E.2 DVT diagnosis (D-dimer)

In people with suspected DVT, what is the effectiveness of D-dimer in ruling out deep vein thrombosis?

Study details	Patients	Diagnostic tools	Outcomes	Results	Comments
Study name: Goodacre 2006 [170] HTA report **Study design:** Systematic review – 99 cohorts included for clinically suspected DVT, 13 for	**Patient group:** clinically suspected DVT **Setting**: Outpatient clinic (21), inpatients (9), emergency department (16), mixed (29), and not stated (14). Recruitment was reported to be consecutive in 76 and prospective in 68. **Exclusion criteria:**	**Assessment tool under investigation:** Threshold value defined before analysis in 82 cohorts, after analysis in 10, and not clear in 7 cohorts. **Reference standard:** (number in brackets denote number of cohorts)	**All assays** **Pooled sensitivity**	90.5% (95% CI 90% to 91%), range 48% to 100%. Heterogeneity: p<0.001 Variation predicted by an outpatient or a mixed setting for patient recruitment, exclusion of patients who were pregnant, anticoagulated or had a long history of symptoms, age, prospective analysis, the D-dimer threshold used and whether the D-dimer threshold was determined before or after the study.	**Funding:** HTA analysis **Limitations:** ▪ In about half of included studies, it was unclear whether D-dimer tests and reference standards were interpreted blind to the results of the other test ▪ Various standard references used

Study details	Patients	Diagnostic tools	Outcomes	Results	Comments
asymptomatic DVT **Duration of follow-up:** Not reported.	No exclusion reported by 50 cohorts. The following criteria were excluded by the number of cohorts in brackets: Postoperative patients(10), pregnant patients(19), anticoagulated patients (33), previous VTE(23), recent trauma(3), sepsis(4), prolonged history (18) **<u>All patients</u>** **N:** 8752 **DVT prevalence**: 2 to 78% median 36% **Age range**: 51 to 69, median 59 years, except one cohort which exclusively recruited people over the age of 70	Venography(34), ultrasound(28), ultrasound with clinical follow up (10), serial ultrasound (6), ultrasound *or* venography (13), others – combinations of ultrasound and plethysmography (8) Reference standard applied independent of D-dimer results in 86 cohorts, dependent in 4 and unclear in 9 cohorts D-dimer was measured blind to reference standard in 43 cohorts and unclear in 56. Reference standard was interpreted blind to D-dimer results in 50 cohorts and unclear in 49 cohorts.	**Pooled specificity**	54.7% (95% CI 54% to 55%), range 5% to 100%. Heterogeneity: p<0.001 Variation predicted by an outpatient, an emergency department or a mixed setting, exclusion of patients who were pregnant, anticoagulated or had a past history of thromboembolism, age, consecutive recruitment, prospective analysis, the reference standard used, and quality criteria relating to blinding of observers measuring D-dimer and blinding or observers interpreting the reference standard.	▪ Heterogeneity not explained when subgroup analysis according to predictors of variability was conducted **Additional tests:** **Notes:** *
			ELISAs **Pooled sensitivity**	91 analyses in 58 cohorts (35 reporting proximal and distal 94% (95% CI 93% to 95%),. Heterogeneity: p<0.001	
			Pooled specificity	45% (95% CI 44% to 46%), Heterogeneity: p<0.001	
			ELISAs **Pooled sensitivity**	74 analyses in 52 cohorts 89% (95% CI 88% to 90%),	

Study details	Patients	Diagnostic tools	Outcomes	Results	Comments
	% Males: 17 to 62% (median 42%) – reported by 81 cohorts **% of proximal DVT (out of all DVT) :** 27% to 100% (median 77%)- reported by 51 cohorts **Drop outs:** N/R		**Pooled specificity**	Heterogeneity: p<0.001 55% (95% CI 54% to 56%),. Heterogeneity: p<0.001	
			ELISAs **Pooled sensitivity**	87% (95% CI 85% to 88%),. Heterogeneity: p<0.001	
			Pooled specificity	68% (95% CI 67% to 69%), Heterogeneity: p<0.001	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Study name: Anoop2009 [27] **Study design:** Prospective cohort (diagnostic)	**Patient group:** Consecutive patient sent for D-dimer testing **Setting:** District general hospital, UK. Conducted from Dec 2007 to March 2008	**Assessment tool under investigation:** **MDA Autodimer ® (**immunoturbidimetric assay using monoclonal antibody) <u>Cut off point:</u> 0.50mcg FEU/mL determined based	**Deep vein thrombosis:** (proximal) **Sensitivity** **Specificity**	<table><tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr><tr><td>D-Di +</td><td>16</td><td>67</td><td>83</td></tr><tr><td>D-Di -</td><td>0</td><td>23</td><td>23</td></tr><tr><td>Total</td><td>16</td><td>90</td><td>106</td></tr></table> 100.0% 25. 6% (95% CI: 17.2-36%)	**Funding:** **Limitations:** ▪ Patients recruited at the point of referral for D-dimer testing, instead of at the point of symptom presentation ie could have missed

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Evidence level:

Duration of follow-up:</td>
<td>Inclusion criteria:
In and out patients

Exclusion criteria:
▪ Intensive care unit patients
▪ Specimen error: D-dimer levels not quantifiable; patients not receiving reference tests or inconclusive results from scans

<u>All patients</u>
N: Total 197 patients, 90 were for suspected DVT, 91 suspected PE

Population characteristics (for patients with suspected DVT)

Median age (range): 70(17-97)

Inpatient/Outpatientr: 41/65</td>
<td>on manufacturer recommendation

<u>Performed by:</u> laboratory personnel blinded to results of pre-test probability score (Wells score)

Reference standard:
Compression ultrasound -
Whole leg (9 common and superficial femoral veins, poplitial trifucation and all three deep vein sets) Unclear whether only symptomatic leg scanned

<u>Performed by:</u>
Not stated</td>
<td>PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN

Deep vein thrombosis:
Patients with Intermediate to High PTP (wells score)
(proximal)

Sensitivity</td>
<td>19.8%
100.0%
Not reported
Not reported
Not reported
23/106 (21.7%)
16/106(15.1%)
1.34
0.00
67
0

