

Critical Review Form

Meta-analysis

Fancher TL, et al. Combined Use of Rapid D-dimer Testing and Estimation of Clinical Probability in the Diagnosis of DVT: A Systematic Review, BMJ 2004; 329: 821-828.

Objectives: “To summarize the evidence supporting the use of rapid D-dimer testing combined with estimation of clinical probability to exclude the diagnosis of deep venous thrombosis among outpatients.” (p. 821)

Methods: After MEDLINE and DARE search English-language articles from 1993-2003 using a combination of MESH headings, two authors independently reviewed abstracts for inclusion in this meta-analysis. They identified 240 relevant abstracts and retrieved 84 of them after reviewing the abstracts. Of these 84, 17 met inclusion criteria and 12 ultimately offered sufficient detail and methodology for inclusion. There were 10 inclusion criteria: clinical study, use of a rapid D-dimer assay, pre-test DVT probability assessment using validated tool, prospective evaluation of consecutive outpatients with outpatients & inpatients analyzed separately if both enrolled, three-month follow-up on all patients, objective documentation of DVT, and sufficient data detail to permit calculation of sensitivity, specificity, and DVT prevalence stratified by pre-test probability level. The results were reported as pooled data based upon two types of study: accuracy and management.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes, to summarize existing evidence supporting rapid D-dimer testing combined with estimation of clinical probability to exclude the diagnosis of DVT among outpatients (p. 821).
2.	Was the search for relevant studies details and exhaustive?	The authors searched MEDLINE and DARE for English-language articles from 1993-2003. They also searched the reference lists of retrieved articles. They utilized an impressive keyword search, but excluded non-English articles and did not utilize such resources as EMBASE or Cochrane Reviews (p. 822).
3.	Were the primary studies of high methodological quality?	“We adapted the assessment of the trial’s quality from the Cochrane methods group on systematic review of screening and diagnostic tests” (p. 822). However, the authors did not attempt to report upon or weigh the level of evidence.
4.	Were the assessments of the included studies reproducible?	Since the authors used the published, accepted, and widely utilized Cochrane criteria, the assessments were presumably reproducible. No attempt to perform a Kappa analysis for study inclusion or quality assessment is reported, however.

II.	What are the results?															
1.	What are the overall results of the study?	<p>The results were split into <i>accuracy</i> and <i>management</i> studies.</p> <p>1. Accuracy (Table 2, p. 824) – These studies are useful for assessing post-test probability and discussing these probabilities with patients and consultants. Based upon six trials enrolling low probability subjects, the incidence of venous thromboembolism at three-months with normal SimplyRED® D-dimer ranges from 0-1.8%. Four of these trials also enrolled moderate and high probability subjects. With a normal SimplyRED®, the incidence of VTE in moderate or high probability subjects was 0-5.9% (3.4% pooled mean) and 13-40% (21% pooled mean), respectively.</p> <p>2. Management (p. 824) – Using a four different D-dimer assays, the authors were able to compare highly specific (SimplyRED®) assays with highly sensitive assays. For SimplyRED® the LR⁻ was 0.16. For the sensitive assay the LR⁻ was 0.05 with the differences in sensitivity and specificity between assay types (sensitive VIDAS versus specific SimplyRED®) highly significant (p<0.001 and p=0.002, respectively).</p> <p><u>The three-month incidence of VTE based upon this review:</u> (Table 4, p. 825)</p> <table border="1" data-bbox="724 1178 1458 1734"> <tbody> <tr> <td>Low Probability</td> <td>12.5%</td> </tr> <tr> <td>Mod or High Probability Normal Doppler Normal D-dimer</td> <td>0%</td> </tr> <tr> <td>Mod or High Probability Normal Doppler Abnormal D-dimer</td> <td>18.1%</td> </tr> <tr> <td>Moderate Probability Normal D-dimer</td> <td>5.8%</td> </tr> <tr> <td>Moderate Probability Abnormal D-dimer</td> <td>25%</td> </tr> <tr> <td>High probability Normal D-dimer</td> <td>25%</td> </tr> <tr> <td>High Probability Abnormal D-dimer</td> <td>80%</td> </tr> </tbody> </table>	Low Probability	12.5%	Mod or High Probability Normal Doppler Normal D-dimer	0%	Mod or High Probability Normal Doppler Abnormal D-dimer	18.1%	Moderate Probability Normal D-dimer	5.8%	Moderate Probability Abnormal D-dimer	25%	High probability Normal D-dimer	25%	High Probability Abnormal D-dimer	80%
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2.	How precise are the results?	The individual studies have a wide range of confidence intervals, but the pooled data yield improved sensitivity and specificity confidence intervals.
3.	Were the results similar from study to study?	For low and moderate probability cumulative VTE incidence. Not so similar for high probability groups.
III.	<i>Will the results help me in caring for my patients?</i>	
1.	How can I best interpret the results to apply them to the care of my patients?	1. Recognize the limitations of SimplyRED® assay (higher specificity at cost of lower sensitivity) to a negative result in a low probability patient. 2. Recognize the low incidence of three-month VTE in low or moderate probability patients with a normal high sensitivity D-dimer assay.
2.	Were all patient important outcomes considered?	Did not consider pain relief, ED length-of-stay, ED recidivism, or perceived inconvenience.
3.	Are the benefits worth the costs and potential risks?	Cost-benefit analysis not performed.

Limitations

1. No intra- or inter-rater reliability of study selection.
2. Five studies identified, but excluded with insufficient data detail.
3. English-bias.
4. All evidence is weighted equally.
5. Review did not include “Forest Plot” of individual studies to fully assess heterogeneity. A “forest plot” presents each individual study’s individual effects measure and 95% confidence intervals graphically.
6. Review did not include “funnel plot” to ensure that all possible studies were included. Funnel plots are a means to detect publication bias since many journals tend to only accept “positive” research results. The funnel plot plots the Log of the Odds Ratio against Standard Error. If all of the data falls on one side of zero, publication bias is suggested.

Bottom Line

This is a limited systematic review of 12 studies combining pre-test probability of DVT and a variety of D-dimer assays which provides a pooled estimate of three-month VTE incidence. The review suggests that the highly specific, but less sensitive SimplyRED® assay should only be used in low probability populations. Furthermore, the results suggest that more sensitive, but less specific assays like VIDAS can safely exclude VTE in both low and moderate risk populations with LR-of 0.05. Given this study’s lack of heterogeneity analysis and questionable inclusiveness, the results suggest avenues for future systematic reviews and/or meta-analysis, but should not necessarily alter current practice patterns.