of or varying adherence to clinical prediction rules (55, 148-151). For instance, the GARFIELD-VTE registry reported a less than 5% use of clinical prediction rules before the patient underwent imaging (5, 152). A recent qualitative study exploring physicians' test choices in the management of patients with suspected PE identified several barriers to adherence to guidelines. Among these were anxiety with the potential severity of PE, time and knowledge barriers, as well as issues regarding the relative complexity of the Wells score (153). Management of patients with suspected DVT would likely encounter

similar issues. As such, the simplicity and objectivity of our strategy may benefit applicability.

However, it would not bypass challenges to adherence entirely. As such, further studies are required to assess the generalizability and applicability of our strategy. As demonstrated in *Table 7*, 43 patients (10.4%) underwent CUS despite negative D-dimer. For some of these patients, CUS was requested to examine an alternative diagnosis, or to evaluate the extent of suspected thrombophlebitis to determine whether anticoagulation therapy was warranted. However, for at least 14 of 43 patients, attending physicians had a strong suspicion of DVT, thus overruling negative D-dimer and protocol to request CUS. While clinical practice warrants occasional deviations from guidelines or best practice for optimal management of patients with any condition, our protocol deviations may also serve as a reminder that there are strong incentives to perform diagnostic testing.

The age-adjusted or C-PTP-adjusted D-dimer strategies may be better suited than our strategy in certain populations. In outpatient populations with a markedly higher median age, the age-adjusted D-dimer may rule out DVT without CUS in a larger proportion of patients. The C-PTP-adjusted D-dimer may be more useful for populations with a consistently high proportion of patients scored in the low C-PTP group. By incorporating a clinical prediction rule, they also include an additional precautionary measure in high-risk patients. Lastly, physicians may be more inclined to refrain from CUS despite positive D-dimer if DVT suspicion is dismissed after evaluation, and further backed up by a low C-PTP score. In these cases, C-PTP assessment could theoretically reduce unnecessary CUS examinations.

7.2 Paper II

In this paper, we demonstrated that a therapeutic dose of empiric rivaroxaban is safe to administer to outpatients with suspected DVT. Moreover, there were no complications from delaying CUS for up to 24 hours while patients were taking rivaroxaban. Our findings were in line with previous studies examining deferred

workup with empiric anticoagulation (100-106). These studies assessed outpatients, hospitalized and primary care patients in both observational and interventional designs, covered unfractionated heparin and various LMWH, and deferred imaging for up to 72 hours. VTE prevalence ranged between 13.1-34.4%. Chaer et al restricted their 24-hour access to CUS by allowing off-hour CUS only in patients who had a moderate or high risk of DVT and a contraindication to LMWH. Low-risk patients were discharged awaiting deferred CUS, whereas the 28 non-low risk patients without contraindications received a single dose of LMWH awaiting deferred CUS. Overall, CUS requests were reduced by 64% the year after implementation without negatively affecting patient care, and the proportion of positive studies increased from 6.7 to 20%. Discharge of patients had similar contraindications to our strategy, being applicable to patients without concurrent conditions necessitating medical attention, (risk of) bleeding, or inconvenience with discharge. Imberti et al administered a single dose of LMWH to 530 primary care patients before subsequent CUS referral within 18 hours, lest they require urgent hospital care due to PE or other conditions, or had contraindications to LMWH. There were no major bleeding episodes or PE in these patients. Siragusa et al demonstrated the safety of an approach deferring imaging with empiric LMWH for up to 72 hours in patients with suspected VTE. In this prospective study, no major bleedings occurred, whereas one patient later diagnosed with proximal DVT had worsening of their symptoms before diagnosis (0.2%; upper 95% CI 0.6%). Langan et al found an 89% reduction in off-hour imaging examinations without complications from anticoagulation therapy or deferred CUS in their prospective study discharging or admitting patients awaiting CUS. Anderson et al similarly did not find any major complications from anticoagulation or deferred CUS in their 344 patients presenting at the Emergency Department with suspected DVT. Bauld et al discharged 128 patients with suspected VTE from the Emergency Department with a therapeutic dose of dalteparin for next-day imaging without compromised patient care. While these studies differed in sample size and protocol for management, they all

stemmed from a need to optimize resource use and to a greater extent schedule workup of these patients rather than performing urgent around-the-clock workup. As such, there are two main clinical contributions of this article. For one, it proposes a strategy that may improve resource use by channeling a substantial proportion of patients from workup during peak hours or off-hours to generally more accommodating time periods. For patients, scheduled workup may reduce waiting time and increase predictability. Additionally, it may aid primary care and emergency department physicians in determining which patients do not require urgent referral or admission. Various benefits of deferring CUS until hospital on-hours have been noted in the abovementioned studies, as elaborated on in Paper II. Briefly, it may contribute to cost savings, more inpatient laboratory time, and improved job satisfaction for ultrasonographers (101, 104, 154).

Secondly, the strategy introduces an alternative anticoagulant for empiric management of these patients which has the benefits of oral administration and, with few exceptions, universal dosing. As only 56% of patients that had received empiric LMWH before referral to our center had received the minimum therapeutic weight-adjusted dosage, standardized dosing might allow for more streamlined management.

In Paper II and Chapter 6, we discussed the implications and limitations of our study, namely balancing the considerations of generalizability to safety. Less conservative criteria would have resulted in more patients being eligible for the strategy, which in turn would likely have increased generalizability and applicability. However, it would have put patients without DVT at a small risk of adverse events from rivaroxaban. Patients with DVT would risk deterioration while they were at home awaiting CUS. We found that an additional 14.8% would have been eligible for scheduled workup had they not already received empiric LMWH in primary care, increasing the proportion of eligible patients to 52.5%. However, for future implementation we would advise that the same general contraindications to

rivaroxaban or any anticoagulant be applied in a scheduled workup strategy rather than our pre-set thresholds for creatinine, hemoglobin and thrombocytopenia. Another consideration for feasibility is that the strategy could have benefited from being divided into the two components of contraindications to rivaroxaban or general anticoagulation therapy, and contraindications to at-home management or delayed CUS. By including the patients who could have received rivaroxaban but could not have been discharged, we would have assessed the safety of the drug in a larger proportion of the outpatient population. However, the strategy was designed as an integrated pathway to assess whether patients could be managed at home until a scheduled CUS appointment. In the future, such a strategy could shift a greater proportion of referrals from urgent to scheduled during hospital on-hours. If integrated with the stand-alone D-dimer approach (*Figure 8*), it could additionally reduce the number of required workups altogether.

The study does not clarify which patients would benefit from receiving or not receiving empiric anticoagulation therapy and to our knowledge, no studies have been conducted on this topic. In line with the suggestions of guidelines and considering that our findings did not yield major adverse events, it seems plausible to offer empiric anticoagulation therapy if workup is delayed or deferred to reduce the potential risk of VTE complications. As the results from the several studies on LMWH, the retrospective chart review of DOACs and our study suggest, this indeed seems to be a safe practice.

8. Conclusions and future perspectives

In this thesis, we have demonstrated the safety and feasibility of a diagnostic pathway for managing outpatients with suspected first or recurrent DVT. Our findings support the safety of a strategy deferring CUS with empiric rivaroxaban, withholding anticoagulation and CUS in patients with negative D-dimer regardless of C-PTP, and excluding DVT with a single negative whole-leg CUS regardless of C-PTP. Additionally, our strategy necessitated fewer CUS examinations than the current diagnostic algorithm incorporating Wells score without compromising safety. By integrating the findings from our three papers, we have suggested a management strategy that may simplify DVT workup while allowing it to be conducted during more feasible times for patients and referral centers. We believe our strategy may be a valuable and clinically relevant contribution to the management of patients with suspected DVT. We acknowledge that some aspects of our study may compromise the generalizability and applicability of our findings, and that validation studies are required to explore this further.

There are several challenges for the future workup of DVT that were beyond the scope of this thesis. Our scheduled workup strategy needs validation to determine its applicability to a broader outpatient population, and whether other DOACs can be applied. Additionally, the strategy could be extended to primary care or PE/VTE populations, as assessed by some of the other studies involving LMWH in deferred imaging approaches (102, 103, 106).

The development of diagnostic algorithms undoubtedly allowed for major progress in the workup of DVT by reducing the proportion of required imaging studies by approximately 30% (62). However, the validity and utility of the current workup strategy may be compromised by several recent developments and observations. These include the development of the more conservative two-level Wells score, which is suggested or preferred by several guidelines (74-76), the discussed real-life deviations from diagnostic algorithms seen in observational studies, as well as the low DVT prevalence reported in recent prospective outcome

studies (136). Recent research efforts employing alternative D-dimer thresholds or simplified algorithms have similarly to our study shown promising results with regards to improving specificity whilst retaining safety. Large prospective head-to-head trials comparing the existing diagnostic algorithm to alternative strategies would be a sensible next step. To mitigate the logistical challenges of such an undertaking, as well as strengthening the internal and external validity of the findings, existing and future collaborative efforts should be developed and strengthened (155). Moreover, increased awareness with regards to the utility of the strategies should be explored. As pointed out by Reilly et al (156), despite major clinical prediction rules having displayed promising reproducibility in validation studies, they have mostly not undergone formal impact analyses to assess how they affect clinical practice. Such studies are warranted and should originate from the needs of clinicians.

As previously mentioned, the generally accepted threshold for safety is set as low as the three-month VTE rate after negative venography of 1.3% (95% CI 0.2%–4.4). Consequently, it may not be feasible to increase specificity substantially without impacting the three-month VTE rate, as elaborated on in the discussion of diagnostic properties. Currently, high sensitivity has been given greater priority when managing VTE patients (137). Although our strategy and those incorporating Wells score or alternative D-dimer cut-offs differed in their advantages of safety versus utility when we compared them, the differences were not substantial. As such, we may be reaching the limits of the diagnostic yield with current methods. The future advances of DVT workup and treatment will likely see increased tailoring of management based on individual risk profile for DVT, recurrence, and complications. The use of big data and machine-learning techniques in VTE diagnostics and management is a step in this direction, where more accurate prediction models for risk is one of the components being investigated (157). In the future, these tools could also incorporate other items such as novel biomarkers, bleeding risk assessments, as well as patient preference evaluations. To further the

advancements of these techniques, venous thrombosis communities should continue developing and expanding high-quality VTE registries, biobanks, and well-designed clinical trials. Additionally, the communities should contribute to selecting appropriate endpoints (158). As alluded to throughout the thesis when discussing controversies surrounding empiric anticoagulation therapy, deferred workup, and the diagnostic evaluations of patients with suspected DVT, any decision in disease management is ultimately a value-based judgement of risk versus benefit. This aspect could profit from consensus-based statements when determining the future of VTE management.

9. References

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10. Papers I-III

I

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ORIGINAL ARTICLE

Safety of D-dimer testing as a stand-alone test for the exclusion of deep vein thrombosis as compared with other strategies

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Essentials

- The aim of deep vein thrombosis (DVT) diagnostic work-up is to maximize both safety and efficiency.
- We explored whether D-dimer is safe and efficient as a stand-alone test to exclude DVT.
- Our findings suggest it is a safe, efficient and simplified diagnostic strategy.
- The safety of age-adjusted D-dimer as a stand-alone test requires further investigation.

Summary. *Background:* Several strategies for safely excluding deep vein thrombosis (DVT) while limiting the number of imaging tests have been explored. *Objectives:* To determine whether D-dimer testing could safely and efficiently exclude DVT as a stand-alone test, and evaluate its performance as compared with strategies that incorporate the Wells score and age-adjusted D-dimer. *Patients/Methods:* We included consecutive outpatients referred with suspected DVT to the Emergency Department at Østfold Hospital, Norway. STA-Liatest D-Di PLUS D-dimer was analyzed for all patients. Patients with a D-dimer level of ≥ 0.5 μg mL^{-1} were referred for compression ultrasonography (CUS). In patients with a D-dimer level of < 0.5 μg mL^{-1}, no further testing was performed and anticoagulation was withheld. Patients were followed for 3 months for venous thromboembolism (VTE). *Results:* Of the 913 included patients, 298 (33%) had a negative D-dimer result. One hundred and seventy-three patients (18.9%) were diagnosed with DVT at baseline. One of 298 patients had DVT despite having a negative D-dimer result, resulting in a failure rate of 0.3% (95% confidence interval [CI] 0.1–1.9%). Adding the modified Wells score would have yielded a failure rate of 0.0% (95% CI 0.0–1.8%) while necessitating 87 more CUS examinations. Age-adjusted D-dimer as a stand-alone test would have necessitated 80 fewer CUS examinations than fixed D-dimer as a stand-alone test, at the cost of a failure rate of 1.6% (95% CI 0.7–3.4%). *Conclusions:* This outcome study shows that a negative high-sensitivity D-dimer result safely excludes DVT in an outpatient population, and necessitates fewer CUS than if used in combination with Wells score. The safety of stand-alone age-adjusted D-dimer needs further assessment in prospective outcome studies.

Keywords: D-dimer; deep vein thrombosis; diagnosis; sensitivity and specificity; venous thromboembolism.

Introduction

Clinical pretest probability evaluation and D-dimer testing have long been the standard initial steps of deep vein thrombosis (DVT) diagnostic work-up [1]. Assessing pretest probability with the support of clinical prediction rules is recommended to guide further testing and to minimize the risk of false-negative D-dimer results among patients with a high pretest probability of having DVT. The most extensively used and validated clinical prediction rule is the Wells score [2–7]. Originally consisting of

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nine items, it utilizes elements from patient medical history and physical examination to add or deduct points in order to produce a total score of DVT likelihood [2,3], whereby patients are stratified into low-risk (≤ 0 points), moderate-risk (1–2 points) and high-risk (≥ 3 points) groups (Table 1). High-risk patients are referred for diagnostic compression ultrasonography (CUS) without D-dimer testing, whereas the remaining patients are referred only in the case of a positive D-dimer result. In a later, modified version of the Wells score, another clinical item was added, yielding 1 point for previously documented DVT [4], and dichotomizing groups into 'DVT unlikely' (< 2 points) and 'DVT likely' (≥ 2 points), whereby the 'DVT likely' group is referred for CUS without D-dimer testing (Table 2).

Despite its extensive validation and wide use in the current diagnostic work-up of DVT, the Wells score has a few limitations. First, it introduces subjectivity into the judgement of whether a competing diagnosis is more likely than DVT [8], and it may be less precise in certain subgroups, such as in older or primary-care patients [5,9]. Interobserver variability has not been extensively evaluated [1]. Moreover, D-dimer testing often forms part of a standard package of laboratory tests performed in patients with suspected DVT, and the results may be analyzed before the Wells score in clinically well and low-triaged patients with suspected DVT in a busy setting in the emergency department. The lack of adherence to clinical prediction rules in daily practice has been addressed in other studies [10,11]. Finally, the differing prevalences of DVT in various studied populations [4,12–14], perhaps owing to the lower diagnostic threshold seen in recent times [15], may further affect the utility of clinical prediction rules, such as the Wells score.