<table><tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr><tr><td>D-Di +</td><td>14</td><td>65</td><td>79</td></tr><tr><td>D-Di -</td><td>0</td><td>22</td><td>22</td></tr><tr><td>Total</td><td>14</td><td>87</td><td>101</td></tr></table></td>
<td>patients who were symptomatic and not sent for D-dimer testing
▪ Unclear how many patients were excluded because of non interpretable results
▪ Results of D-dimer and imaging interpreted together by haematologists to diagnose DVT (not blinded)

Additional tests:
Junior doctors completed Wells score for DVT or PE

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td>Drop outs: not stated</td><td></td><td>
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate

Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN
</td><td>
100.0%
25.3%
17.7%
100.0%
Not reported
Not reported
Not reported
21.8%
13.9%
1.34
0.0
65/79 (82.3%)
0
</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Deep vein thrombosis:
Patients with Low PTP (wells score)
(proximal)</td><td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr>
<tr><td>D-Di +</td><td>2</td><td>2</td><td>4</td></tr>
<tr><td>D-Di -</td><td>0</td><td>1</td><td>1</td></tr>
</table>
</td><td></td></tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
				Total 2 3 5	
			Sensitivity		
			Specificity	100.0%	
			PPV	33.3%	
			NPV	50.0%	
			ROC for varying cut offs	100.0%	
			3 month VTE rate	Not reported	
			Mortality	Not reported	
			% negative test result*	Not reported	
			Prevalence	20.0%	
			Positive LR	40.0%	
			Negative LR	1.50	
			FP	0	
			FN	2/4 (50%)	
				0/2(0)	

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study name:
Dempfle 2006 [106]

Study design:
Prospective cohort (diagnostic)

Evidence level:

Duration of follow-up: not reported</td>
<td>Patient group: Patients with clinically suspected acute DVT.

Setting: multi-centre 19 study sites in 3 countries.

Inclusion criteria:
clinically suspected acute (defined as clinical symptoms for 7 days or less) DVT.

Exclusion criteria:
▪ unclear duration of symptoms violated the single entry criterium ‘acute deep venous thrombosis’ (clinical symptoms were present for more than seven days)
▪ hospitalised for more than 72 hours at the time of inclusion;</td>
<td><u>Assessment tool under investigation:</u>

Cardiac D-dimer assay (POCT)

<u>Cut off point:</u> 0.5ug/ml prespecified

<u>Performed by:</u> not reported. Blood was drawn into heparinised syringe, and test were performed within 4 hours

Tina-quant D-dimer

<u>Cut off point:</u> 0.5ug/ml determined on ROC curve

<u>Performed by:</u> ** see notes

VIDAS D-dimer

<u>Cut off point:</u> 0.5ug/ml determined on ROC curve

<u>Performed by:</u> **see notes

<u>Reference standard(RS):</u>

Ultrasound (US)- including</td>
<td>Cardiac C® D-dimer assay (POCT)

Deep vein thrombosis:

all samples available for individual assays</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>216</td><td>132</td><td>348</td></tr>
<tr><td>D-Di -</td><td>7</td><td>205</td><td>212</td></tr>
<tr><td></td><td>223</td><td>337</td><td>560</td></tr>
</table>
Sensitivity 96.9% (95% CI 93.6 to 98.7)
Specificity 60.8% (95% CI 55.4 to 66.1)
PPV 62.1 % (95% CI 56.7 to 67.2)
NPV 96.7% (95% CI 93.3 to 98.7)

ROC for varying cut offs Not reported
3 month VTE rate Not reported
Mortality Not reported
% negative test result * 212/560(37.9%)
Prevalence 223/560 (39.8%)
Positive LR 2.47
Negative LR 0.05 2
</td>
<td>Funding: not reported.

Limitations:
▪ Time between withdrawal of blood sample and ultrasound not reported
▪ Unclear if person performing D-dimer test blinded to results US

Additional tests:
The sensitivity and specificity of D-dimer grouped by Wells scores (>2 vs ≤2).

Notes:
* % of people with negative test result</td>
</tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
	▪ treated with therapeutic doses of UFH or LMWH for more than 24 hours, or vitamin K antagonists ▪ surgical interventions within 30 days before ▪ earlier proven DVT in the same leg (patients not excluded if earlier DVT had been in opposite leg) ▪ trauma needing medical attention ▪ Pregnancy ▪ patients younger than 18 years	compression ultrasound and color Doppler of the the symptomatic leg (minimum specification was B mode ultrasnography with high resolution real time scanner equipped with a 5Mhz electronially focused linear array transducer – better equipments could be used) *Veins examined:* Common femoral vein,	**False positive** **False negative**	132/348 (37.9%) 7/216(3.2%)	indicates the % of patients who will not be undergoing further diagnostic imaging if test is used as a "rule out" criteria. **The remaining whole blood sampled were centrifuged. The heparinised plasma were frozen at -20C, before thawed in the central lab for analysis using 37C water bath.

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>▪ If exclusion criteria were discovered after blood sampling patients were excluded from further analysis s.

<u>All patients</u>

N: 637 recruited

Drop outs: 77/637 (12.1%) mainly due to quality control measures inadequate (34/637)

Mean age (range): 57.7 (18-93)

DVT diagnosed by reference test: 223/560(39.4%)

Malignant disease: 37/560(6.6%)

Treatment with heparin (less than therapeutic dose): 40/560(7.1%)

Mean symptom onset mean±SD (days): 3.1±1.80

Previous DVT: 29/560(5.2%)</td>
<td>popliteal vein at the popliteal fossa down to point of the trifurcation in the prone position.

<u>Performed by:</u>

“local experts” according to standardised protocol

Patients classified as DVT, no DVT or “unclear”. “unclear” patients excluded from analysis.

