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


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Safety of D-dimer in deep vein thrombosis exclusion

Essentials

- The aim of deep vein thrombosis 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.

Background

Several strategies for safe exclusion of deep vein thrombosis (DVT) while limiting the number of imaging tests have been explored.

Objectives

We aimed to determine whether D-dimer could safely and efficiently exclude DVT as a stand-alone test and evaluate its performance compared to strategies that incorporate 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 D-dimer ≥0.5 µg/mL were referred for compression ultrasonography (CUS). In patients with D-dimer <0.5 µg/mL, no further testing was performed and
anticoagulation was withheld. Patients were followed for three months for venous thromboembolism (VTE).

**Results**

Of the 913 included patients, 298 (33%) had negative D-dimer. 173 patients (18.9%) were diagnosed with DVT at baseline. One of 298 patients had DVT despite a negative D-dimer, resulting in a failure rate of 0.3% (95% 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. Age-adjusted D-dimer as a stand-alone test would have necessitated 80 fewer CUS 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 negative high-sensitivity D-dimer safely excludes DVT in an outpatient population, and necessitating fewer ultrasound examinations 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 step of deep vein thrombosis (DVT) diagnostic work-up [1]. Assessing pretest probability supported by clinical prediction rules is recommended to guide further testing and to minimize the risk of false negative results among patients with high pretest probability of DVT. The most extensively used and validated clinical prediction rule is the Wells score [2-7]. Originally consisting of nine items, it utilizes elements from patient medical history and physical examination to add or deduct points for a total score of DVT likelihood [2, 3] whereby patients are stratified in low (≤0 points), moderate (1-2 points) and high-risk groups (≥3 points) (Table 1). High-risk patients are referred for diagnostic compression ultrasonography (CUS) without D-dimer testing, while the remaining patients are referred only in the case of a positive D-dimer. In a later modified version of Wells score, another clinical item was added, yielding one point for previously documented DVT [4] and dichotomizing groups into ‘DVT unlikely’ (<2 points) and ‘DVT likely’ (≥2 points), where the ‘DVT likely’ group is referred for CUS without D-dimer testing (Table 2).

Despite its extensive validation and wide use in current diagnostic work-up of DVT, the Wells score has a few limitations. First, it introduces subjectivity in the judgment 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]. Inter-observer variability has not been extensively evaluated [1]. Moreover, D-dimer often forms part of a standard package of laboratory tests obtained in patients with suspected DVT, and results may be analyzed...
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before 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]. Lastly, the differing prevalence of DVT in various studied populations [4, 12-14], perhaps due to the lower diagnostic threshold seen in recent times [15], may further affect the utility of clinical prediction rules, such as Wells score.

The other main component of DVT diagnostic work-up is D-dimer. Its main advantages include wide availability, high negative predictive value, and sensitivity for venous thromboembolism (VTE) (ranging between 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 diagnosis of DVT when employing age-adjusted D-dimer, without safety being compromised [23, 24].

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

This management outcome study aims to assess 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 Wells score, to find the optimal diagnostic strategy.

**Materials and method**

*Study population*

Outpatients referred to the Emergency Department of Østfold Hospital, Norway, are at the time of writing evaluated for enrolment 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 is to assess the safety of rivaroxaban, administered according to predefined criteria, in the pre-diagnosis phase of DVT. Among its other aims is to evaluate D-dimer as a stand-alone test for DVT. This sub-study was conducted when approximately half of the patients had been enrolled.

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 three months or inability or unwillingness to provide written consent. Furthermore, patients with expected survival < three months are excluded from the analysis of developed VTE within three months.

Additional criteria for eligibility for management with rivaroxaban (maximum 2 tablets within 24 hours) 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 sub-study consisted of all patients included in the Ri-Schedule study until August, 2017, including those who received rivaroxaban 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), to which five additional strategies were compared retrospectively. These five, summarized in Figure 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; as well as 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 (REK), 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 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 by the immuno-turbidometric method of STA®-Liatest® D-Di Plus (Stago Diagnostics,
Asnieres, France). A positive fixed D-dimer was defined as levels ≥0.5 µg/mL. Patients with D-dimer <0.5 µg/mL 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 ≥ age x 0.01 µg/mL for patients ≥50 years [22]. For younger patients we used a positivity threshold of ≥0.5 µg/mL.