Table 1 The Wells clinical model for predicting the pretest probability of deep vein thrombosis

Clinical feature	Score
Active cancer (treatment ongoing or within t he previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden for > 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by > 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	− 2

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

Table 2 The modified Wells clinical model for predicting the pretest probability of deep vein thrombosis

Clinical feature	Score
Active cancer (treatment ongoing or within the previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden for > 3 days or major surgery, within 12 weeks	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 (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as ikely as deep vein thrombosis	− 2

A score of ≥ 2 indicates that the probability of deep vein thrombosis is likely; a score of < 2 indicates that the probability of deep vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

The other main component of DVT diagnostic work-up is D-dimer testing. Its main advantages include wide availability, a high negative predictive value, and sensitivity for venous thromboembolism (VTE) (97–100% and 93–100% for high-sensitivity assays, respectively) [16–19]. One disadvantage is the relatively low specificity in certain clinical subgroups, such as older patients [20,21]. Age-adjusted D-dimer thresholds have been proposed to account for the effect of age on average D-dimer levels [22]. Some studies have reported higher specificity for the diagnosis of DVT when age-adjusted D-dimer is employed, without safety being compromised [23,24].

An approach to the diagnostic work-up of DVT that relies on a stand-alone D-dimer test, omitting clinical prediction rules, may be preferable because of its simplicity and ease of standardization, provided that it does not compromise safety.

This management outcome study was aimed at assessing the safety and efficiency of applying fixed D-dimer as a stand-alone test to exclude DVT in an outpatient population. We also conducted *post hoc* analyses to evaluate and compare the diagnostic performance of fixed and age-adjusted D-dimer thresholds, with and without the Wells score, to find the optimal diagnostic strategy.

Materials and methods

Study population

Outpatients referred to the emergency department of Østfold Hospital, Norway are, at the time of writing, being evaluated for enrollment in the Ri-Schedule study (Rivaroxaban

for scheduled work-up of DVT; NCT02486445). It is a single-center prospective outcome study recruiting outpatients with suspected DVT referred from general practitioners to the emergency department. The main goal of the study was to assess the safety of rivaroxaban, administered according to predefined criteria, in the prediagnosis phase of DVT. Among its other aims was the evaluation of D-dimer as a stand-alone test for DVT. This substudy was conducted when approximately half of the patients had been enrolled.

The inclusion criteria of the Ri-Schedule study are age $\geq$ 18 years and referral for first or recurrent clinically suspected lower-extremity DVT. Exclusion criteria are previous inclusion in the Ri-Schedule study within the past 3 months, or inability or unwillingness to provide written consent. Furthermore, patients with expected survival of < 3 months are excluded from the analysis of VTE developing within 3 months.

Additional criteria for eligibility for management with rivaroxaban (maximum of two tablets within 24 h) in the Ri-Schedule study are absence of active cancer, current pregnancy or nursing, or suspicion of active bleeding. However, all patients, whether eligible for treatment with rivaroxaban or not, are managed according to the D-dimer strategy described in this article.

In summary, this substudy consisted of all patients included in the Ri-Schedule study until August 2017, including those who received rivoraxaban while awaiting CUS and those who did not.

Study design

The study was designed as a prospective evaluation of one diagnostic strategy (fixed D-dimer as a stand-alone test), with which five additional strategies were compared retrospectively. These five, summarized in Fig. 1, included: fixed D-dimer combined with the original, three-category Wells score [3]; fixed D-dimer combined with the modified, two-category Wells score [4]; age-adjusted D-dimer as a stand-alone test; age-adjusted D-dimer combined with the original, three-category Wells score; and age-adjusted D-dimer combined with the modified, two-category Wells score.

The Ri-Schedule study was approved by the Regional Committee for Medical and Health Research Ethics, reference number 2014/377. The researchers adhered to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Diagnostic procedure

All included patients were evaluated according to the Wells clinical score before the D-dimer results were available. According to the study protocol, the score was obtained for later use in the *post hoc* analyses of diagnostic performance of the different strategies. The study personnel were instructed to not use it to guide initial management. D-dimer was analyzed with the immunoturbidometric method of STA-Liatest D-Di Plus (Stago Diagnostics, Asnieres, France). A positive fixed D-dimer result was defined as a level of ≥ 0.5 μg mL^{-1}. Patients with a D-dimer level of < 0.5 μg mL^{-1} were considered not to have DVT regardless of Wells score, and remained untreated with no further diagnostic tests at baseline. For age-adjusted D-dimer, we used a positivity threshold of $\geq$ age $\times$ 0.01 μg mL^{-1} for patients aged $\geq$ 50 years [22]. For younger patients, we used a positivity threshold of ≥ 0.5 μg mL^{-1}.

Patients with positive D-dimer results were referred for whole-leg CUS. All veins were assessed for compressibility. The iliac vein, the femoral veins and the popliteal vein were scanned continuously along their entire length with a linear probe (5–10 MHz) with the patient in a supine position. Axial calf veins were normally scanned with the patient seated. In selected cases, scanning in a prone or standing position was performed. The preferred criterion for DVT was incompressibility [1]. If this was not possible, a gray-scale visualization of the thrombus was accepted. The diagnostic criterion for recurrent DVT was non-compressibility of a venous segment that was previously fully recanalized or that was not initially involved according to the reference CUS.

All patients considered to be DVT-negative according to either negative D-dimer or CUS results were discharged and followed up at 3 months to determine the occurrence of VTE. Patients were advised to seek medical attention if symptoms progressed or persisted, or if they developed other symptoms of DVT or pulmonary embolism. At the end of the follow-up period, all patients received a telephone call from study personnel to establish whether they had been diagnosed with VTE or had been started on anticoagulation for any reason. Patients in whom anticoagulation had been initiated for reasons other than VTE within the 3-month follow-up period were excluded from analyses. Patients with suspected concurrent pulmonary embolism at baseline were managed according to hospital guidelines instead of according to the trial protocol.

Post hoc *analyses of different diagnostic strategies*

As these analyses were performed after the study had ended, we used the criteria that would have led to a referral for CUS in each strategy, as illustrated in Fig. 1. If we had used D-dimer testing in combination with the original, three-category Wells score, all patients with a D-dimer level of ≥ 0.5 μg mL^{-1} or defined as a high-risk category patient with a Wells score of ≥ 3 points would have been referred for CUS. When D-dimer testing was used in combination with the modified, two-category Wells score, all patients with a D-dimer level of ≥ 0.5 μg mL^{-1} or defined as a 'DVT likely' category patient according to a Wells score of ≥ 2 would have been

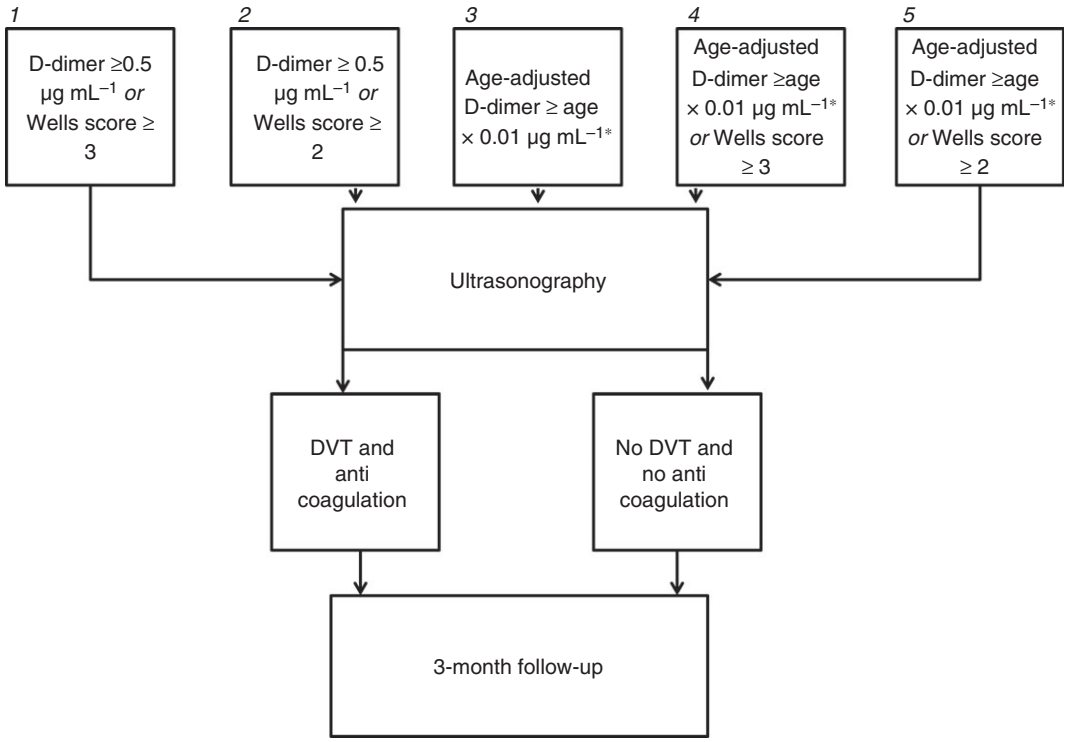

Fig. 1. Diagnostic work-up of deep vein thrombosis (DVT) according to strategies applied in *post hoc* analyses. *If age ≥50, otherwise D-dimer ≥0.5 μg mL^{-1}

referred for CUS. Age-adjusted D-dimer as a stand-alone test would have resulted in patients being referred for CUS with a D-dimer of ≥ age × 0.01 μg mL^{-1} for patients aged ≥ 50 years or ≥ 0.5 μg mL^{-1} for younger patients.

As for strategies 4 and 5, patients would have been referred for CUS if they had at least a positive age-adjusted D-dimer or Wells scores of ≥ 3 or ≥ 2 for the original and modified Wells scores, respectively.

If the patient did not meet the criteria for CUS as defined by each strategy, we considered that they would not have been referred for CUS, and would have remained without further diagnostic testing or anticoagulation at baseline.

Outcomes

The primary outcome was the failure rate of the primary diagnostic strategy, defined as the proportion of patients either diagnosed with symptomatic VTE or deceased, possibly because of VTE, within 3 months among patients in whom DVT had been ruled out because of a negative D-dimer result and who were left untreated (number of patients diagnosed with VTE at baseline or at 3-month follow-up with a negative D-dimer result/all patients with a negative D-dimer result). Efficiency was expressed as the proportion of patients requiring CUS because of a positive D-dimer result (number of patients with a positive D-dimer result/all included patients).

The secondary outcomes were the failure rate, proportion of required CUS examinations and diagnostic performance of the five additional strategies as compared with the primary strategy. Failure rate was defined as the proportion of patients who did not meet the criteria for undergoing CUS as defined by each strategy (i.e. considered to be DVT-negative), but who were nevertheless diagnosed with VTE either at baseline or during the 3-month follow-up period. The proportion of required CUS examinations was considered to be the proportion of all patients fulfilling the criteria for undergoing CUS according to each strategy. Diagnostic performance was expressed as sensitivity, specificity, negative predictive value, and positive predictive value.

Statistical analysis

The analyses were not planned for in the original protocol of the Ri-Schedule study, but it was later decided to conduct them when 50% of the patients had been enrolled to evaluate the safety and feasibility of age-adjusted D-dimer as a stand-alone test for the rest of the patients in the study. On the basis of previous studies, negative D-dimer results were expected in 23–35% of patients [25], yielding an estimate of 300 patients in whom DVT was ruled out on the basis of a negative D-dimer result.

A *post hoc* power calculation showed that a sample size of 306 patients would be needed to detect an incidence

rate of < 2% with a power of 80% at a 5% significance level.

The failure rates of the different diagnostic strategies with 95% confidence intervals (CIs) were compared with the failure rate of fixed D-dimer as a stand-alone test with a 95% CI. The proportion of CUS examinations yielded by each diagnostic strategy was compared with that of D-dimer as a stand-alone test, all according to absolute differences and with corresponding 95% CIs.

The diagnostic performances of the six strategies were expressed as sensitivity, specificity, positive predictive value and negative predictive value with their respective 95% CIs. Percentages and degree of overlapping of CIs were used to compare strategies.

Diagnostic properties were calculated with OPENEPI statistical software, Version 3.01 (OpenEpi, Atlanta, GA, USA), and Wilson method was used for calculation of binomial 95% CIs.

Results

General findings

The demographic characteristics of the patients are outlined in Table 3.

Of the 1338 patients screened for participation, 973 were found to be eligible, provided written consent, and were included (Fig. 2). Of these, 60 patients received anticoagulation for reasons other than VTE between inclusion and the 3-month follow-up, and were excluded from further analyses, resulting in a total of 913 patients in the final analysis. Fourteen patients were enrolled in the study twice.

Six hundred and fifteen patients (67%, 95% CI 64.3–70.3%) had positive fixed D-dimer results, whereas 298 patients (33%, 95% CI 29.7–35.8%) had negative D-dimer results (Fig. 3). The proportion of patients with positive fixed D-dimer results and a 'DVT likely' pretest probability was 40% (364 patients). The proportion of patients with positive age-adjusted D-dimer results and a 'Wells likely' pretest probability was 36% (327 patients).

Thirty-six patients were referred for CUS despite having a negative D-dimer result, of whom one was diagnosed with DVT. The reasons for undergoing CUS despite a negative D-dimer result are summarized in Fig. 3. One hundred and seventy-three patients (18.9%, 95% CI 16.5–21.6%) were diagnosed with DVT at baseline. One hundred and twenty-nine DVTs (75%) were proximal and 44 (25%) were distal.

Table 3 Demographics and characteristics

	All patients $n = 913$	DVT patients $n = 176$	No-DVT patients $n = 737$
Age (years), median (IQR)	64 (22)	63 (22)	64 (22)
Symptom duration (days), median (IQR)	7 (11)	5 (5)	7 (11)
Female sex, *n* (%)	490 (54)	74 (42)	416 (56)
Modified Wells score (DVT likely), *n* (%)	452 (49)	140 (80)	312 (42)
Modified Wells score (DVT unlikely), *n* (%)	461 (51)	36 (20)	425 (58)
Previous VTE, *n* (%)	152 (17)	51 (29)	101 (14)
VTE in first-degree relatives, *n* (%)	179 (20)	38 (22)	141 (19)
Active cancer within the past 6 months, *n* (%)	47 (5)	16 (9)	31 (4)
Surgery or immobilization for >3 days, *n* (%)	49 (5)	14 (8)	35 (5)
Hormonal contraceptives, *n* (%)	22 (2)	7 (4)	15 (2)
Hormone replacement therapy, *n* (%)	88 (10)	12 (7)	76 (10)
Known thrombophilia, *n* (%)	28 (3)	9 (5)	19 (3)

DVT, deep vein thrombosis; IQR, interquartile range; VTE, venous thromboembolism.