Negative results documented.</td>
<td>VIDAS-D-dimer

Deep vein thrombosis:

all samples available for individual assays

Sensitivity
Specificity
PPV
NPV

ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN</td>
<td><table><tr><td></td><td>RS +</td><td>RS-</td><td></td></tr><tr><td>D-Di +</td><td>160</td><td>160</td><td>320</td></tr><tr><td>D-Di -</td><td>3</td><td>110</td><td>113</td></tr><tr><td></td><td>163</td><td>270</td><td>433</td></tr></table>
98.2% (95% CI 94.7 to 99.6)

40.7% (95% CI 34.8 to 46.9)

97.3% (95% CI 92.4 to 99.5)

50% (95% CI 44.4 to 55.6)

Not reported

Not reported

Not reported

113/433(26.1%)

163/433(37.6%)

1.66

0.05

160/433

3/113</td>
<td>The D-dimer values were corrected for the difference in plasma dilution resulting from the use of heparinised plasma rather than citrated plasma.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>Tina-quant D-dimer

Deep vein thrombosis:

Total per protocol population (all samples available for individual assays)</td><td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>204</td><td>116</td><td>320</td></tr>
<tr><td>D-Di -</td><td>11</td><td>214</td><td>225</td></tr>
<tr><td></td><td>215</td><td>330</td><td>545</td></tr>
</table>
</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Sensitivity</td><td>94.9% (95% CI 91.0 to 97.4)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Specificity</td><td>64.8% (95% CI 59.4 to 70)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>PPV</td><td>63.8% (95% CI 58.2 to 69.0)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>NPV</td><td>95.1% (95% CI 91.4 to 97.5)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>ROC for varying cut offs</td><td>Not reported</td><td></td></tr>
<tr><td></td><td></td><td></td><td>3 month VTE rate</td><td>Not reported</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Mortality</td><td>Not reported</td><td></td></tr>
<tr><td></td><td></td><td></td><td>% negative test result*</td><td>225/545 (41.3%)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Prevalence</td><td>215/545 (39.4%)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Positive LR</td><td>2.70</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Negative LR</td><td>0.08</td><td></td></tr>
<tr><td></td><td></td><td></td><td>FP</td><td>116/320</td><td></td></tr>
<tr><td></td><td></td><td></td><td>FN</td><td>11/225</td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study name:
Diamond 2005[110]

Study design:
Diagnostic study

Evidence level:

Duration of follow-up: not reported.</td>
<td>Patient group: Patients in the emergency department with suspected DVT.

Exclusion criteria: not reported

<u>All patients</u>

N: 148

Mean age (range): 57.2 years (18 - 92)

Drop outs: not reported.</td>
<td><u>Assessment tool under investigation:</u>

D-dimer – Tina-quant immunoturbidimetric test using latex agglutination (ATL HDI 5000 scanner). The common femoral, deep femoral, femoral, popliteal, posterior tibial, peroneal, gastrocnemious and soleus veins were scanned in the transverse and longitudinal plane.

D-dimer less than 0.5ug/ML was assessed as negative.

Performed by: not stated. Not stated if blinded to reference standard.

Reference standard: Venous duplex by colorflow Doppler. Criteria for diagnosing acute DVT included visualisation of thrombius on B-mode, lack of venous compressibility, and the absence of doppler flow signals distal to the site of suspected thrombosis.

Whole leg- the common femoral, deep femoral, femoral, popliteal,</td>
<td>Deep vein thrombosis:

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>19</td><td>66</td><td>85</td></tr>
<tr><td>D-Di -</td><td>0</td><td>63</td><td>63</td></tr>
<tr><td></td><td>19</td><td>129</td><td>148</td></tr>
</table>
100%
48.8%
22.4%
100%
Not reported
Not reported
Not reported
63/148(42.6%)
12.8%
1.95
0
</td>
<td>Funding: Not reported.

Limitations:
▪ Does not report who undertook the D-dimer assay and whether they were blinded to the gold standard results. Study did not report the time period between the index test and reference standard.

Additional tests: None.

Notes: four patients had a clot limited to the calf veins and 15 had clot extending into the ileofemoral system.</td>
</tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
		posterior tibial, peroneal, gastrocnemious, and soleus veins were scanned in the tranverse and longitudinal plane. **Performed by:** physicians and technologist who were blinded to the results of the D-dimer assay.	**FP** **FN**	66/85 (77.6%) 0/63	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Study name: Dinisio 2006[108] **Study design:** Prospective diagnostic study	**Patient group:** Consecutive outpatients referred for clinically suspected DVT from November 1995 to December 2004 in the Netherlands. Cancer status was recorded at presentation and patients were considered to have active cancer if they were	**Assessment tool under investigation:** **Test1:** Clincial pretest propbabiity (wells score) . **Test 2:** D-dimer test (SimpliRED test). Cut off point**:** DD concentrations >200 mg L^{-1} within 2 min, determined based on agglutination	**D-dimer test** **Patients with cancer** Proximal DVT **False positive** **False negative** **True negative**	<table><tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr><tr><td>D-Di +</td><td>96</td><td>75</td><td>171</td></tr><tr><td>D-Di -</td><td>4</td><td>69</td><td>73</td></tr><tr><td>Total</td><td>100</td><td>144</td><td>244</td></tr></table> 96 75 4	**Funding:** not reported. Authors declared no financial interest in the article. **Limitations:** **Additional tests:**

<table>
<tr>
<td>Duration of follow-up:

3 months</td>
<td>receiving treatment for malignancy, if treatment for cancer was stopped within the last 6 months, or if they were receiving palliative treatment for cancer.

Setting: Netherlands.

Exclusion criteria: None reported.

<u>All patients</u>
N: 2066
With cancer: 244
Without cancer: 1822
Mean Age: With/without cancer 64/58 years</td>
<td><u>Performed and interpreted by:</u> the technicians who were unaware of the results of the diagnostic tests for DVT as well as of the cancer status.

Reference standard: Serial compression ultrasound. In case of an initial normal ultrasound, serial testing was performed 1 week later and if still negative, patients were followed up for 3 months.

The compression ultrasound; performed on the transverse plane of the common femoral vein and the popliteal vein down to the trifurcation of the calf veins.

<u>Performed by: not reported</u>

(blinded to index test)</td>
<td>
Sensitivity
Specificity
NPV
PPV
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR

<u>D-dimer test</u>

<u>Patients without cancer</u>

Proximal DVT

True positive
False positive
False negative
True negative
</td>
<td>
69
96
47
95
56
Not reported
Not reported
73/244 (29.9%)
100/244 (41.0%)
1.8
0.08

<table>
<tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr>
<tr><td>D-Di +</td><td>375</td><td>534</td><td>909</td></tr>
<tr><td>D-Di -</td><td>30</td><td>883</td><td>913</td></tr>
<tr><td>Total</td><td>405</td><td>1417</td><td>1822</td></tr>
</table>
375
534
30
883
</td>
<td>Notes:</td>
</tr>
</table>