Patients with positive D-dimer 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 select cases, scanning in 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 which was not initially involved according to reference CUS.

All patients considered DVT negative by either negative D-dimer or CUS were discharged and followed up at three months to determine 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 by study personnel to establish whether they had been diagnosed with VTE or initiated anticoagulation for any reason. Patients in whom anticoagulation had been initiated for other reasons than VTE within the three-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 Figure 1. If we had used D-dimer in combination with the original, three-category Wells score, all patients with a D-dimer of ≥0.5 µg/mL or defined as a high-risk category patient with Wells score of ≥3 points would have been referred for CUS. When used in combination with the modified, two-category Wells score all patients with a D-dimer of ≥0.5 µg/mL or defined as a ‘DVT likely’ category patient by Wells score ≥2 would have been referred for CUS. Age-adjusted D-dimer as a stand-alone test would have resulted in patients being referred to CUS with a D-dimer ≥age x 0.01 µg/mL for patients ≥50 years or ≥0.5 µg/mL for younger patients. Combined with the original and modified Wells scores, patients would have been referred for CUS if they had at least a positive age-adjusted D-dimer or Wells scores ≥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 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 (1) diagnosed with symptomatic VTE or (2) deceased, possibly attributable to VTE within three months in patients where DVT had been ruled out due to negative D-dimer and whom were left untreated (n patients diagnosed with VTE at baseline
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or at three-month follow-up with a negative D-dimer/all patients with negative D-dimer).

Efficiency was expressed as the proportion of patients requiring CUS due to positive D-dimer
(n patients with positive D-dimer/all included patients).

The secondary outcomes were the failure rate, proportion of required CUS and diagnostic
performance of the five additional strategies compared to the primary strategy, evaluated
by failure rate, proportion of required CUS and diagnostic performance. 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 DVT negative), but who were nevertheless
diagnosed with VTE either at baseline or during the three-month follow-up period. The
proportion of required CUS was considered the proportion of all patients fulfilling the criteria
for undergoing CUS according to each strategy. Diagnostic performance was expressed by
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 were
later decided to be conducted when approximately 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
remainder of patients in the study. Based on previous studies negative D-dimer was
expected in 23-35 % of patients [25], yielding an estimate of approximately 300 patients in
whom DVT was ruled out based on a negative D-dimer.

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

The diagnostic performance of each of the six strategies was expressed by 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 using OpenEpi statistical software, Version 3.01, Atlanta, GA, USA, and Wilson method for calculating binomial 95% CI.

Results

General findings

Demographic characteristics are outlined in Table 3.

Of the 1338 patients screened for participation, 973 patients were found eligible, provided written consent, and were included (Figure 2). Of these, 60 patients received anticoagulation for reasons other than VTE between inclusion and the three-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 fifteen patients (67%, 95% CI 64.3-70.3%) had positive fixed D-dimer, while 298 patients (33%, 95% CI 29.7-35.8%) had negative D-dimer (Figure 3). The percentage of patients with positive fixed D-dimer and a ‘DVT likely’ pretest probability was 40% (364
patients). The percentage of patients with positive age-adjusted D-dimer and a ‘Wells likely’ pretest probability was 36% (327 patients).

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

**Study performance and three-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 was diagnosed with DVT at baseline. This was one of the 36 patients who underwent CUS at baseline despite a negative D-dimer. She was in her early fifties and had a two-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 was normal except for unilateral pitting edema and tenderness along the deep venous system, resulting in a Wells score of 2. She was referred to CUS despite negative D-dimer due to 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 were diagnosed with VTE during the three-month follow-up.
As such, one of 298 patients with a negative D-dimer who were analyzed had DVT at the three-month follow-up, yielding a failure rate of 0.3% (95% CI 0.1-1.9%).

Study performance and three-month outcomes of the various strategies

Patient outcomes and diagnostic performance of all the diagnostic strategies are outlined in Table 4. Adding 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 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 the age-adjusted D-dimer as a stand-alone test would have resulted in an additional five patients with false negative D-dimer at inclusion, two with distal and three with proximal DVT. Adding the modified Wells score to age-adjusted D-dimer generated a similar safety profile as the fixed D-dimer as a stand-alone test, though necessitating an additional 44 CUS examinations.