Study performance and 3-month outcome of D-dimer as a stand-alone test

There were no losses to follow-up or deaths in this group. Table 4 shows the diagnostic performance of the test. One of 298 patients with negative D-dimer results was diagnosed with DVT at baseline. This was one of the 36 patients who underwent CUS at baseline despite a negative D-dimer result. She was in her early fifties and had a 2-day history of calf swelling and pain. Her only established risk factor for DVT was medication with medroxyprogesterone (Depo-Provera), the indication for which was not documented in hospital records. Clinical examination gave normal findings, except for unilateral pitting edema and tenderness along the deep venous system, resulting in a Wells score of 2. She was referred for CUS despite a negative D-dimer result, because of severe pain. CUS revealed incompressibility immediately distal to the bifurcature of the popliteal vein, indicative of a 1–2-cm-long thrombus.

No patients with negative D-dimer results were diagnosed with VTE during the 3-month follow-up.

One of 298 patients with negative D-dimer results who were analyzed had DVT at the 3-month follow-up, yielding a failure rate of 0.3% (95% CI 0.1–1.9%).

Study performance and 3-month outcomes of the various strategies

Patient outcomes and the diagnostic performances of all of the diagnostic strategies are outlined in Table 4. Addition of the modified Wells score to the fixed D-dimer strategy would have detected the one patient missed by fixed D-dimer as a stand-alone test, but would have necessitated

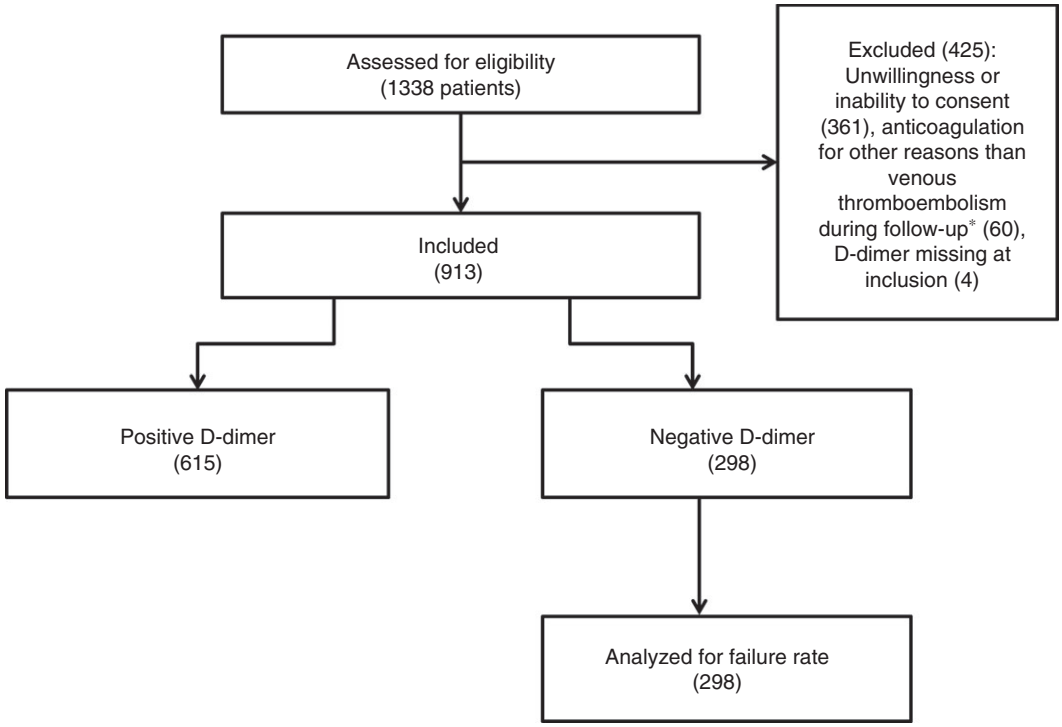

Fig. 2. Study population and design. *Superficial thrombophlebitis diagnosed by ultrasound at baseline (56), clinically suspected thrombophlebitis (1), atrial fibrillation (2), DVT prophylaxis during immobilization (1).

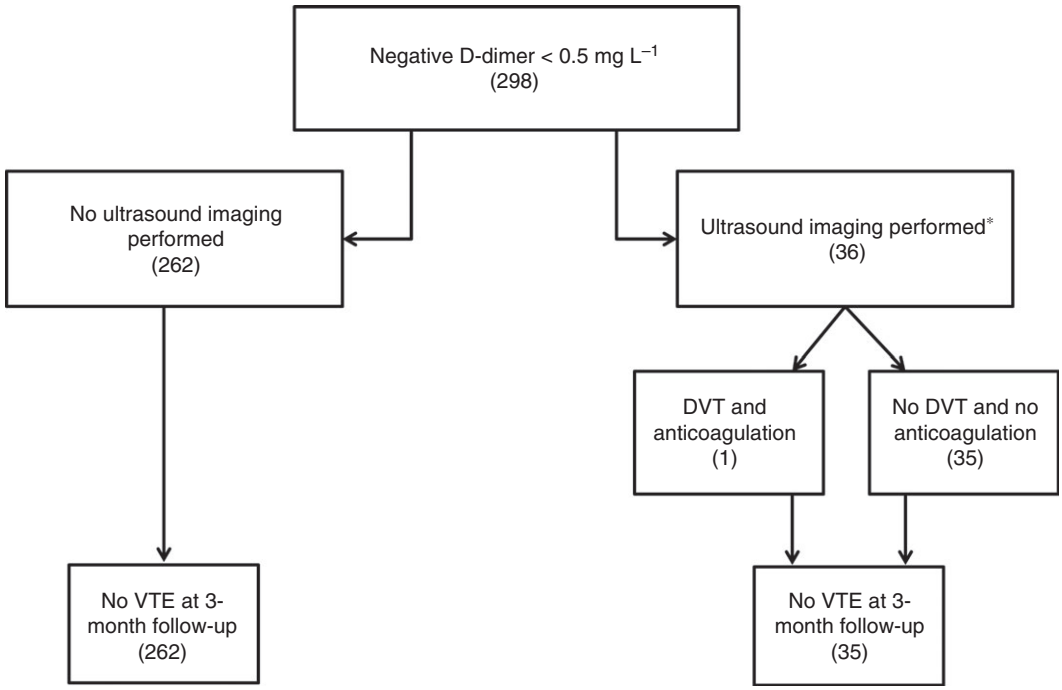

Fig. 3. Fixed D-dimer as a stand-alone test for excluding deep vein thrombosis (DVT). VTE, venous thromboembolism. *Reasons for undergoing ultrasound imaging despite negative D-dimer: Evaluate extent of clinically suspected thrombophlebitis for diagnosis and determining whether or not to administer anticoagulant therapy (2), second evaluation in Emergency Department due to persisting symptoms (6), diagnose other suspected condition (4), other causes (12), no available information recorded on reason for undergoing ultrasound imaging (12).

702 CUS examinations (76.9%, 95% CI 74.1–79.5%) instead of 615 (67.4%, 95% CI 64.3–70.3%) – a difference of 9.5% patients (95% CI 5.4–13.6%).

Applying age-adjusted D-dimer as a stand-alone test would have resulted in an additional five patients with false-negative D-dimer results at inclusion, two with

Table 4 Diagnostic performance of the different strategies (n = 913)

	Fixed D-dimer			Age-adjusted D-dimer		
		or Wells score ≥ 3	*or* Wells score ≥ 2		*or* Wells score ≥ 3	*or* Wells score ≥ 2
Sensitivity						
TP/(TP + FN)	175/176	175/176	176/176	170/176	171/176	175/176
Estimate (%)	99.4	99.4	100	96.6	97.2	99.4
95% CI	96.9–99.9	96.9–99.9	97.9–100	92.8–98.4	93.5–98.8	96.9–99.9
Specificity						
TN/(TN + FP)	297/737	270/737	211/737	372/737	339/737	253/737
Estimate (%)	40.3	36.6	28.6	50.5	46.0	34.3
95% CI	36.8–43.9	33.2–40.2	25.5–32.0	46.9–54.1	42.4–49.6	31.0–37.8
Negative predictive value						
TN/TN + FN	297/298	270/271	211/211	372/378	339/344	253/254
Estimate (%)	99.7	99.6	100	98.4	98.5	99.6
95% CI	98.1–99.9	97.9–99.9	98.2–100.0	96.6–99.3	96.6–99.4	97.8–99.9
Positive predictive value						
TP/TP + FP	175/615	175/642	176/702	170/535	171/569	175/659
Estimate (%)	28.5	27.3	25.1	31.8	30.1	26.6
95% CI	25.0–32.2	24.0–30.8	22.0–28.4	28.0–35.9	26.4–33.9	23.3–30.1
Positive likelihood ratio						
Sensitivity/(1 – specificity)	0.994/(1 – 0.403)	0.994/(1 – 0.366)	1.00/(1 – 0.286)	0.966/(1 – 0.505)	0.972/(1 – 0.460)	0.994/(1 – 0.343)
Estimate (ratio)	1.7	1.6	1.4	2.0	1.8	1.5
95% CI	1.6–1.8	1.5–1.7	1.3–1.5	1.8–2.1	1.7–1.9	1.4–1.6
Negative likelihood ratio						
(1 – sensitivity)/specificity	(1 – 0.994)/0.403	(1 – 0.994)/0.366	(1 – 1.00)/0.286	(1 – 0.966)/0.505	(1 – 0.972)/0.460	(1 – 0.994)/0.343
Estimate (ratio)	0.0	0.0	0.0	0.1	0.1	0.0
95% CI	0.0-0.1	0.0-0.1		0.0-0.2	0.0-0.2	0.0-0.1
VTE at 3-month follow-up*						
FN/FN + TN	1/298	1/271	0/211	6/378	5/344	1/254
Estimate (%)	0.3	0.4	0.0	1.6	1.5	0.4
95% CI	0.1–1.9	0.1–2.1	0.0–1.8	0.7–3.4	0.6–3.4	0.1–2.2
Required ultrasonography examinations†						
TP + FP/TP + FN + FP + TN	615/913	642/913	702/913	535/913	569/913	659/913
Estimate (%)	67.4	70.3	76.9	58.6	62.3	72.2
95% CI	64.3–70.3	67.3–73.2	74.1–79.5	55.4–61.8	59.1–65.4	69.2–75.0

CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive; VTE, venous thromboembolism. *In patients with negative diagnostic work-up at baseline. †According to the criteria warranting ultrasonography in each strategy.

distal DVT and three with proximal DVT. Adding the modified Wells score to age-adjusted D-dimer generated a similar safety profile as fixed D-dimer as a stand-alone test, although necessitating an additional 44 CUS examinations.

Two of the strategies had a lower proportion of required CUS examinations than fixed D-dimer as a stand-alone test: age-adjusted D-dimer as a stand-alone test generated 80 fewer CUS examinations (8.8%, 95% CI − 13.2% to − 4.4%), whereas the negative predictive value was reduced from 99.7% (95% CI 98.1–99.9%) to 98.4% (95% CI 96.6–99.3%).

Adding the original, three-category Wells score yielded 46 fewer CUS examinations (5.1%, 95% CI − 9.5% to − 0.7%) at the cost of a lower negative predictive value, i.e. 98.5% (95% CI 96.6–99.4%).

Adding the Wells score generated more CUS examinations than both D-dimer thresholds as stand-alone tests, and the modified Wells score generated more CUS examinations than the original Wells score. Applying the modified Wells score to the fixed and age-adjusted cut-offs yielded 9.5% (95% CI 5.4–13.6%) and 4.8% (95% CI 0.6–9.0%) more CUS examinations than fixed D-dimer as a stand-alone test, respectively. The negative predictive value increased to 99.6% (95% CI 97.8–99.9%) when the modified Wells score was added to fixed D-dimer, and remained unchanged for age-adjusted D-dimer with the modified Wells score.

Discussion

Safety of fixed D-dimer as a stand-alone test

In this study, we found that D-dimer testing as a stand-alone test in the diagnostic work-up safely excluded DVT.

To our knowledge, only two other prospective outcome studies have evaluated D-dimer testing as a stand-alone test for excluding VTE [26,27], and, as far as we know, ours is the only recent study to do so for DVT. The previous studies found similar overall negative predictive values of 99.3% and 99.8%, respectively. The studies had similar sample sizes, used other D-dimer assays, and had prevalences of VTE of 23% and 12%, respectively, supporting our findings.

In spite of high negative predictive value for D-dimer testing, the safety of D-dimer testing as a stand-alone test for pulmonary embolism is subject to ongoing debate, even when a higher positivity threshold for D-dimer is applied, i.e. 750 μg L^{-1}, than used in our study [28].

The failure rate of 0.3% (95% CI 0.1–1.9%) of fixed D-dimer as a stand-alone test corresponds to the failure rates yielded by negative CUS results, ranging between 0.57% and 2.0%, with 95% CIs ranging from lower to upper limits of 0.2% to 5.1% [29,30]. Moreover, it compares favorably with the failure rate after a negative venography result (1.3%) [31], which is the reference standard for DVT diagnostic tests or algorithms [1]. Finally, the upper limit of the CI of the post-test probability of DVT for fixed D-dimer as a stand-alone test was < 2%. This is considered to be a satisfactory degree of certainty in diagnostic testing for withholding treatment [1].

Comparison of fixed D-dimer as a stand-alone test with other strategies

Regarding our secondary outcome measures, we found that fixed D-dimer as a stand-alone test was equally safe as established diagnostic strategies incorporating the Wells score in the algorithm. Furthermore, of the two strategies with an upper 95% CI failure rate limit of ≤ 2%, fixed D-dimer as a stand-alone test generated the fewest number of CUS examinations.

Early published evaluations of combined Wells score and D-dimer strategies found similar failure rates as described in our study (0.4% [95% CI 0.05–1.5%] and 0.6% [95% CI 0.1–1.8%]) [3,4]. The Wells score has subsequently been extensively validated and clinically employed, spanning at least 14 studies with > 10 000 patients [32].

Age-adjusted D-dimer as a stand-alone test had the highest specificity and resulted in the fewest CUS examinations of all strategies. However, it was associated with lowered sensitivity and an additional five false-negative cases, of whom three had proximal thrombi, as compared with fixed D-dimer as a stand-alone test. Given that the analysis was conducted retrospectively, the clinical significance of missing these thrombi is uncertain.