			Sensitivity	92.5%	
			Specificity	62.3%	
			NPV	96.7	
			PPV	41.3	
			3 month VTE rate	Not reported	
			Mortality	Not reported	
			% negative test result*	913/1822 (50.1%)	
			Prevalence	405/1822(22.2%)	
			Positive LR	2.46	
			Negative LR	0.12	
			D-dimer test **All patients** **Proximal DVT**	<table><tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr><tr><td>D-Di +</td><td>471</td><td>609</td><td>1080</td></tr><tr><td>D-Di -</td><td>34</td><td>952</td><td>986</td></tr><tr><td>Total</td><td>505</td><td>1561</td><td>2066</td></tr></table>	
			True positive	471	
			False positive	609	
			False negative	34	
			True negative	952	
			Sensitivity	93.27%	

			Specificity	60.99%	
			NPV	96.6%	
			PPV	43.6%	
			3 month VTE rate	Not reported	
			Mortality	Not reported	
			% negative test result*	986/2066 (47.7%)	
			Prevalence	505/2066 (24.4%)	
			Positive LR	2.4	
			Negative LR	0.11	

Study details	**Patients**	**Diagnostic tools**	**Measure of Disorders**	**Results**	**Comments**
Study name: Fukuda 2007[148] **Study design: diagnostic study**	**Patient group:** consecutive outpatients with clinically suspected DVT of a lower limb. **Exclusion criteria:** Previous episode of DVT, stable symptoms at presentation or prophylactic anticoagulants already applied at presentation.	**Assessment tool under investigation**: **PATHFAST D-dimer assay** (chemiluminescent enzyme immunoassay) **Cut off point:** 0.570ug/mL, determined based on ROC curve from 124 healthy	**PATHFAST D-dimer assay** Cut off point 0.570ug/mL **Sensitivity** **Specificity** **PPV** **NPV** **AUV of ROC curve**	 100% (87.7 to 100) 63.2% (46 to 78.2) 66.% 100% 0.957(0.918 to 0.996)	**Funding:** Test kits provided by Mitsubishi Kagaku Iatron Inc, Japan. Staff of manufacturer provided blood samples for the "healthy control".

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Evidence level: **Duration of follow-up:**	**<u>All patients</u>** **N:** 82 **Age range:** 23-85 years **Drop outs:** not stated Prevalence: 28/82(34.1%)	volunteers (see "Funding"). No specific cut off point recommended by manufacturer <u>Performed by:</u> not reported. **Reference standard:** Compression ultrasonography **<u>Performed by:</u>** not reported.	**Prevalence** **Positive LR** **Negative LR** **Efficiency**	28/82(34.1%) 78.8%	**Limitations:** No description of how reference test was conducted, or basis of classifying patients as having DVT or not **Additional tests:** **Venography** **computed tomography** **VIDAS D-dimer assay.** ELFA assay principle, combining the ELISA test method with a final blue fluorescent reading Correlation between the two tests noted
			Cut off point at 0.800ug/mL **Sensitivity** **Specificity** **PPV** **NPV** **Positive LR** **Negative LR** **Efficiency**	(95% CI) 96.4 (81.7 to 99.9) 71.1 (54.1 to 84.6) 71.1% 96.4% 81.8%	
			Cut off point at 1.280 **Sensitivity** **Specificity** **PPV**	(95% CI) 92.9 (76.5 to 99.1) 84.2 (68.7 to 94.0) 81.3%	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
			NPV	94.1%	**Notes:**
			Positive LR		
			Negative LR		
			Efficiency	87.9%	
			Cut off point at 1.500	(95% CI)	
			Sensitivity	92.9% (76.5 TO 99.1)	
			Specificity	86.8% (71.9 TO 95.6)	
			PPV	83.9%	
			NPV	94.3%	
			Positive LR		
			Negative LR		
			Efficiency	89.4%	

<table>
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<tr>
<td>Study name:
Ilkhanipour 2004[203]

Study design:
Prospective diagnostic study

Duration of follow-up:
None</td>
<td>Patient group: adult (over 18 years) emergency department patients suspected of having lower extremity acute DVT, and had symptoms for less than 1 month.

Setting: conducted at 2 sites, a university hospital and a community teaching hospital in US. From June 2000 and February 2002.

Exclusion criteria: excluded if refused to participate, or had symptoms for longer than one month.

<u>All patients</u>
N: 336 (365 before excluded)
Mean age (range):54 (19-95)
F/M ratio: 65/35</td>
<td>Assessment tool under investigation:

VIDAS D-dimer

<u>Cut off point:</u> 0.5ug/ml determined on ROC curve

<u>Performed by:</u> not reported

Reference standard:

Duplex ultrasound of the lower extremities using a 128 XP scanner with a 5 MHz linear array probe. The pelvic inguinal, and femoral veins were evaluated with the patient in a supine position.

Patients with a high Wells</td>
<td><u>D-dimer test</u>

<u>All patients</u>

DVT

Sensitivity
Specificity
PPV
NPV
% negative test result*
Prevalence
3 month VTE rate
Mortality
Positive LR
Negative LR

<u>D-dimer test</u>

<u>Low pretest probability(Wells score)</u></td>
<td>
<table>
<tr><th></th><th>RS +</th><th>RS-</th><th>Total</th></tr>
<tr><td>D-Di +</td><td>31</td><td>159</td><td>190</td></tr>
<tr><td>D-Di -</td><td>2</td><td>144</td><td>146</td></tr>
<tr><td>Total</td><td>33</td><td>303</td><td>336</td></tr>
</table>
93.9%
47.5%
16.3%
98.6%
43.5%
9.8%
Not reported
Not reported
1.79
0.13

<table>
<tr><th></th><th>RS +</th><th>RS-</th><th>Total</th></tr>
</table>
</td>
<td>Funding: unrestricted educational grant and D-dimer kits from bioMerieux Vitek, Inc manufacturer of test kits

Limitations:
Blinding unclear

Additional tests:
Wells score performed by emergency care physicians, residents or certfied nurse practitioners

Notes:
Rapid ELISA D-dimer</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Drop outs: 29 incomplete data</td>
<td>clinical probability for DVT but had a negative ultrasound were recommended to have a repeat duplex ultrasound study in one week.