Two of the strategies had a lower proportion of required CUS compared to the 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 from -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 from -9.5 to -0.7%) at the cost of a lower negative predictive value at 98.5% (95% CI 96.6-99.4%).
Adding Wells score generated more CUS examinations than both D-dimer thresholds as stand-alone tests, and the modified Wells score generated more CUS 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. As for the negative predictive value, this increased to 99.6% (95% CI 97.8-99.9%) when adding the modified Wells score to the 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 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 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 a prevalence of VTE of 23 and 12%, respectively, supporting our findings.

In spite of high negative predictive value for D-dimer, the safety of D-dimer as a stand-alone for pulmonary embolism is subject to ongoing debate, even when applying a higher positivity threshold for D-dimer than used in our study, of 750 µg/L [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, ranging between 0.57-2.0%, with 95% CIs ranging from lower to upper limits of 0.2-5.1% [29, 30]. Moreover, it compares favorably to the failure rate after a negative venography (1.3%) [31], which is the reference standard for DVT diagnostic tests or algorithms [1]. Lastly, the upper limit of the CI of the post-test probability of DVT for fixed D-dimer as a stand-alone test was less than 2%. This is considered a satisfactory degree of certainty in diagnostic testing to withhold treatment [1].

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

As for our secondary outcome measures, we found that the fixed D-dimer as a stand-alone test was equally safe as established diagnostic strategies incorporating 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.

Early published evaluations of combined Wells score and D-dimer strategies have 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]. Wells score has subsequently been extensively validated and clinically employed, spanning at least 14 studies with over 10,000 patients [32].

The age-adjusted D-dimer as a stand-alone test had the highest specificity and resulted in the fewest CUS of all strategies. However, it was associated with lowered sensitivity and an additional five false negative cases compared to the fixed D-dimer as a stand-alone test, of whom three had proximal thrombi. 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 consideration clinical practice. Current prospective studies validating age-adjusted D-dimer may help 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, as well as no losses to follow-up in the group with negative D-dimer who did not undergo CUS. Additionally, the DVT prevalence of 19% in our study is comparable to other similarly designed diagnostic studies [3, 4, 26, 27]. This relatively high prevalence decreases the likelihood of a low failure rate resulting from 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 a possibly weaker generalizability than a multi-center study would yield. Another limitation is the protocol deviations whereby patients did and did not undergo CUS despite negative and positive D-dimer, respectively. These deviations would likely 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, to evaluate the extent of clinically suspected thrombophlebitis, or that clinicians may for other reasons wish to exclude DVT despite negative D-dimer or clinical prediction rules. Of the 36 patients who underwent CUS despite a negative D-dimer, 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 strategies but not by fixed D-dimer, remain
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theoretical. As such, 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 enrolment in the study was not an exclusion criterion so long as the previous inclusion was more than three months previous. As the patients enrolled twice were few (14) and only two were not managed per protocol (one patient did not undergo CUS despite a positive D-dimer, and one patient underwent CUS despite a negative D-dimer), we believe 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 observations could limit testing for statistically significant differences between strategies.

While our findings are likely to be generalizable to other outpatient populations with similar DVT prevalence, this may not be the case for inpatient settings or in populations with markedly higher DVT prevalence. Although D-dimer was analyzed by only one method, other studies document 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 high-risk patients for DVT were not excluded in 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% of patients were pregnant. Although none of these patients had false negative D-dimer, the number of patients in the subgroups was too small to conclude regarding the safety of D-
dimer 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 as a stand-alone test was found to be equally safe and to generate fewer CUS than D-dimer combined with Wells score. As the strategy has the additional advantage of being easily adhered to in clinical practice while avoiding subjectivity in evaluation, we believe it is a preferred approach to simplify the diagnostic work-up of DVT.

In conclusion

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

Age-adjusted D-dimer as a stand-alone test generated the lowest number of CUS, but the safety of the strategy needs to be evaluated in prospective outcome studies before being 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 revising of the manuscript. A. Dahm participated in protocol drafting and study management, and interpretation and revising of the manuscript. C.T. Jørgensen participated in data acquisition and daily management of the study, and revising of the manuscript. J. Gleditsch participated in management of the study,
and drafting and revising of the manuscript. N. Raouf participated in data acquisition and study management, and revising of the manuscript. F.A. Klok participated in study design and concept, and interpreting and revising 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 conflicts of interest**

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