Prospective outcome studies to explore the safety of age-adjusted D-dimer as a stand-alone test are needed before its use in clinical practice can be considered. Current prospective studies validating age-adjusted D-dimer may help to guide future diagnostic work-up of DVT (NCT02384135).

Strengths and limitations

The strengths of our study include its prospective outcome design and collection of data, standardized assessment, including the same D-dimer assay in all patients, and no losses to follow-up in the group with negative D-dimer results who did not undergo CUS. Additionally, the DVT prevalence of 19% in our study is comparable to that in other similarly designed diagnostic studies [3,4,26,27]. This relatively high prevalence decreases the likelihood of a low failure rate resulting from a low prevalence, which may arise as a result of the lower diagnostic threshold seen in recent times [15].

A limitation of our single-center study is possibly weaker generalizability than a multicenter study would yield. Another limitation is the protocol deviations whereby patients did and did not undergo CUS despite negative and positive D-dimer results, respectively. These

deviations would probably continue to exist in the case of implementation of D-dimer as a stand-alone test, as there would be a need to clarify other conditions, or to evaluate the extent of clinically suspected thrombophlebitis; also, clinicians may, for other reasons, wish to exclude DVT despite a negative D-dimer result or clinical prediction rules. Of the 36 patients who underwent CUS despite a negative D-dimer result, one was diagnosed with DVT, whose 2-cm-long distal thrombus might have resolved spontaneously. The clinical course and optimal management of distal thrombi are subject to ongoing debate [33,34]. Furthermore, as analyses for five of the strategies were conducted retrospectively, the clinical significance of the thrombi missed by age-adjusted D-dimer but not by fixed D-dimer remain theoretical. Therefore, our conclusion that the safety of age-adjusted D-dimer as a stand-alone test is uncertain could only be verified or falsified through prospective outcome studies.

Earlier enrollment in the study was not an exclusion criterion so long as the previous inclusion occurred > 3 months previously. As the patients who were enrolled twice were few in number (14), and only two were not managed per protocol (one patient did not undergo CUS despite a positive D-dimer result, and one patient underwent CUS despite a negative D-dimer result), we believe that the potential resulting bias is limited. Despite the potential benefits of including patients repeatedly, such as the ability to establish recurrence rates and explore mechanisms of recurrent DVT, the lack of independence between these observations could limit testing for statistically significant differences between strategies.

Although our findings are likely to be generalizable to other outpatient populations with similar DVT prevalences, this may not be the case for inpatient settings or in populations with markedly higher DVT prevalences. Although D-dimer was analyzed with only one method, other studies have documented similar negative predictive values for high-sensitivity assays [19]. We therefore believe that our D-dimer results can be extrapolated to these assays.

It is also worth noting that, although patients at high risk for DVT were not excluded from the study, their contribution to the total patient number was limited. For instance, only 5% had cancer, 5% had undergone surgery within the 12 weeks preceding admission, and 0.8% were pregnant. Although none of these patients had false-negative D-dimer results, the numbers of patients in the subgroups were too small to enable conclusions to be drawn regarding the safety of D-dimer testing as a stand-alone test in these groups. Consequently, the results of our study do not warrant changing existing diagnostic evaluation of these patients.

In summary, D-dimer testing as a stand-alone test was found to be equally safe as and to generate fewer CUS examinations than D-dimer testing combined with the Wells score. As the strategy has the additional advantage of being easily adhered to in clinical practice while avoiding subjectivity in evaluation, we believe that it is a preferred approach to simplify the diagnostic work-up of DVT.

Conclusion

Our findings suggest that D-dimer testing as a stand-alone test with levels of < 0.5 μg mL^{-1} can safely exclude DVT while necessitating fewer CUS examinations than a combined approach using D-dimer testing and the Wells score. We believe that this strategy has the potential to standardize and simplify the diagnostic process for DVT.

Age-adjusted D-dimer as a stand-alone test generated the lowest number of CUS examinations, but the safety of the strategy needs to be evaluated in prospective outcome studies before it is considered for clinical use.

Addendum

S. G. Fronas participated in data acquisition and management of the trial, analyzed and interpreted the data, and drafted and revised the manuscript. H. S. Wik participated in protocol drafting, data interpretation, and revision of the manuscript. A. Dahm participated in protocol drafting, study management, and interpretation and revision of the manuscript. C. T. Jørgensen participated in data acquisition, daily management of the study, and revision of the manuscript. J. Gleditsch: participated in management of the study, and drafting and revision of the manuscript. N. Raouf participated in data acquisition, study management, and revision of the manuscript. F. A. Klok participated in study design and concept, and analyze and revision of the manuscript. W. Ghanima was trial manager, designed, initiated and managed the study, participated in data acquisition and interpretation, and revised the manuscript.

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Disclosure of Conflict of Interests

S. G. Fronas and C. T. Jørgensen report receiving grants from Bayer AG and the South-Eastern Norway Regional Health Authority for the Ri-Schedule study but did not receive personal fees. A. Dahm reports receiving grants and personal fees from Pfizer AS, and personal fees from Bristol-Myers Squibb and Novartis

Norway AS, outside the submitted work. W. Ghanima reports receiving grants from Bayer AG and South-Eastern Norway Regional Health Authority during the conduct of the study but did not receive personal fees, and grants from Bayer AG, Bristol-Myers Squibb and Novartis outside the submitted work, and participating on advisory boards for Amgen and Novartis. H. S. Wik, J. Gleditsch, N. Raouf and F. A. Klok state that they have no conflict of interest.

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II

REGULAR ARTICLE

blood advances

Safety and feasibility of rivaroxaban in deferred workup of patients with suspected deep vein thrombosis

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Key Points

- Deferring ultrasound imaging for ≤24 hours with empiric rivaroxaban in patients with suspected DVT is a safe strategy.
- The strategy may simplify the diagnostic approach to DVT while improving resource use.

Guidelines suggest using empiric low-molecular-weight heparin if the diagnostic workup of deep vein thrombosis (DVT) is expected to be delayed. The role of direct oral anticoagulants for deferred compression ultrasound imaging (CUS) in patients with suspected DVT remains unexplored. The main objective of the study was to assess the safety of deferring CUS with therapeutic doses of rivaroxaban. We prospectively included consecutive outpatients referred to the Emergency Department at Østfold Hospital, Norway, with suspected first or recurrent lower-extremity DVT between February 2015 and November 2018. Patients were discharged with rivaroxaban 15 mg twice daily while awaiting CUS within 24 hours if D-dimer level was ≥0.5 mg/L fibrinogen-equivalent units. The primary outcome was the rate of major bleeding incidents from study inclusion until DVT was confirmed and anticoagulation therapy continued, or otherwise up to 48 hours following administration of the last tablet of rivaroxaban. The secondary outcome was the rate of progressive DVT symptoms or symptoms or signs of pulmonary embolism between hospital discharge until venous thromboembolism was diagnosed. Six hundred twenty-four of 1653 patients referred with suspected DVT were included (37.7%; 95% confidence interval [CI], 35.4-40.1). DVT was diagnosed in 119 patients (19.1%; 95% CI, 16.1-22.3). There were no major bleeding incidents, yielding an observed major bleeding rate of 0% (1-sided 95% CI <0.4). No patients experienced major complications in the interval that CUS was deferred (0%; 95% CI, 0.0-0.6). Deferring CUS for up to 24 hours in patients with suspected DVT with therapeutic doses of rivaroxaban is a safe strategy. This trial was registered at www.clinicaltrials.gov as #NCT02486445.

Introduction

The workup of deep vein thrombosis (DVT) starts with pretest probability assessment and D-dimer testing to determine which patients should be referred for diagnostic compression ultrasonography (CUS) to establish a final diagnosis.[1] Guidelines suggest empiric treatment with low-molecular-weight heparin (LMWH) if the workup is prolonged, and the patient has no major risk factors for bleeding.[2] Prompt administration of LMWH is recommended in patients with a high pretest probability of DVT. For

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Deidentified individual participant data that underlie the reported results may be requested after publication to investigators, whose proposed use of the data has been approved by an independent review committee identified for this purpose to achieve aims in the approved proposal. Information regarding accessing data and obtaining study protocol can be directed to the corresponding author, Synne G. Fronas (e-mail: s.g.fronas@gmail.com).

patients with moderate or low pretest probability, LMWH is suggested if the workup is expected to exceed 4 and 24 hours, respectively.[2] Several studies have demonstrated the safety of deferring CUS until on-hours with therapeutic doses of LMWH or unfractionated heparin,[3-9] which may alleviate the resource burden of around-the-clock referrals for CUS at hospitals.

Although direct oral anticoagulants are increasingly used in the treatment of DVT, their safety has not been prospectively assessed for suspected DVT in a diagnostic approach deferring CUS. This is important to establish before it may be routinely prescribed in daily practice, as the majority of patients who receive empiric anticoagulation do not have DVT.

In this study, we evaluated the safety and feasibility of deferring CUS for up to 24 hours with therapeutic doses of rivaroxaban in patients with suspected DVT.

Methods

Study population and design

The Rivaroxaban for Scheduled Work-up of Deep Vein Thrombosis Study (the Ri-Schedule study, www.clinicaltrials.gov identifier NCT02486445) was a prospective outcome trial including consecutive outpatients referred from primary care centers to the Emergency Department at Østfold Hospital, Norway, between February 2015 and November 2018. The hospital is the primary referral center for ~300 000 inhabitants.

Inclusion criteria were ≥18 years of age, referral for first or recurrent suspected lower-extremity DVT, ability and willingness to provide written consent, and no enrollment in the study within the past 3 months. Exclusion criteria were conditions associated with a higher risk of adverse outcomes with rivaroxaban and/or with being discharged awaiting CUS (Table 1). These included expected workup completion within 2 hours, contraindications to rivaroxaban, hemoglobin <11 g/dL, thrombocyte count $<100 \times 10^9$/L, glomerular filtration rate (GFR) <45 mL/min per 1.73 m^2, cancer or chemotherapy in the past 6 months, suspected concurrent pulmonary embolism (PE), comorbidities necessitating admission, suspected leg ischemia or eligibility for thrombolysis, logistical challenges with at-home observation, patient objection to discharge, or physician deeming discharge to be unsafe.

Interventions

The study design is outlined in Figure 1. Dedicated study nurses and doctors screened patients for enrollment. If the patient was ≥18 years old, had not been included in the study within the past 3 months, and provided written consent, study personnel obtained pregnancy tests for women of childbearing age, as well as hemoglobin and GFR levels with point-of-care devices. If the patient did not meet any of the predefined exclusion criteria for discharge with rivaroxaban and deferred CUS as outlined in Table 1, the patient was enrolled in the study. Excluded patients remained in the Emergency Department until the relevant workup had completed.

Included patients underwent a clinical examination including assessment of the 3-tier Wells score before admission blood tests, including D-dimer, were obtained,[10] as per routine management. Wells score was assessed for later analyses and did not guide further management. Patients were next administered 1 tablet of rivaroxaban 15 mg and discharged with another tablet of 15 mg to take at home. The patients were advised to contact the Emergency Department if they experienced symptom progression, symptoms of PE, or bleeding complications. Study personnel contacted patients by phone when D-dimer results were available. D-dimer was analyzed by the immunoturbidometric method of STA-Liatest D-Di Plus (Stago Diagnostics, Asnieres, France) on the STA-R Evolution Analyzer. If D-dimer levels were <0.5 mg/L fibrinogen-equivalent units (FEUs), then DVT was considered to be ruled out. Patients were instructed not to take the second tablet of rivaroxaban and consult their family doctor for evaluation of other diagnoses.

If D-dimer levels were ≥0.5 mg/L FEUs, patients were instructed to take the second tablet of rivaroxaban 12 hours after the first. They were given an appointment for whole-leg CUS the following morning and within 24 hours of inclusion. The final diagnosis was based on this CUS examination. As such, we considered DVT ruled out in patients who had either negative D-dimer or where CUS did not reveal DVT. The safety of ruling out venous thromboembolism (VTE) on the basis of a negative D-dimer without clinical pretest probability assessment is an investigational practice with a low risk of a missed diagnosis suggested by some studies,[11,12] including a prior study of our department.[13] Validation of these findings was outside the scope of the current study.

Patients were contacted by phone 48 hours after taking the last tablet of rivaroxaban to assess for bleeding events. The 48-hour range was chosen based on the time needed to eliminate rivaroxaban.[14] For patients who had been diagnosed with VTE and therefore had

Table 1. Exclusion criteria for deferred imaging and empiric rivaroxaban

Factors with a higher risk of adverse effects of rivaroxaban
Concomitant anticoagulation*
Suspected active or recent bleeding
Major risk factors for bleeding†
Active cancer or chemotherapy within the past 6 mo
Pregnancy or lactation
Hemoglobin <11 g/dL or thrombocytes $<100 \times 10^9$/L
GFR <45 mL/min per 1.73 m^2
Liver disease with coagulopathy or other bleeding risk
Concomitant medications possibly interacting with rivaroxaban
Conditions or situations in which scheduled workup is deemed inappropriate
Suspicion of concurrent PE
Comorbidities necessitating admission
Suspected ischemia or eligibility for thrombolysis
Physician considers discharge unsafe
Patient objects to discharge
Logistical challenges
Workup can be completed within 2 h

*Regular prescription or empiric anticoagulation for suspected DVT.
†Current or recent gastrointestinal ulceration; presence of malignant neoplasms at high risk of bleeding; recent brain or spinal injury; recent brain, spinal, or ophthalmic surgery; recent intracranial hemorrhage; known or suspected esophageal varices; arteriovenous malformations; vascular aneurysms; major intraspinal, or intracerebral vascular abnormalities.