<u>Performed by:</u> experienced vascular technicians blinded to the results of ELISA test and clinical probability score. Vascular surgeon over read the initial classifications and classify these into acute or chronic thrombosis</td>
<td>DVT

Sensitivity
Specificity
PPV
NPV
% negative test result*
Prevalence
3 month VTE rate
Mortality
Positive LR
Negative LR

<u>D-dimer test</u>
<u>Intermediate to high pretest probability (Wells Score)</u>
DVT</td>
<td>
<table>
<tr><td>D-Di +</td><td>2</td><td>56</td><td>58</td></tr>
<tr><td>D-Di -</td><td>0</td><td>60</td><td>60</td></tr>
<tr><td>Total</td><td>2</td><td>116</td><td>118</td></tr>
</table>
100.0%
51.7%
3.4%
100.0%
50.8%
1.7%
Not reported
Not reported
2.07
0.0

<table>
<tr><td></td><td>RS +</td><td>RS-</td><td>Total</td></tr>
<tr><td>D-Di +</td><td>29</td><td>103</td><td>132</td></tr>
<tr><td>D-Di -</td><td>2</td><td>84</td><td>86</td></tr>
</table>
</td>
<td>test carried out.</td>
</tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
				Total 31 187 218	
			Sensitivity	93.5%	
			Specificity	44.9%	
			PPV	22.0%	
			NPV	97.7%	
			% negative test result*	39.4%	
			Prevalence	14.2%	
			3 month VTE rate	Not reported	
			Mortality	Not reported	
			Positive LR	1.70	
			Negative LR	0.1436	

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study name:
Neale 2004[293]

Study design:
Prospective cohort (diagnostic)

Evidence level:

Duration of follow-up: not reported.</td>
<td>Patient group: Patients with clinically suspected DVT.

Setting: Emergency Department, Wales

Exclusion criteria: less than 18 years old; had experienced recent trauma (<6 weeks); had undergone recent surgery (< 6 weeks); were pregnant; had an underlying malignancy; having anticoagulant treatment; if the investigators were unable to perform venography (because of technical difficulties, or previous reaction to contrast).

<u>All patients</u>

N: 187</td>
<td>Assessment tool under investigation: Simplify D-dimer;

<u>Cut off point:</u> 80ng/ml

Venous blood taken from each patient then Simplify D-dimer test performed immediately.

Test 2: SimpliRED D-dimer

<u>Cut off point:</u> 120ng/ml

Test 3: Auto D-dimer (latex agglutination test).

<u>Cut off point:</u> 120ng/ml

Determined based on ROC.

Blood sent to haematology lab for the SimpliRED and latex agglutination tests.</td>
<td>Simplify D-dimer

Deep vein thrombosis:

Cut-off point of 80ng/ml

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>48</td><td>81</td><td>129</td></tr>
<tr><td>D-Di -</td><td>3</td><td>55</td><td>58</td></tr>
<tr><td></td><td>51</td><td>136</td><td>187</td></tr>
</table>
94.1% (87.7 to 100)
40.4% (32.2 to 48.7)
37.2% (28.9 to 45.6)
94.8% (91.0 to 98.6)
Not reported
Not reported
Not reported
Not reported
0.273
1.58
0.15
81
3
</td>
<td>Funding: None.

Limitations:
▪ No details on contrast venography method-Does not report how much of the leg was scanned.
▪ unclear if consecutive patients.

Additional tests: n/a

Notes: n/a</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Mean age (range): not reported.

Drop outs: n/a</td>
<td><u>Performed by:</u> haematology staff who were blinded to the venogram results.

Reference standard: Contrast venography

<u>Performed by:</u>

Radiology staff who were blinded to D-dimer results.</td>
<td>AUTO D-dimer

Cut-off point of 120ng/ml

Deep vein thrombosis

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>46</td><td>77</td><td>123</td></tr>
<tr><td>D-Di -</td><td>5</td><td>59</td><td>64</td></tr>
<tr><td></td><td>51</td><td>136</td><td>187</td></tr>
</table>
90.2 (82.0 to 98.4)
43.4 (35.1 to 51.7)
37.4 (28.8 to 45.9)
92.2 (87.4 to 96.9)
Not reported
Not reported
Not reported
Not reported
0.273
1.59
0.23
77
5
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>SimpliRED D-dimer
Deep vein thrombosis:

Cut-off point of 120ng/ml

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN</td><td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>38</td><td>23</td><td>61</td></tr>
<tr><td>D-Di -</td><td>13</td><td>113</td><td>126</td></tr>
<tr><td></td><td>51</td><td>136</td><td>187</td></tr>
</table>
74.5 (62.5 to 86.5)
83.1 (76.8 to 89.4)
62.3 (50.1 to 74.5)
89.7 (82.0 to 97.3)
Not reported
Not reported
Not reported
Not reported
0.273
4.41
0.31
23
13
</td><td></td></tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Study name: Palen 2005[310] **Study design:** Observational cohort (diagnostic) **Evidence level:** **Duration of follow-up:** 1st part of the study; 3 months (in most cases 12 months)	**Patient group:** Outpatients in a large group model managed healthcare organization with clinically suspended DVT, who were referred to the radiology department for lower extremity compression ultrasound. **Setting:** **Inclusion criteria:** **Exclusion criteria:** **All patients** **1st study period**	**Assessment tool under investigation:** Vidas D-Di ™ bioMerieux (Marcy l'Etoile, France), D-Di Lia® test Diagnostica Stago (Asnieres, France), MiniQuant ™ D-dimer Assay Biopool International (Ventura, CA). Cut off point: different cut off points used in the three D-dimer types. Results are reported by D-dimer type and cut off point. Performed by: (blinded to reference standard?) **Reference standard:** duplex ultrasound imaging of lower	**1st study period (n=117)** **Vidas D-dimer (cut off point 500 ng/Ml FEU)** **Deep vein thrombosis:** **Sensitivity** **Specificity** **PPV** **NPV** **b)Vidas D-dimer (cut off point 1000 ng/Ml FEU)** **Deep vein thrombosis:** **Sensitivity** **Specificity** **PPV** **NPV** **ROC (largest area under the curve)** **3 month VTE rate**	94.7 (71.9-99.7) 39.8 (30.2-50.2) 23.4 (14.8-34.7) 97.5 (90.2-99.6) 94.7 (71.9-99.7) 39.8 (30.2-50.2) 23.4 (14.8-34.7) 97.5 (90.2-99.6) 0.821 (0.746-0.941)	**Funding:** Not reported **Limitations:** very poor methodology. **Additional tests:** **Notes:** no clear if patients were consecutive. *study reported 100% sensitivity, which is not possible for the other values provided