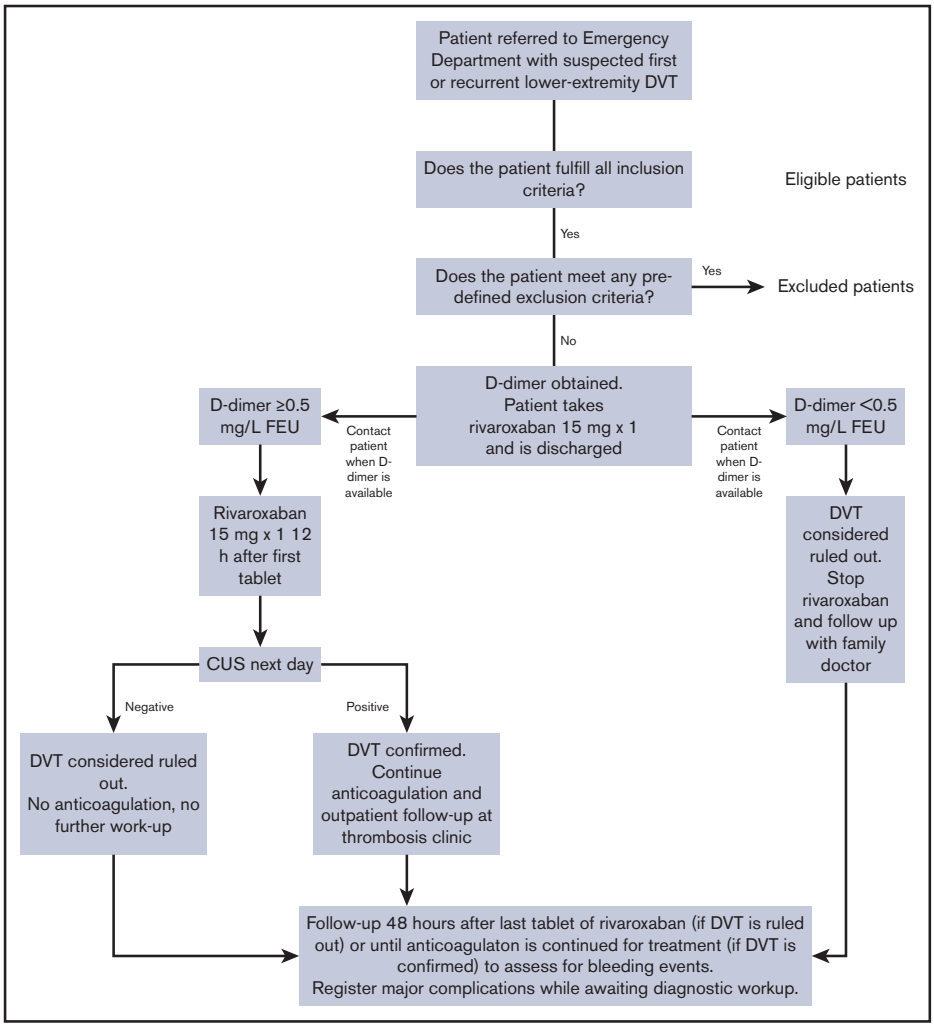

Figure 1. Study design.

continued anticoagulation treatment, we assessed for bleeding events in the interval preceding DVT being confirmed and anticoagulation continued for treatment purposes. Additionally, we registered whether the patients who had been diagnosed with VTE had experienced progressive symptoms or symptoms or signs of PE before the diagnosis was confirmed.

Objectives and end points

The main objective of the study was to determine the safety of rivaroxaban in the prediagnostic phase of DVT workup, ie, the interval from when the patient was included until the diagnosis could be confirmed or ruled out.

The secondary objectives were to determine the overall safety and feasibility of the deferred workup strategy.

The primary outcome was the proportion of patients in whom DVT had been ruled out who suffered a major bleeding incident within 48 hours after ingesting the last tablet of rivaroxaban or otherwise until DVT had been confirmed and anticoagulation continued for treatment purposes. Bleeding events were classified according to the criteria of the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis,[15,16] whereby major bleeding is defined as fatal or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin level of $\geq$20 g/dL or leading to transfusion of $\geq$2 U whole blood or red cells.

The secondary safety outcomes were the incidence of clinically relevant nonmajor and minor bleeding events[16] and major complications while awaiting CUS. Major complications were defined as the worsening of DVT symptoms or the development of symptoms or signs of PE (number of patients with major complications/number of patients diagnosed with VTE). This was based on any of the following criteria occurring: hemodynamic instability, worsening of vital signs (increased respiratory or resting pulse rate after 15 minutes of rest, decrease in resting systolic blood pressure, or decrease in SaO_2 by $>$20% compared with baseline), increased leg circumference by $>$10%, and/or progressive symptoms, such as worsening pain or dyspnea until VTE was confirmed.

Moreover, we assessed the rate of VTE events within 3 months of follow-up in patients in whom DVT was ruled out at baseline either by negative D-dimer or negative CUS.

The secondary feasibility outcome was the proportion of patients who did not meet any of our predefined exclusion criteria for deferred CUS with rivaroxaban (Table 1) and were included in the study out of all otherwise eligible patients (patient age ≥18 years, able and willing to provide written consent, and not included within the past 3 months).

Statistical analyses

We estimated the expected bleeding rate based on the number of patients in studies on LMWH (n = 729 patients), in whom no major bleeding events were observed.[3-5,7] This yielded an observed major bleeding rate of 0% and 95% confidence interval (CI) of 0.0% to 0.6%. Based on this, we assumed a frequency of observed major bleeding with rivaroxaban at ≤0.2% with a 1-sided 95% confidence limit of <0.8%. With these assumptions, a significance level of 5% and a power of 80% (β = 20%), we set the sample size at 620 patients.

The study outcomes are expressed as proportion in descriptive summary percentage and 95% CIs, calculated by Clopper-Pearson exact method.[17] Baseline characteristics are expressed in median with interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. The software package used was IBM SPSS Statistics, Version 25.

Safety and adjudication

One fatal bleeding event or 2 nonfatal, major bleeding events were set as criteria for stopping the study. An independent adjudication committee would determine causes of bleeding or death, and an independent safety committee was responsible for terminating the study if deemed necessary.

Ethics approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK), reference number 2014/377. The researchers adhered to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and the International Conference on Harmonisation–Good Clinical Practice Guideline.

Results

Baseline characteristics

Figure 2 provides an overview of the patient flow. Screening of consecutive outpatients mainly took place when dedicated study personnel recruited from the pool of the Emergency Department staff was working, 8 to 13 hours of the day during weekdays.

Two thousand three hundred forty-seven patients who presented to the Emergency Department with suspected DVT were screened for participation. Of these, 1653 patients (70.4%; 95% CI, 78.5-72.3) were ≥18 years of age, provided written consent, and were not included in the past 3 months.

One thousand twenty-nine of the 1653 patients (62.3%; 95% CI, 59.9-64.6) met ≥1 exclusion criterion for deferred workup with rivaroxaban (Table 2). Of these 1029 patients, 185 patients (18.0%; 95% CI, 15.7-20.5) were diagnosed with DVT.

Renal function was assessed with the point-of-care device in 388 patients. In the remaining patients, laboratory renal function results were either available at inclusion or the physician attending preferred to wait for these. All 388 patients either had previously known renal function impairment or GFR >45 mL/min per 1.73 m^2.

Six hundred twenty-four patients (37.7%; 95% CI, 35.4-40.1) were included. Their baseline characteristics are summarized in Table 3. Median age was 65 years (IQR, 54-73), and 342 patients (54.8%; 95% CI 50.8-58.8) were female. One hundred nineteen patients (19.1%; 95% CI, 16.1-22.4) were diagnosed with DVT at baseline. Of these, 89 (74.8%; 95% CI, 66.0-82.3) were proximal and 30 (25.2%; 95% CI, 17.7-34.0) were isolated distal thromboses. D-dimer was positive in 475 patients (76.1%), negative in 143 patients (22.9%), and missing in 6 patients (1.0%). In patients with positive D-dimer, 137 (28.8%), 261 (54.9%), and, 77 (16.2%) patients were classified as high, moderate, and low probability, respectively. In patients with negative D-dimer, 20 (14.0%), 83 (58.0%), and 40 (28.0%) patients were classified as high, moderate, and low probability, respectively.

Enrollment ended when reaching the predefined sample size.

Study outcomes

The study outcomes are summarized in Table 4. All patients were followed up according to study protocol. There were no major bleeding events in patients in whom DVT was ruled out or in patients with confirmed DVT (0/624 [0.0%]; 1-sided 95% CI < 0.4). Moreover, no patients (0/624 [0.0%]; 95% CI, 0.0-0.6) suffered worsening of presenting symptoms or developed symptoms or signs of PE in the interval between inclusion until VTE was diagnosed. There were 505 patients in whom DVT was ruled out at baseline either by negative D-dimer or negative CUS. No patients with initial negative CUS were diagnosed with VTE within 3 months of follow-up for a 3-month VTE rate of 0.0% (95% CI, 0.0-1.0). Two patients who did not undergo CUS at baseline because of negative D-dimer were diagnosed with DVT for a 3-month VTE rate of 1.4% (95% CI, 0.2-5.0). One patient was in the low-probability subgroup, and the other patient was in the high-probability subgroup.

Notably, 1 patient suffered a major bleeding event, which was adjudicated not to meet the primary end point for 2 reasons. First, the patient in question was included despite experiencing melena, hence fulfilling the exclusion criterion for scheduled workup of active bleeding (Table 1). Second, the event occurred beyond the predefined study period, 70 hours after taking 1 tablet of rivaroxaban. The event therefore was adjudicated as protocol violation. Taking it into account would have yielded a major bleeding rate of 0.2% (1-sided 95% CI <0.7).

In total, 63 minor and clinically relevant nonmajor bleedings occurred in 61 patients (10.1%; 95% CI, 7.8-12.7). Figure 3 provides an overview of number and origin of bleeding events. In patients where DVT was confirmed, there were 9 bleeding events in 9 patients (7.6%; 95% CI, 3.5-13.9). Of these, all were minor but for one clinically relevant nonmajor incident of hematuria. In patients where DVT was ruled out, there were 54 bleeding events in 52 patients (10.5%; 95% CI, 8.0-13.0). Of these, 52 were minor and 2 were adjudicated as clinically relevant nonmajor: 1 incident of epistaxis and 1 incident of hematuria.

All 60 minor bleeding events were mild, and at follow-up, 37 had recovered spontaneously and 23 were recovering. Of the bleedings still recovering, 1 patient had experienced increased though currently diminishing menstrual bleeding, while the remainder were either

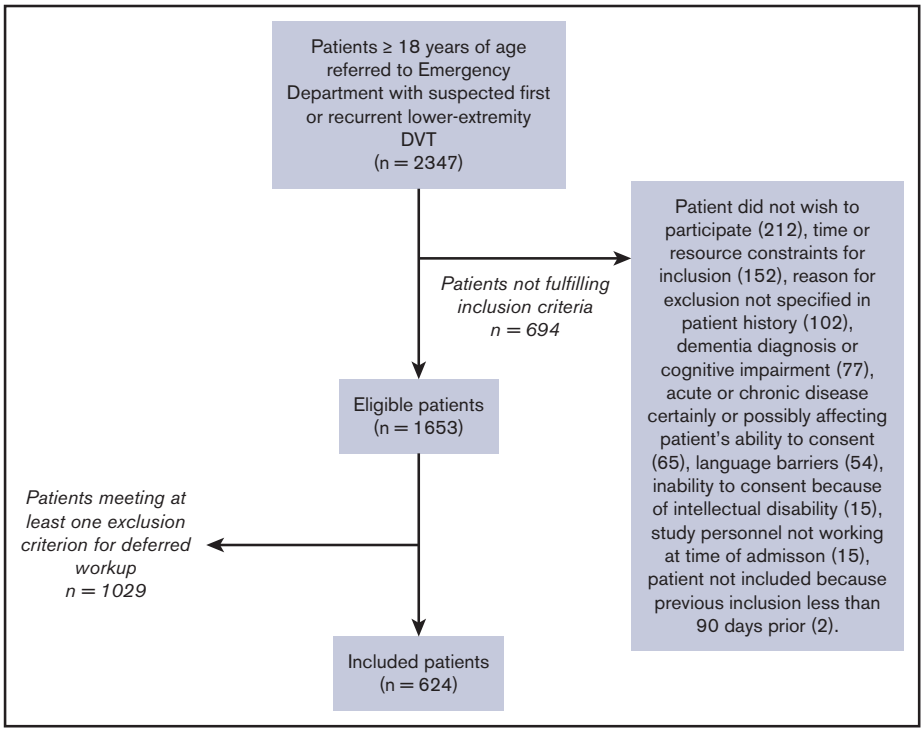

Figure 2. Eligibility and inclusion of patients.

recovering subcutaneous hematomas (n = 9) or hematomas detected on CUS (n = 13) while the patients were worked up for DVT.

As for the secondary feasibility outcome, 1029 patients (62.3%) met at least 1 exclusion criterion for scheduled workup. Numbers and percentages meeting the different criteria are detailed in Table 2. Three hundred twenty-eight patients (19.8%; 95% CI, 17.9-21.9) had received empiric LMWH in primary care before referral, and it was the only exclusion criterion for 245 patients (14.8%; 95% CI, 13.1-16.6). Of the 328 patients who had received LMWH in primary care before referral, weight and dosage were available in patients' records for 286 patients. Of these, 159 patients (55.6%; 95% CI, 49.6-61.4) had received at least the minimum therapeutic dosage for VTE.

Eighty-nine patients (5.4%) only met the criterion of "physician deems discharge unsafe," and the 73 patients with documented reasons did so because more likely or concurrent diagnoses needed management (n = 51), the Emergency Department physician attending deemed DVT unlikely after evaluation (n = 14), or they had pronounced DVT symptoms needing instant consideration (n = 8).

Discussion

Principal findings

We found that deferring CUS for up to 24 hours with therapeutic rivaroxaban is a safe and feasible strategy for patients with suspected DVT. While others have suggested that direct oral anticoagulants may be safe in the diagnostic workup of VTE,[18] our study is to our knowledge the first prospective trial to assess this question.

There have been no clinical trials addressing the benefits and disadvantages of administering vs withholding anticoagulants in prolonged workup of DVT, and guidelines have a grade 2C level of recommendation.[2] The main benefit of empiric anticoagulation is faster initiation of treatment in patients who are ultimately diagnosed with DVT, preventing proximal extension of the clot, PE, and perhaps postthrombotic syndrome. A disadvantage is system and patient cost, albeit subject to varying legislation between countries.[19-21] However, the main potential disadvantage is risking bleeding complications in patients without DVT. The favorable safety profile demonstrated in this and similarly designed studies applying LMWH or unfractionated heparin for deferred workup, all yielding no major bleedings,[3-9] support the use of empiric anticoagulation in prolonged workup of DVT. Our conclusion is in line with suggestions from guidelines and what is, in our experience, already a relatively commonplace practice despite the grade 2C evidence. A recent article describing anticoagulation therapy patterns in the ~10 000 patients included in the large prospective observational GARFIELD-VTE registry demonstrated that 13.4% of patients had started anticoagulant treatment before the diagnosis being confirmed, of whom 17.0% started on a direct oral anticoagulant without parenteral bridging despite guidelines recommending LMWH in this setting.[22]

A fair amount of patients (10.1%) experienced a bleeding event (Figure 3), of which 95.2% were minor. Minor or "nuisance" bleeding events lack a rigorous definition, may be underreported in large data trials,[16] and may be more open to interpretation and the physician's inclination to report. We believe several aspects of our study contributed to the observed bleeding rate. First, we documented all bleeding events to avoid reporting bias. Several

Table 2. Exclusion criteria for deferred workup in eligible patients (N = 1653)

	n (%) with criterion	n (%) with only criterion
Anticoagulation*	447 (27.0)	329 (19.9)
Empiric anticoagulation treatment in primary care before referral	328 (19.8)	245 (14.8)
Regular prescription of anticoagulation treatment	129 (7.8)	76 (4.6)
Both empiric and regular use of anticoagulation treatment	10 (0.6)	8 (0.5)
Patient objects to discharge	192 (11.6)	117 (7.1)
Physician deems discharge unsafe	189 (11.4)	89 (5.4)
Suspected active or recent bleeding	70 (4.2)	11 (0.7)
GFR <45 mL/min per 1.73 m^2	66 (4.0)	17 (1.0)
Active cancer or chemotherapy within the past 6 mo	65 (3.9)	23 (1.4)
Major risk factors for bleeding	59 (3.6)	4 (0.2)
Logistical challenges for at-home observation	45 (2.7)	16 (1.0)
Workup expected to complete within 2 h	44 (2.7)	28 (1.7)
Medications possibly interacting with rivaroxaban	44 (2.7)	10 (0.6)
Hemoglobin <11 g/dL and/or thrombocytes $<100 \times 10^9$/L	39 (2.4)	6 (0.4)
Pregnancy or lactation	23 (1.4)	14 (0.8)
Suspected concurrent PE	22 (1.3)	2 (0.1)
Comorbidities necessitating admission	20 (1.2)	2 (0.1)
Suspected ischemia or eligibility for thrombolysis	4 (0.2)	0 (0)
Liver disease†	2 (0.1)	0 (0)

*Regular prescription or empiric anticoagulation for suspected DVT.
†Associated with coagulopathy or other bleeding risk.

Table 3. Demographics and characteristics

	Included patients (N = 624)
Age, median (IQR), y	65 (54-73)
Female sex, n (%)	342 (55)
Symptoms duration, median (IQR), d	7 (4-14)
Positive D-dimer,* n (%)	475 (76)
Low probability for DVT,† n (%)	117 (19)
Moderate probability for DVT,† n (%)	348 (56)
High probability for DVT,† n (%)	159 (25)
DVT at baseline, n (%)	119 (19)
Risk factors for VTE, n (%)	
Previous VTE	91 (15)
VTE in first-degree relatives	118 (19)
Current smoking	129 (21)
Recent travel >4 h	194 (31)
Recent inactivity	84 (14)
Surgery within past 12 wk	37 (6)
Known thrombophilia	17 (3)
Hormonal contraceptives	23 (4)
Hormone-replacement therapy	46 (7)

*D-dimer missing in n = 6.
†According to the 3-tier Wells score.

of these were trivial, such as light recurrent or light epistaxis when blowing the nose (8/15), habitual or light gum bleed when brushing teeth (3/6), or easier bruising (n = 9). Second, we reported bleeding events despite probable causative factors. For instance, judging by presenting history and symptoms, it is likely that many of the lower-extremity hematomas detected by CUS were present before the patient received rivaroxaban. However, as CUS was performed after the patients had taken rivaroxaban, we cannot conclude whether hematomas preceded rivaroxaban administration. Third, the study design involving thorough patient information and follow-up may have affected the patient's propensity for reporting bleeding events.

Summarized, we cannot conclude whether the observed proportion of 10.1% is particularly high or low, but we believe there was an overall low threshold for reporting bleeding events and overall low clinical relevance of the majority of the bleeding events.

This notwithstanding, our patient with melena adjudicated as protocol violation underlines the importance of precluding patients at high risk of bleeding from empiric anticoagulation treatment. Although we do not know the natural progression in this case, rivaroxaban likely exacerbated or accelerated the course of the patient's signs and symptoms.

Regarding feasibility of the strategy, 37.7% of patients did not meet any of our predefined exclusion criteria for deferred workup with rivaroxaban (Table 2), and we believe more patients would be included in future implementation. The 245 patients with empiric LMWH in primary care as their only exclusion criterion would likely add to the eligible proportion if scheduled workup had been standard management and could have increased the number to 869 patients (52.6%; 95% CI, 50.1-55.0).

Eighty-nine patients were excluded because the treating physicians deemed discharge unsafe. In most cases, this was because other workup was necessary to rule out other conditions, or the suspicion of DVT was withdrawn upon closer look. In a clinical setting, the criteria for deferred workup would only apply to patients with a primary DVT suspicion in the first place. Therefore, we consider that this criterion will not exclude as many patients in future implementation.

A few other aspects of our predefined criteria merit mentioning. For future implementation, we would recommend establishing hemoglobin levels and pregnancy status for eligible women through point-of-care devices. Estimating point-of-care GFR did not yield previously unknown GFR <45 mL/min per 1.73 m^2. As such, we believe there is no need to determine GFR levels, as long as the patient's history is not suggestive of compromised renal function. As for platelets, we did not routinely await laboratory results before administering rivaroxaban and instead asked all patients about signs suggestive of thrombocytopenia.

We have previously found that stand-alone D-dimer may safely rule out DVT with a 3-month VTE rate of 0.3% (95% CI, 0.1-1.9) in 298 patients with negative D-dimer.[13]

Table 4. Primary and secondary outcomes

	n (%)	95% CI
Safety, bleeding events		
Major	0 (0)	<0.4
Clinically relevant nonmajor	3 (0.5)	0.1-1.4
Minor	60 (9.6)	7.4-12.2
Major complications*	0 (0)	0.0-0.6
Feasibility		
Patients included in the study	624 (37.7)	35.4-40.1

*Worsening of symptoms, development of symptoms, or signs of PE between inclusion and diagnosis of VTE.

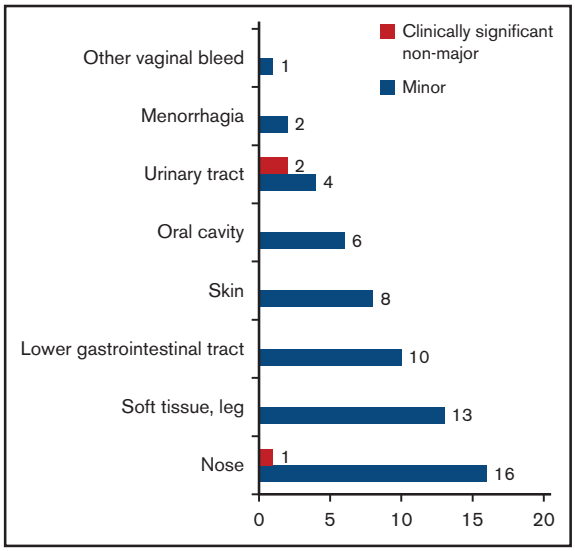

Figure 3. Origin and number of bleeding events.

In the current study, there was a low 3-month VTE rate with a higher upper limit of the 95% CI than yielded in our previous study. Regardless, the aim of this study was to explore whether the diagnostic workup of DVT could safely be deferred for up to 24 hours with empiric rivaroxaban without adversely affecting patients in this time frame, not to determine whether it is safe to withhold CUS in select patients altogether. No patients experienced major complications from deferring CUS, whereas stand-alone D-dimer in ruling out DVT need validation before their safety in routine use may be considered as supported by the findings of this study.

Several benefits of deferring CUS until hospital on-hours have been described in previous studies conducted at university and community hospitals. Arnaoutakis et al estimated an annual cost savings of ~$12 000 with the termination of off-hour imaging without affecting patient outcomes, possibly a higher figure if other reimbursements had been taken into account as well.[23] Potential cost savings was also suggested by Bauld et al.[9] Langan et al found increased retention of sonographers after off-hour CUS had decreased by 89%, which could possibly be attributed to satisfaction with diminished off-hour workload.[7] Improved sonographer satisfaction was also a benefit noted in a study conducted by Chaer et al, as well as more laboratory time for inpatient studies.[4]

Our study has several novel implications elaborating on the findings of previous trials.

First, it introduces an alternative empiric anticoagulant for patients with suspected DVT, which has the benefits of oral administration, potentially lower cost, as well as standard, not weight-required dosing. The latter may be of particular benefit, as only 56% of patients in our study received the minimum therapeutic dosage of LMWH according to weight. Second, our criteria will aid primary and emergency care physicians in deciding which patients can wait for referral until hospital on-hours. Deferred workup strategies may reduce wait time for patients and improve resource use during hospital peak or off-hours, possibly channeling 40% to 50% of patients to on-hour workup.

Strengths and limitations

The strengths of our study include its prospective design, standardized assessment, collection of data, and classification of bleeding events for all patients. No patients were lost to follow-up, and outcomes were adjudicated by an independent adjudication committee. Unlike other studies, we included patients with suspected recurrent DVT, who comprised a considerable proportion of the study cohort of 15%. Moreover, we applied the same diagnostic strategy to all patients irrespective of pretest likelihood of DVT (to our knowledge only the second study to do so).[9] As such, our findings suggest that rivaroxaban may safely be administered to low-risk patients and that CUS may safely be deferred for up to 24 hours in high-risk patients. Both are groups where the benefits to risk ratio might be more uncertain and where it is particularly desirable to avoid adverse effects of the respective interventions.

A limitation of our study is that it was conducted in a single center. Hence, external validity of our findings remains to be established. Moreover, we performed a single-arm study rather than a randomized controlled trial, which would have required a larger sample size than feasible for the scope of this study. Lastly, our exclusion criteria for scheduled workup limit generalizability to the whole outpatient population, and our findings cannot be extrapolated to patients with suspected concurrent PE, cancer, lower hemoglobin, or GFR than predefined. Ultimately, there were several reasons for why we erred on the side of caution at the expense of generalizability. First, based on previous studies from our department, we expected that ~80% of the included patients would end up having DVT ruled out,[13] and less conservative criteria would particularly disfavor these patients in case of bleeding. Second, there have to our knowledge not been studies randomizing patients with suspected DVT to receive or not empiric treatment, and the uncertainty of potential benefits warranted a cautious approach. Lastly, as patients were discharged and not observed in hospital, we decided that additional safety considerations were necessary.

Importantly, a strategy involving deferred workup and empiric anticoagulation will likely always be inappropriate for a substantial proportion of any outpatient population depending on the characteristics of the population in question.

However, some of the criteria might be modified for future implementation. A high GFR threshold was chosen as a moderately reduced renal function of creatinine clearance <50 mL/min warrants dose reduction in certain situations. Hemoglobin <11 g/dL was raised during the study from <10 g/dL as an extra safety precaution after the inclusion of a patient with ongoing

melena. Lastly, cancer patients were excluded, as the role of direct anticoagulants in these patients was unknown at the time of designing the study.

In conclusion, we found that deferring CUS with therapeutic doses of rivaroxaban in patients with suspected DVT where CUS was not readily available was not associated with major bleeding or other major adverse events. Our strategy resulted in 37.7% of patients being discharged to await further diagnostic considerations at home. The strategy may simplify the diagnostic workup of DVT while improving resource use.

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Authorship

Contribution: S.G.F. participated in data acquisition and management of the trial, analyzed and interpreted the data, and drafted and revised the manuscript; A.E.A.D. participated in protocol drafting, study management, interpretation, and revision of the manuscript; H.S.W. participated in protocol drafting, data interpretation, and revision of the manuscript; C.T.J. participated in data acquisition and daily management of the study and revision of the manuscript; J.G. participated in study management and drafting and revising the manuscript; N.R. participated in data acquisition and study management and revision of the manuscript; R.H. participated in study design, input regarding end-point selection and statistical analyses, and revision of the manuscript; F.A.K. participated in data analyses, interpretation, and revision of the manuscript; and W.G. was trial manager and responsible for the design, planning, initiation, and conduction of the study and participated in data acquisition and interpretation and revision of the manuscript.

Conflict-of-interest disclosure: S.G.F. and C.T.J. received grants from Bayer, the South-Eastern Norway Regional Health Authority, and the Østfold Hospital Trust to the conduct of the study (no personal fees). A.E.A.D. received grants and personal fees from Pfizer AS and personal fees from Bristol-Myers Squibb and Novartis Norway AS outside the submitted work. F.A.K. received research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart foundation, and the Dutch Thrombosis association outside the submitted work. W.G. received grants from Bayer, the South-Eastern Norway Regional Health Authority, and Østfold Hospital Trust for the conduct of this study; received grants from Bayer, Bristol-Myers Squibb, and Novartis outside the submitted work; and participated on advisory boards for Amgen and Novartis. The remaining authors declare no competing financial interests.

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III

REGULAR ARTICLE

blood advances

Safety of a strategy combining D-dimer testing and whole-leg ultrasonography to rule out deep vein thrombosis

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Key Points

- Negative D-dimer safely ruled out DVT as a stand-alone test.
- A single negative whole-leg ultrasonography safely ruled out DVT in patients with positive D-dimer irrespective of pretest probability.

Guidelines for the diagnostic workup of deep vein thrombosis (DVT) recommend assessing the clinical pretest probability before proceeding to D-dimer testing and/or compression ultrasonography (CUS) if the patient has high pretest probability or positive D-dimer. Referring only patients with positive D-dimer for whole-leg CUS irrespective of pretest probability may simplify the workup of DVT. In this prospective management outcome study, we assessed the safety of such a strategy. We included consecutive outpatients referred to the Emergency Department at Østfold Hospital, Norway, with suspected DVT between February 2015 and November 2018. STA-Liatest D-Di Plus D-dimer was analyzed for all patients, and only patients with levels ≥0.5 μg/mL were referred for CUS. All patients with negative D-dimer or negative CUS were followed for 3 months to assess the venous thromboembolic rate. One thousand three hundred ninety-seven patients were included. Median age was 64 years (interquartile range, 52-73 years), and 770 patients (55%) were female. D-dimer was negative in 415 patients (29.7%) and positive in 982 patients (70.3%). DVT was diagnosed in 277 patients (19.8%). Six patients in whom DVT was ruled out at baseline were diagnosed with DVT within 3 months of follow-up for a thromboembolic rate of 0.5% (95% confidence interval, 0.2-1.2). A simple diagnostic approach with initial stand-alone D-dimer followed by a single whole-leg CUS in patients with positive D-dimer safely ruled out DVT. We consider this strategy to be a valuable alternative to the conventional workup of DVT in outpatients. This trial was registered at www.clinicaltrials.gov as #NCT02486445.