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
	N: 117 patients were evaluated by Vidas D-dimer test, 76 patients received both Vidas and BioPool Miniquant tests, and 80 patients received both the Vidas and the Stago LIA tests. **Proportion of patients under 65 years:** 43.5% **Drop outs:** not reported (1 patient was found to have undergone a follow up ultrasound exam for a previously diagnosed DVT	extremity <u>Performed by:</u> Radiologists were blinded to results of the D-dimmer assays.	**Miniquant D-dimer (cut off point 500 ng/Ml FEU)** **Deep vein thrombosis:** **Sensitivity** **Specificity** **PPV** **NPV**	92.3 (62.1-99.6) 60.3(47.2-72.2) 32.4 (18.6-49.9) 97.4 (84.4-99.9)	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
	and was excluded from the study).		**Miniquant D-dimer (cut off point 800 ng/Ml FEU)** **Deep vein thrombosis:** **Sensitivity** **Specificity** **PPV** **NPV** **ROC (largest area under the curve)** **3 month VTE rate** **Mortality** **% negative test result*** **Prevalence** **Positive LR** **Negative LR** **FP** **FN**	92.3 (62.1-99.6) 74.6(61.8-84.4) 42.9 (25.0-62.6) 97.9 (81.9-100) 0.800 (0.744-0.950)	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
			Stago D-dimer (cut off point 400 ng/Ml FEU) **Deep vein thrombosis:** **Sensitivity** **Specificity** **PPV** **NPV**	 100 (73.2-99.3) 72.7(60.2-82.6) 43.8 (26.8-62.1) 100 (86.7-99.7)	
			f)Stago D-dimer (cut off point 500 ng/Ml FEU) **Deep vein thrombosis:** **Sensitivity** **Specificity** **PPV** **NPV**	 Reporting error *(73.2-99.3) 77.3(65.0-86.3) 48.3 (29.9-67.1) Reporting error *(85.4-99.7) 0.885 (0.723-0.938)	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Study name: Rectenwald 2005[349] **Study design:** Prospective (diagnostic) **Evidence level:** **Duration of follow-up:**	**Patient group:** Patients who completed a lower extremity duplex ultrasound examination. Controls were recruited randomly from the laboratory of one of the co-authors. 3 groups were included; Group 1 (normal volunteers), Group 2 (patients positive for DVT on duplex ultrasound), Group 3 (patients with symptoms of leg pain but negative duplex ultrasound for DVT) **Symptomatic patients:** those who exhibited unilateral leg pain or swelling, or bilateral leg pain or swelling with a compelling history for DVT and the absence of uncompensated congestive heart failure, hypoalbuminemic state, or anasarca. **Criteria for a positive duplex ultrasound:** 1) Incompressibility of the dilated vein 2) lack of color flow and pulse wave Doppler signal with distal augmentation in the vein congruent with a significant lack of echogenicity of the thrombus, 3) presence of few collateral veins.	**Assessment tool under investigation: Advanced D-dimer;** a latex enhanced automated turbidometric assay (Dade-Behring, Deerfield, IL). **Cut off point**: 3 mg/l Performed by: all analyses performed in a blinded fashion **Reference standard:** duplex ultrasound imaging of lower extremity Performed by: not reported	**Deep vein thrombosis:** (cut off point:3 mg/l) Use of D-dimer as dichotomous variable **Sensitivity** **Specificity** **PPV** **NPV**	 64% 76% not reported not reported	**Funding:** not reported **Limitations:** no information on prevalence, unable to calculate the true, false positve and negative, PPV, NPV, PLR, NLP. **Additional tests:** Soluble P-selectin, Total microparticles **Notes:** not clear if patients were consecutive

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
	Setting: University of Michigan Diagnostic Vascular Unit **Inclusion criteria:** 1) aged 18 years or over, 2) confirmed diagnosis of iliofemoral or femoropopliteal DVT by duplex ultrasound or symptomatic for DVT clinically but negative for DVT by duplex ultrasound 3) willingness to sign informed consent and 4) control subjects with no clinical signs, symptoms or history of DVT **Exclusion criteria:** 1) pregnancy 2) immunosuppressive medications 3) presence of calf level venous thrombosis only without more proximal location. **All patients** **N:** 73, Group 1 (30), Group 2 (22), Group 3 (21). **Mean age (sd):** Group 1; 28.7 (11), Group 2; 48.2 (19), Group 3; 51.1 (17) **Drop outs:** not reported				

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study name:

RUIZGIMENEZ2004[368]

Study design:

Prospective cohort (diagnostic)

Evidence level:

Duration of follow-up:

Up to 3 months

Patients with DVT excluded were followed up by phone or medical reports to monitor</td>
<td>Patient group:

Consecutive outpatients with suspected DVT of the lower limbs

Setting:

Emergency department

May 2000 to Sept 2001

Inclusion criteria:

Presented with signs and symptoms of DVT – pain swelling, and/or erythema in the lower extremity.

Exclusion criteria:
▪ Pregnant women and children
▪ Clinical suspicion of pulmonary embolism
▪ Anticoagulant</td>
<td>Assessment tool under investigation:

Test1:

<u>Wells score</u> (<u>original model Wells1995)</u>

<u>Performed by:</u> Not stated

Test 2:

<u>VIDAS D-dimer Assay</u>
(bioMerieux, France)

<u>Cut off point:</u>

1mcg/mL determined based on ROC, &

500ng/mL (manufacturer recommendation)

<u>Performed by:</u> Not stated

Reference standard:

<u>Ultra sonography</u></td>
<td>Deep vein thrombosis:

Cut off point of 1mcg/mL for VIDAS D-dimer

2x2 table is based on follow up of up to 3 months.

Sensitivity
Specificity
PPV
NPV
3 month VTE rate
Mortality

% negative test result*
Prevalence
Positive LR
Negative LR
FP</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>100</td><td>136</td><td>236</td></tr>
<tr><td>D-Di -</td><td>2</td><td>145</td><td>147</td></tr>
<tr><td></td><td>102</td><td>281</td><td>383</td></tr>
</table>
98.0%
51.6%
42.4%
98.6%
102/383
Not reported

38.4%
26.6%
2.03
0.0380
</td>
<td>Funding:

Limitations:

Additional tests:

Notes:
* % of people with negative test result indicates the % of patients who will not be undergoing further diagnostic imaging if test is used as a “rule out” criteria.</td>
</tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
development of symptomatic VTE. Patients were instructed to return to the emergency department if signs and symptoms of DVT or PE appeared.	▪ treatment for more than 48 hours before referral ▪ non availability for follow up **<u>All patients</u>** **N:** 401 included from 473 screened **Mean age (range):** **Drop outs:**	<u>Performed by:</u> 1. general radiologist or 3rd or 4th year resident (on the same day). Entire proximal deep vein system was explored for compressability. Coloour doppler imaging was helpuful in indentifying venous vessels but not mandatory. **2.** Expert vascular radiologist (one week later). Failure to compress the lumen of the vein fully with the ultrasonic transducer or the presence of an intraluminal filling defect inside the vein was criteria for presence of DVT. DVT excluded if both common and popliteal veins were fully compressible and no residual lumen seen.	**FN**		
			Deep vein thrombosis: Using 500mcg/L **Sensitivity** **Specificity** **PPV** **NPV** **ROC for varying cut offs** **3 month VTE rate** **Mortality** **% negative test result***	 99 (93.8-99.9) 32(26.6-37.8) 98.9(93-99.9) 1.4%(0.4% to 3.7%)	

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study name: Subramaniam2006C [415]

Study design:
Prospective cohort (diagnostic)

Evidence level:

Duration of follow-up: 3 months</td>
<td>Patient group: Ambulatory outpatients with suspected lower limb DVT.

Setting: emergency department of a tertiary centre.

Inclusion criteria: consecutive patients at the Emergency department with suspected lower limb DVT.

Exclusion criteria: on current anticoagulation therapy (n=7); failure to perform a D-dimer blood test before sonographic examination (n=5); technical inability to perform an adequate complete compression sonographic examination (n=4).</td>
<td>Assessment tool under investigation:

Simplify D-dimer

<u>Cut off point:</u> not reported.

<u>Performed by:</u> (blinded to reference standard?)

Hamilton score

<u>Cut off point:</u> not reported.

<u>Performed by:</u> (blinded to reference standard?)

Hamilton score and simplify D-dimer

<u>Cut off point:</u> not reported.

Reference standard:</td>
<td>Deep vein thrombosis:

Simplify D-dimer

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs

3 month VTE rate

Mortality

% negative test result*

Prevalence</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>59</td><td>109</td><td>168</td></tr>
<tr><td>D-Di -</td><td>8</td><td>136</td><td>144</td></tr>
<tr><td></td><td>67</td><td>245</td><td>312</td></tr>
</table>
88.00% (77.82 to 94.74)
55.51% (49.0 to 61.8)
35.12% (27.93 to 42.85)
94.44% (89.35 to 97.57)

1 patient at follow up was diagnosed with PE. 10 patients who had second sonography had no DVT.

0/312

0.215

1.98
</td>
<td>Funding: Not reported.

Limitations: Unclear reporting of first 214 patients.

Additional tests: Hamilton score and Hamilton score plus simplify D-dimer

Notes: the first 214 patients recruited for the study were given D-dimer testing. On the basis of this analysis, the Hamilton score was developed (aim of study) which was then validated and compared with the modified Wells scores in another 312 patients. The D-dimer results are given for this population of 312.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td><u>All patients</u>

N: 542 (recruited), n=526 after excluded (see above); 214 entered the D-dimer test and 312 were tested with the Hamilton score.

Mean age range (in patients tested with D-dimer): 18-88 years

Drop outs:</td><td>Duplex compression sonography

Whole leg from inguinal ligament to the medial malleolus

<u>Performed by:</u>

Experienced sonographers and radiology residents under supervision of consultant radiologists.

Doppler examination of veins performed as supplemental information as a road map but not for deciding the result.</td><td>Positive LR
Negative LR
FP
FN
Accuracy</td><td>0.22

0.625</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Deep vein thrombosis:

Hamilton score and simplify D-dimer

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality</td><td><table><tr><td></td><td>RS +</td><td>RS-</td><td></td></tr><tr><td>D-Di +</td><td></td><td></td><td></td></tr><tr><td>D-Di -</td><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td><td></td></tr></table>
98.51 (92.0 to 99.96)
41.63 (35.4 to 48.0)
31.60 (25.34 to 38.35)
99.00 (94.71 to 99.98)</td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Deep vein thrombosis:
Hamilton score

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs</td><td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td></td><td></td><td></td></tr>
<tr><td>D-Di -</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
66.67 (54.0 to 77.8)
71.14 (65.64 to 76.72)
38.26 (29.35 to 47.79)
88.83 (83.58 to 92.87)</td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study name: Subramaniam 2006A [416]

Study design:
Prospective cohort (diagnostic)

Evidence level:

Duration of follow-up: 3 months</td>
<td>Patient group: Patients with suspected lower limb DVT

Setting: Emergency department, Australia.

Inclusion criteria: referred by gps to the emergency department with suspected lower limb DVT.

Exclusion criteria: history of objectively confirmed lower limb DVT; currently on anticoagulation, failure to perform immunochromatographic D-dimer assay before ultrasound examination and inability to perform an adequate complete lower limb compression ultrasound examination.</td>
<td>Assessment tool under investigation:

Simplify D-dimer (Agen Biochemical, Australia)

<u>Cut off point:</u> not reported.

<u>Performed by:</u> Department of Haematology staff with minimal training.

Reference standard: duplex compression ultrasound (Acuson Sequoia 512, USA).

”Doppler examination used as a road map but not to decide result”??

Whole leg – from the level of inguinal ligament to</td>
<td>Deep vein thrombosis:

Proximal and distal

Simplify D-dimer

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate

Mortality
% negative test result*
Prevalence
Positive LR
Negative LR</td>
<td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>74</td><td>152</td><td>226</td></tr>
<tr><td>D-Di -</td><td>13</td><td>214</td><td>227</td></tr>
<tr><td></td><td>87</td><td>366</td><td>453</td></tr>
</table>
85.1% (75.8 to 91.8)
58.5% (53.4 to 63.5)
32.7% (26.6 to 38.9)
94.3% (90.9 to 96.9)

11/453 readmitted with suspected episodes for DVT or PE and 0/453 found to have by US or US + CTPA
0/453

0.192
2.05
0.26
</td>
<td>Funding: Department of radiology research fund, New Zealand. States no funding from manufacturers of D-dimer.

Limitations:

Additional tests: Hamilton score for DVT.