Introduction

Current guidelines for the diagnostic workup of deep vein thrombosis (DVT) recommend incorporating clinical pretest probability (C-PTP) assessment, D-dimer results, and compression ultrasonography (CUS).[1,2] Each of the components has been widely assessed,[3-5] although no 1 diagnostic strategy has been deemed superior to others. Guidelines recommend first assessing C-PTP using a validated prediction rule, followed by a high-sensitivity D-dimer assay for patients with non-high C-PTP, and either single whole-leg or proximal CUS for patients with high C-PTP or positive D-dimer. For proximal CUS, a repeat examination or negative D-dimer is required to rule out DVT in patients with moderate or high C-PTP, whereas a single negative proximal CUS suffices in patients with low C-PTP.

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Deidentified individual participant data that underlie the reported results may be requested after publication to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose, to achieve aims in the approved proposal. Information regarding accessing data and obtaining study protocol can be directed to corresponding author, Synne G. Fronas, at s.g.fronas@gmail.com.

In a recent study, we found that negative stand-alone D-dimer safely ruled out DVT irrespective of C-PTP while necessitating fewer CUS examinations than if C-PTP had also been considered.[6]

We believe a diagnostic strategy in which only patients with positive D-dimer are referred for a single whole-leg CUS regardless of C-PTP may simplify the workup of DVT without compromising safety. As such, this prospective management trial aimed to determine the safety and feasibility of such a strategy.

Methods

Study population and design

The Ri-Schedule study (clinicaltrials.gov NCT02486445) was a prospective outcome trial including consecutive outpatients referred from primary care to the Emergency Department at Østfold Hospital, Norway, between February 2015 and November 2018. Inclusion criteria were ≥18 years of age and referral for suspected first or recurrent DVT. Exclusion criteria were failure to consent, and previous inclusion in the study within the past 3 months. Furthermore, the following patients were excluded from analyses: patients with missing D-dimer results at baseline, patients who were prescribed anticoagulants for other indications than empiric anticoagulation for suspected DVT at the time of inclusion, and patients who were prescribed anticoagulants for indications other than venous thromboembolism (VTE) in the interval from inclusion until the end of the 3-month follow-up.

Interventions

Designated study personnel screened patients for inclusion. Included patients underwent clinical examination and blood admission tests including D-dimer. C-PTP was assessed according to the 3-tier Wells score for later analyses and before D-dimer was obtained,[7] but was not used to guide further management. D-dimer was analyzed by the immunoturbidometric method of STA-Liatest D-Di Plus (Stago Diagnostics, Asnières, France). Positive D-dimer was defined as levels ≥0.5 μg/mL fibrinogen-equivalent units. Patients with D-dimer <0.5 μg/mL were considered not to have DVT, did not undergo CUS, and remained untreated at baseline.

Patients with positive D-dimer were referred for whole-leg CUS. The deep and saphenous veins were scanned with a linear probe (5-10 MHz). For first DVT, recurrent contralateral DVT, recurrent ipsilateral DVT with documented resorption of thrombus, or recurrent DVT without available images for comparison, the diagnostic criterion was incompressibility of the vein or a grayscale visualization of the thrombus.[8] Recurrent ipsilateral DVT was defined as noncompressibility of, or visualization of, the thrombus in a venous segment not involved from reference CUS,[9] as magnetic resonance direct thrombus imaging to distinguish between acute and chronic DVT was not established as an alternative at the time the study was designed.[10]

Patients diagnosed with DVT at baseline started anticoagulation treatment. Patients with suspected concurrent pulmonary embolism at baseline were managed according to hospital guidelines instead of according to the trial protocol.

Patients in whom we considered DVT to be ruled out either due to negative D-dimer or CUS were discharged to be followed up for 3 months. Patients were advised to seek medical attention if symptoms progressed, or if other symptoms of DVT or pulmonary embolism developed, in which case they would undergo diagnostic imaging. At the end of the follow-up period, patients were contacted by phone to determine whether they had been diagnosed with VTE since inclusion, and/or had been treated with anticoagulation during this time.

Objectives and end points

The study aimed to assess the safety and feasibility of a diagnostic strategy ruling out DVT in patients with negative D-dimer, and ruling out DVT with normal findings on a single whole-leg CUS for patients with positive D-dimer.

The primary end point was the failure rate of the strategy, defined as the proportion of patients in whom DVT had been ruled out (ie, patients with either negative D-dimer or normal CUS at baseline) who developed VTE or died of unknown cause possibly attributable to VTE within 3 months of follow-up out of all patients in whom DVT had been ruled out.

The secondary safety objectives were to assess the safety of stand-alone D-dimer and single whole-leg CUS, respectively. The secondary safety end points were determining

- the failure rate of stand-alone D-dimer, defined as the proportion of patients with negative D-dimer at baseline who developed VTE or died of unknown cause possibly attributable to VTE within 3 months of follow-up out of all patients with negative D-dimer, and
- the failure rate of whole-leg CUS, defined as the proportion of patients with normal CUS at baseline who developed VTE or died of unknown cause possibly attributable to VTE within 3 months of follow-up out of all patients with normal CUS.

The feasibility of the strategy was defined as the proportion of patients managed according to the strategy out of all patients.

All potential outcome events were adjudicated by an independent committee.

We have previously reported on the safety of stand-alone D-dimer for the exclusion of DVT in 913 of the patients included in this study, and compared its safety and feasibility to standard diagnostic workup, as well as age-adjusted D-dimer.[6] Our findings were recently validated in a retrospective study.[11]

Statistical analyses

We would accept a failure rate of the strategy of 2% with an upper limit of the 95% confidence interval (CI) of 4%. This was based on the rate of symptomatic VTE within 3 months of a negative venography (1.3%; 95% CI, 0.2% to 4.4%), which is the reference standard against which diagnostic management studies of DVT are typically evaluated.[2,12] For a power of 80% at a 5% significance level, we estimated a sample size of at least 500 patients in whom DVT was ruled out at baseline according to the strategy. As the study was part of the larger Ri-Schedule study addressing several objectives with different sample size calculations, we allowed for >500 patients to be included in the study.

The study outcomes are expressed as proportions with percentages and corresponding 95% CIs, calculated by the Clopper-Pearson exact method. Baseline characteristics are expressed as median with interquartile range (IQR) for continuous variables, and numbers and percentages for categorical variables. IBM SPSS Statistics software (version 25) was used.

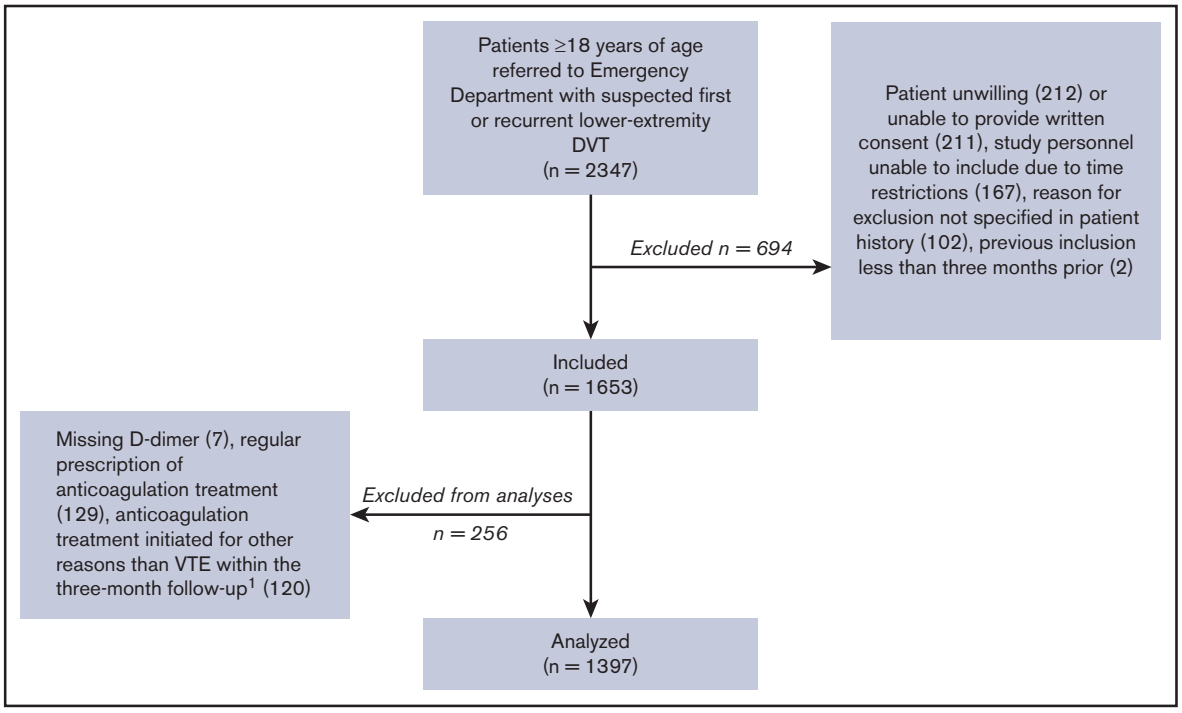

Figure 1. Inclusion of patients. [1]Ninety-three due to superficial thrombophlebitis.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK; reference number 2014/377). The researchers adhered to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and the International Council for Harmonisation–Good Clinical Practice.

Results

Baseline results

In the 46 months of inclusion, 2347 patients aged ≥18 years, referred with first or recurrent lower-extremity DVT, were screened for participation (Figure 1).

Of these, 1397 patients were included in the analyses. Their baseline characteristics are outlined in Table 1. DVT was diagnosed in 277 patients (19.8%): 187 of these DVT cases (67.5%) were proximal and 90 (32.5%) were isolated distal DVT. Thirty-three patients were included twice, and 1 patient was included 3 times. The diagnostic properties of the implemented strategy vs strategies including the Wells score in the diagnostic algorithm are shown in Table 2.

Outcomes

Outcomes are summarized in Figure 2. Six of the 1113 patients with negative D-dimer and/or normal CUS were diagnosed with DVT within 3 months for a failure rate of 0.5% (95% CI, 0.2-1.2).

Three of 415 patients with negative D-dimer were diagnosed with DVT: 2 proximal and 1 distal. These had Wells scores of −1, 1, and 3. As such, the failure rate for D-dimer as a stand-alone test was 0.7% (95% CI, 0.1-2.1).

Of the 698 patients with normal CUS at baseline, 3 patients were diagnosed with DVT within the 3-month follow-up, with Wells scores of 1, 3, and 4. As such, the failure rate for whole-leg CUS was 0.4% (95% CI, 0.1-1.3).

Two patients were lost to follow-up. They both had negative D-dimer and did not undergo CUS at baseline.

Additionally, 3 patients in whom DVT was ruled out by a normal CUS at baseline died within the 3-month follow-up: none underwent autopsy. VTE was adjudicated to not be the likely cause of death in any of the 3 patients, but cannot be definitely ruled out as autopsies were not performed. Considering these 5 cases as failures would have yielded 11 failures out of 1113 patients (1.0; 95% CI, 0.5-1.8) with negative workup: a figure with an upper bound of the 95% CI still well below the predefined acceptable safety margin.

As for the feasibility outcome of adherence, CUS was not performed in 50 of the 982 patients with positive D-dimer (5.1%) and was performed in 43 of the 415 patients with negative D-dimer (10.4%). As such, 1304 of 1397 patients (93.3%; 95% CI, 91.9-94.6) were managed according to protocol. In all cases in which CUS was not performed despite positive D-dimer, the suspicion of DVT was discarded after evaluation by the emergency department attending physician. Reasons given by physicians for requesting CUS despite negative D-dimer are listed in Table 3.

Discussion

Principal findings

In this prospective management study, we found that our simple approach of performing a single whole-leg CUS only in patients with D-dimer ≥0.5 μg/mL and withholding CUS in patients with D-dimer <0.5 μg/mL was a safe strategy associated with a low failure rate.

Table 1. Demographic and clinical characteristics of patients

	All, N = 1397	DVT,* n = 277	No DVT,* n = 1120
Age, median (IQR), y	64 (52-73)	65 (53-73)	64 (51-73)
Symptom duration, median (IQR), d	7 (3-14)	5 (3-7)	7 (3-14)
Female sex, n (%)	770 (55)	114 (41)	656 (59)
Positive D-dimer, n (%)	982 (70)	275 (99)	707 (63)
Low probability for DVT,† n (%)	383 (27)	23 (8)	360 (32)
Moderate probability for DVT,† n (%)	670 (48)	121 (44)	549 (49)
High probability for DVT,† n (%)	344 (25)	133 (48)	211 (19)
Positive D-dimer and/or high probability for DVT†	1024 (73)	276 (99)	748 (67)
DVT likely,‡ n (%)	698 (50)	216 (78)	482 (43)
DVT unlikely,‡ n (%)	699 (50)	61 (22)	638 (57)
Positive D-dimer and/or DVT likely,‡ n (%)	1105 (79)	276 (99)	829 (74)
Previous VTE, n (%)	203 (15)	73 (26)	130 (12)
VTE in first-degree relatives, n (%)	266 (19)	57 (21)	209 (19)
Active cancer within 6 mo, n (%)	62 (4)	21 (8)	41 (4)
Travel >4 h, n (%)	368 (26)	76 (27)	292 (26)
Immobilization due to trauma, n (%)	64 (5)	17 (6)	47 (4)
Hormonal contraceptives, n (%)	37 (3)	8 (3)	29 (3)
Hormone-replacement therapy, n (%)	121 (9)	15 (5)	106 (10)
Known thrombophilia, n (%)	45 (3)	15 (5)	30 (3)
Pregnancy or puerperium, n (%)	19 (1)	1 (0.4)	18 (2)
Recent surgery, n (%)	109 (8)	32 (12)	77 (7)

*At baseline visit.
†According to the original, 3-level Wells score.
‡According to the modified, 2-level Wells score.

The upper limit of the 95% CI of 1.2% was well below the predefined accepted 3-month VTE rate of 4%. Moreover, both components of the strategy, stand-alone D-dimer and whole-leg CUS, had comparably low failure rates, similar to previous literature.[6,13,14] To our knowledge, this is the first study to assess the clinical outcomes of withholding anticoagulation treatment in a diagnostic strategy combining stand-alone D-dimer and single whole-leg CUS.

Many management strategies incorporating C-PTP assessment, D-dimer results, and various CUS techniques have been studied.[5,15-18] These lay the foundation for existing recommendations of the diagnostic workup of DVT.[1,2] With some variation, the general recommendation is to conduct either proximal or whole-leg CUS in all patients with a high likelihood of DVT or positive D-dimer. Ruling out DVT on the basis of normal CUS or otherwise negative D-dimer when adhering to 1 of these strategies is associated with a VTE rate similar to that found in our study: between 0.4% and 2.0%,[7,15,17,19-24] with an upper limit of the 95% CI of mostly ≤2.2%.

Guidelines currently recommend against using stand-alone D-dimer to rule out DVT. However,[1,2] the studies upon which they are based were largely not prospective outcome studies using clinical follow-up as reference standard, and were instead based on D-dimer assessment against reference imaging at inclusion for the whole study population or for patients with high C-PTP.[3,25-28] This approach does not necessarily reflect clinical outcomes after a follow-up period, and may result in detecting clinically insignificant DVT with subsequent risk of overdiagnosis. Moreover, generalizing failure rates of D-dimer yielded by universal imaging of high-risk populations to the general outpatient population may not be appropriate, and most prospective outcome studies of outpatients do not have a DVT prevalence nearing the ≥50% defined as a high-risk population.[18] Rathbun et al conducted 2 studies withholding diagnostic workup in patients with negative D-dimer for suspected first and recurrent DVT, respectively.[29,30] They found failure rates for stand-alone D-dimer of 0.0% (95% CI, 0-4.4) and 0.75% (95% CI, 0.02-4.1). However, the study populations were relatively small compared with ours with 81 and 134 patients with negative D-dimer. Moreover, in both studies, there were patients in whom VTE could not be definitely ruled out, yielding a worst-case upper limit of the 95% CI of 11.4%.

With the failure rate of our strategy being 0.5% (95% CI, 0.2-1.2) and well within our preaccepted safety margin, we would not suggest systematic follow-up of patients with negative D-dimer or negative CUS; the latter is in line with current guidelines.[1,2,31] This does not preclude individual exceptions, and all patients with negative workup were encouraged to contact health care providers for renewed evaluation if they experienced recurring, persisting, or worsening symptoms, or symptoms of PE.

In addition to comparable safety, we believe our strategy has several advantages over current diagnostic algorithms and should therefore be seen as a valuable alternative. First, it may reduce the amount of CUS examinations, thereby decreasing cost,[30] time, and resources required for the management of individual patients. According to

Table 2. Diagnostic performance of stand-alone D-dimer vs other strategies (n = 1397)

	D-dimer				
	≥0.5 mg/L	*or* Wells score ≥3	*or* Wells score ≥2	Age-adjusted DD$^+$	C-PTP adjusted DD$^+$
Positive predictive value,* n	278/982	279/1024	279/1105	273/928	271/917
Estimate, %	28.3	27.2	25.2	29.4	29.6
95% CI	25.5-31.2	24.5-30.1	22.7-27.9	26.5-32.5	26.6-32.6
VTE within 3 mo despite negative workup,† n	3/415	2/371	2/290	8/469	10/480
Estimate, %	0.7	0.5	0.7	1.7	2.1
95% CI	0.1-2.1	0.1-1.9	0.1-2.5	0.7-3.3	1.0-3.8
Required D-dimer tests according to strategy,‡ n	1397/1397	1053/1397	699/1397	1053/1397	1053/1397
Estimate, %	100	75.3	50.0	75.4	75.4
95% CI	99.7-100	73.0-77.6	47.4-52.7	73.0-77.6	73.0-77.6
Required CUS examinations according to strategy,§ n	982/1397	1024/1397	1105/1397	928/1397	917/1397
Estimate, %	70.3	73.3	79.1	66.4	65.6
95% CI	67.8-72.7	70.9-75.6	76.9-81.2	63.9-68.9	63.1-68.1

DD, D-dimer.
*Number of DVT in all patients requiring workup according to each strategy; true positive/true positive + false positive.
†According to the criteria ruling out DVT in each strategy; false negative/false negative + true negative.
‡Required in all patients or non–high-risk patients.
§Required if positive D-dimer or high-risk patients.

current guidelines, all patients in the high-risk group should be referred for CUS, as well as patients with positive D-dimer in the low- or moderate-risk groups. Because our strategy entails referring only patients with positive D-dimer irrespective of pretest probability, fewer CUS examinations would be required in the group conventionally stratified as high risk. Notably, several recent guidelines have applied and/or stated their preference for the 2-tier Wells score in their recommendations.[1,31,32] The modified score classifies a larger proportion of patients as high risk than the original 3-tier Wells score, resulting in more required CUS examinations. Although we did not conduct a formal comparison between the strategies, obtaining the Wells score at inclusion enabled us to retrospectively assess the diagnostic properties of strategies including the Wells score in the diagnostic algorithm (Table 2).

Taking Wells score into consideration for our patients would have resulted in 3.0% and 8.8% more CUS according to the 3- and 2-tier scores, respectively, for a similar failure rate. In a recent retrospective study of 1765 patients, Rinde et al similarly found that stand-alone D-dimer would have required 9.6% less CUS than D-dimer incorporated with the 2-tier Wells score for a similar failure rate (1.8% [95% CI, 0.8% to 3.5%] vs 1.6% [95% CI, 0.5% to 3.6%], respectively).[33]

Recent attempts to increase specificity and reduce the number of unnecessary CUS examinations include increasing thresholds for positive D-dimer in older patients or in patients with low C-PTP.[34] In our study, both strategies would have required CUS in 66% of patients because of positive D-dimer or high C-PTP, 4% less than our strategy albeit at the cost of a slightly higher failure rate (Table 2).

In addition to reducing CUS examinations by omitting clinical prediction rules, our strategy obviates the repeat examinations required in the case of a negative proximal CUS in moderate- or high-risk patients with positive D-dimer.[1,2,32] As for choice of modality in CUS, both whole-leg and proximal CUS are acceptable options,[19,21] and there is no favored consensus.[1,2] Disadvantages of whole-leg CUS include being more skill- and resource-demanding, in addition to the potential disadvantage of treating distal DVT that would otherwise resolve without complications. However, we prefer whole-leg CUS to obviate repeat testing, and provide alternative explanations for the patient's symptoms.

A second advantage of our strategy is avoiding the challenges with clinical prediction rules. These include the inherent weakness of subjectivity,[35,36] not widely validated interrater reliability,[2] and incorrect use. The latter may partly result from the fact that, in some emergency departments, standard blood samples including D-dimer are obtained before clinical evaluation to improve efficiency. Knowledge of D-dimer results prior to C-PTP assessment may influence scoring,[37] contrary to the intended use. Lastly, real-life data show varying or limited adherence to prediction rules in clinical practice.[16,38-41] The GARFIELD-VTE registry found that <5% of patients underwent C-PTP evaluation before imaging.[42,43] We believe that simplifying the workup may increase clinical adherence and usefulness, supported by the 93% adherence to the strategy in our study. Additionally, the clinician's familiarity with a score as well as clinical experience would be of less importance with our strategy.

Strengths, limitations, and clinical implications

Strengths of our study include its relatively large patient number, prospective design, standardized assessment and collection of data, and few losses to follow-up. The baseline prevalence of DVT of 19.8% was in the same range or higher than similarly designed studies.[14,29,30,44] C-PTP was fairly evenly distributed between low, moderate, and high subgroups. All of these factors diminish the risk of an artificially high negative predictive value that a low prevalence could yield.

Our trial has several limitations, 1 being its monocentric design due to feasibility considerations. This may in turn adversely affect the generalizability of our findings, and external validity remains to be

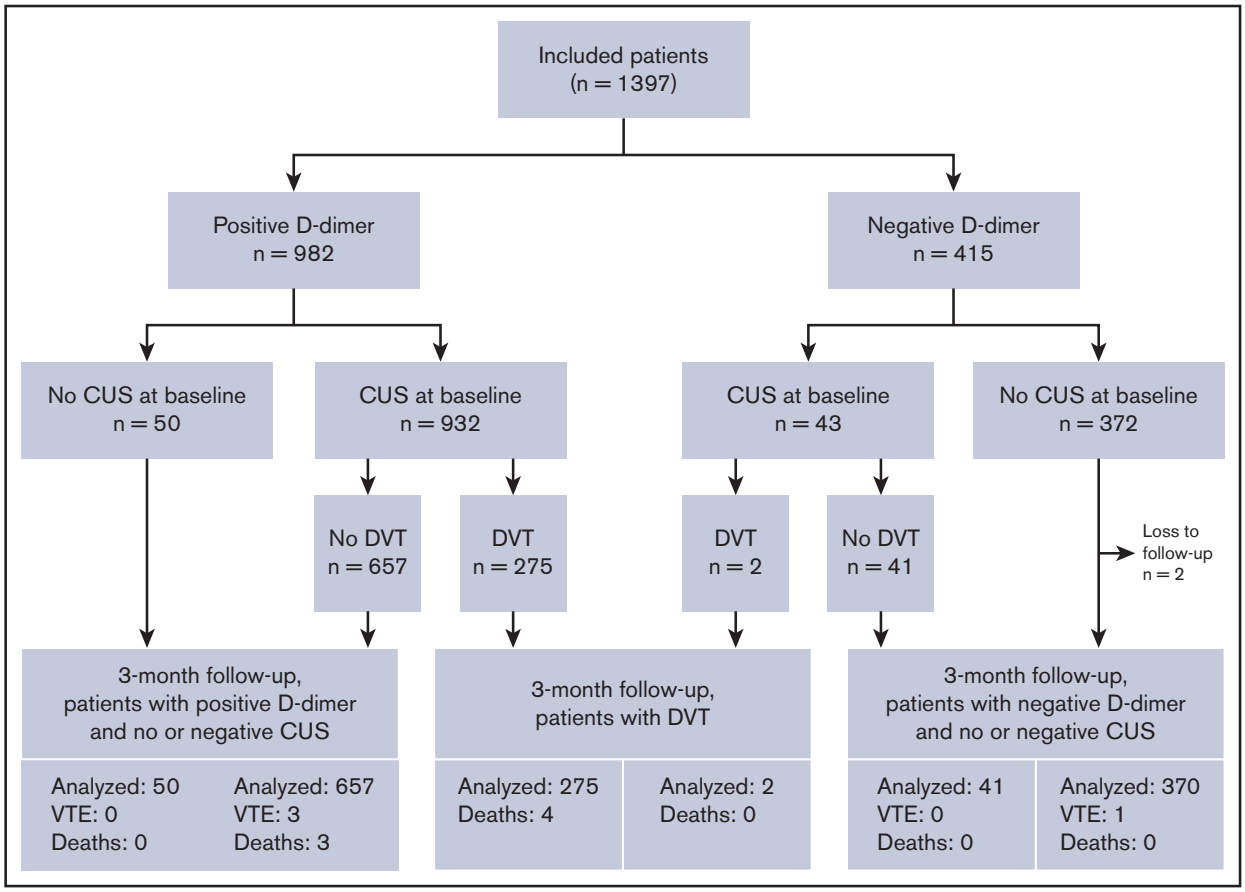

Figure 2. Study flow and outcomes.

established. Nonetheless, consisting of consecutive outpatients with an overall intermediate DVT prevalence,[1] a fairly even distribution of different C-PTP subgroups, as well as comparable failure rates to other studies examining stand-alone D-dimer, we believe our findings are likely to be generalizable to other emergency department populations with similar or lower prevalence.

Only 1 D-dimer assay was studied, which could limit extrapolation of our findings to other assays, such as point-of-care devices. As the negative predictive value of the STA-Liatest has been found to be comparable to that of other high-sensitivity assays,[3] we expect these to be similarly safe granted internal quality control measures are in place.

Moreover, the study was not powered to include sample sizes for high-risk subgroups that would have benefited from clear management guidance, as this would have warranted a larger population and scope than feasible for the study. The strategy may be less specific for inpatients,[45] or in other conditions or situations in which D-dimer could be expected to be increased, such as in pregnant patients and in patients with cancer[46] who comprise 4% and 1% of the study population, respectively. False-negative D-dimer could occur in patients with DVT on anticoagulation treatment. Although its effects on D-dimer are still largely unknown,[1] some studies have suggested decreasing D-dimer levels after initiation of anticoagulation therapy.[47] For this reason, patients on a regular prescription of anticoagulants were excluded in this study.

We cannot eliminate the possibility that removing C-PTP assessment led to more DVT being diagnosed and treated. In the event of low C-PTP, physicians might be more inclined not to refer the patient for CUS despite positive D-dimer, or to dismiss an uncertain radiologic finding. However, when performed correctly, falsely interpreted CUS examinations for first DVT are rare. For suspected recurrent ipsilateral DVT, magnetic resonance direct thrombus imaging is an alternative to distinguish between acute and chronic

Table 3. Reasons given by physicians for requesting CUS despite negative D-dimer

	Total, N	No DVT, n	DVT, n
No recorded reason in patient files	14	14	0
Strong suspicion of DVT due to specific symptoms or signs	14	12	2
Evaluate extent of suspected thrombophlebitis to determine treatment	2	2	0
Evaluate other suspected diagnosis than DVT	7	7	0
High C-PTP	4	4	0
Lack of alternative diagnosis to DVT	2	2	0
Total	43	41	2

Reasons as recorded in patient files.

DVT, which would reduce the risk of falsely interpreted CUS in these patients.[10]

Regardless, our strategy should only be used when DVT is suspected and where D-dimer is useful. Conversely, false-positive results could similarly occur with current recommendations referring all perceived high-risk patients for CUS regardless of D-dimer as this is based on subjective evaluation.

To our knowledge, comparisons between alternative D-dimer thresholds, such as stand-alone, age-adjusted, and C-PTP–adjusted D-dimer, have been retrospective.[6,11,34] For future research, a prospective multicenter study with a head-to-head comparison of the various strategies would be useful in determining the optimal strategy. Future research efforts aimed at obviating unnecessary diagnostic workup altogether would further advance the management of patients with suspected DVT, for instance, by identifying new biomarkers and/or developing machine-learning strategies. Increased knowledge of which DVT should be managed conservatively or pharmacologically would aid these efforts.

In conclusion, a single negative whole-leg CUS safely ruled out DVT in patients with positive D-dimer, and negative D-dimer safely ruled out DVT, both irrespective of C-PTP. We consider this strategy to be a valuable alternative to the conventional diagnostic workup of DVT in outpatients.

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Authorship

Contribution: S.G.F. participated in study design, data acquisition, and management of the trial, analyzed and interpreted the data, and drafted and revised the manuscript; C.T.J. participated in data acquisition, daily management of the study, data analyses, and revision of the manuscript; A.E.A.D. participated in protocol drafting, study management, interpretation and revision of the manuscript; H.S.W. participated in protocol drafting, data interpretation, and revision of the manuscript; J.G. participated in study management and drafting and revising of the manuscript; N.R. participated in data acquisition and study management, and revision of the manuscript; R.H. participated in study design, input regarding end-point selection and statistical analyses, and revision of the manuscript; F.A K. participated in data analyses and interpretation and revision of the manuscript; and W.G. was trial manager, was responsible for the design, planning, initiation, and conduction of the study, and participated in data acquisition and interpretation and revision of the manuscript.

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