Notes: Of 227 with negative D-dimer, 13 had isolated calf DVT. States in conclusion that D-dimer has a very high NPV for both proximal and isolated calf DVT.</td>
</tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
	<u>All patients</u> **N:** 453 **Mean age (s.d): 55.8 years (20.3)** **Drop outs:**	medial malleolus. **<u>Performed by:</u>** 7 consultant radiologists who were blinded to the D-dimer results.	**FP** **FN**		

Studies with cut off levels determined based on predetermined sensitivity levels

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Study name: Stevens 2005[413] Study design: Prospective cohort (diagnostic) Evidence level: Duration of follow-up: 3 months.	Patient group: Inpatients and outpatients with susepected lower extremity DVT. Setting: LDS Hospital, USA. Inclusion criteria: 18 years of age or older; who provided informed consent and were referred to the peripheral vascular laboratory of the LDS Hospital, because symptoms suggested a first-episode of lower extremity DVT. Exclusion criteria: pregnant; referred to the	**Assessment tool under investigation:** **Test 1: VIDAS D-dimer assay (bioMErieux, USA)** Cut off point: **160ng/ml** **Test 2: STA LIATEST D-DI (Diagnostica Stago, USA)** Cut off point: **530ng/ml** **Test 3: MiniQuant (BioPool International Inc, USA)** Cut off point: **160ng/ml**	**Deep vein thrombosis:** **VIDAS D-dimer** **Sensitivity** **Specificity** **PPV** **NPV** **ROC for varying cut offs** **3 month VTE rate** **Mortality** **% negative test result*** **Prevalence** **Positive LR** **Negative LR**	<table><tr><td></td><td>RS +</td><td>RS-</td><td></td></tr><tr><td>D-Di +</td><td>53</td><td>166</td><td>218</td></tr><tr><td>D-Di -</td><td>1</td><td>158</td><td>159</td></tr><tr><td></td><td>54</td><td>323</td><td>377</td></tr></table> 0.982 0.488 (0.434 to 0.542) Not reported 0.994 Not reported Not reported Not reported 42.1% 14.2% 1.92 0.04	**Funding:** Not stated apart from the provision of anallyszers and reagents from companies. **Limitations:** ▪ The sensitivity was 'chosen' for all tests and cut off points derived from ROC curve ▪ We had to calculate the results from the sensitivity and specificity given. **Additional tests:** **Notes:** A blood sample was taken and an aliquot of plasma frozen at -70

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>peripheral vascular laboratory for any reason other than a first episode lower extremity DVT; anticipated geographical inaccessibility for follow-up; treatment with therapeutic doses of heparin or low molecular weight heparin for greater than 24 hours prior to enrolment; a requirement for long-term anticoagulation for any other cause, technical inability to perform duplex ultrasonography or lack of informed consent.

<u>All patients</u>
N: 436
Mean age, s.d (range): 56 +/-17.3 (19-94)
Drop outs:</td>
<td>Test 4: MDA D-dimer assay (bioMeieux)

<u>Cut off point:</u> 520ng/ml

Test 5: AUTO D-dimer (Sigma, USA)

<u>Cut off point:</u> 220 FEU

<u>Performed by:</u> Technicians who were blinded to the ultrasound results

Reference standard: Comprehensive duplex ultrasonography (CDU)

<u>Performed by:</u>
Vascular surgical staff</td>
<td>FP
FN

Deep vein thrombosis:
STA LIATEST D-DI

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*
Prevalence</td>
<td>

<table><tr><td></td><td>RS +</td><td>RS-</td><td></td></tr><tr><td>D-Di +</td><td>53</td><td>149</td><td>201</td></tr><tr><td>D-Di -</td><td>1</td><td>175</td><td>176</td></tr><tr><td></td><td>54</td><td>323</td><td>377</td></tr></table>0.982
0.540 (0.486 to 0.594)
Not reported
0.994
Not reported
Not reported
Not reported
46.6%
14.2%
2.13</td>
<td>degrees centigrade and stored. The D-dimer assays were performed in batches with thawed specimens.

The sensitivity was chosen for all tests at 0.982.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td>Refusal of phlebotomy, failure to report for phlebotomy after enrolment and errors in specimen processing resulted in inability to analyse all five D-dimer assays in 59 specimens (13.5%).

377 had all assays performed.</td><td>interpreted the CDU according to clinical protocols;</td><td>Positive LR
Negative LR
FP
FN</td><td>0.03</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Deep vein thrombosis:
MiniQuant</td><td><table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>53</td><td>231</td><td>283</td></tr>
<tr><td>D-Di -</td><td>1</td><td>93</td><td>94</td></tr>
<tr><td></td><td>54</td><td>323</td><td>377</td></tr>
</table></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
Mortality
% negative test result*</td><td>0.982
0.287 (0.238 to 0.336)
Not reported
0.989
Not reported
Not reported
Not reported
24.9%</td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>
Prevalence
Positive LR
Negative LR
FP
FN
</td><td>
14.2%
1.38
0.06
</td><td></td></tr>
<tr><td></td><td></td><td></td><td>
Deep vein thrombosis:
MDA D-dimer

Sensitivity
Specificity
PPV
NPV
ROC for varying cut offs
3 month VTE rate
</td><td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>53</td><td>164</td><td>216</td></tr>
<tr><td>D-Di -</td><td>1</td><td>160</td><td>161</td></tr>
<tr><td></td><td>54</td><td>323</td><td>377</td></tr>
</table>
0.982
0.494 (0.440 to 0.548)
Not reported
0.994
Not reported
Not reported
Not reported
</td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Diagnostic tools</th><th>Measure of Disorders</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>
Mortality
% negative test result*
Prevalence
Positive LR
Negative LR
FP
FN
</td><td>
42.6%
14.2%
1.94
0.04
</td><td></td></tr>
<tr><td></td><td></td><td></td><td>
Deep vein thrombosis:
AUTO D-dimer

Sensitivity
Specificity
PPV
NPV
</td><td>
<table>
<tr><td></td><td>RS +</td><td>RS-</td><td></td></tr>
<tr><td>D-Di +</td><td>53</td><td>111</td><td>164</td></tr>
<tr><td>D-Di -</td><td>1</td><td>213</td><td>213</td></tr>
<tr><td></td><td>54</td><td>323</td><td>377</td></tr>
</table>
98.2%
65.7% (60.5% to 70.9%)
Not reported
99.5%
Not reported
</td><td></td></tr>
</table>

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
			ROC for varying cut offs	Not reported	
			3 month VTE rate	Not reported	
			Mortality	63.8%	
			% negative test result*	14.2%	
			Prevalence	2.86	
			Positive LR	0.03	
			Negative LR		
			FP		
			FN		