Critical Review Form
Meta-analysis

Serum D-dimer is a Sensitive Test for the Detection of Acute Aortic Dissection: A Pooled Meta-analysis. *J Emerg Med* 2008; 34: 367-376

Objectives: **"To define the sensitivity of D-dimer for acute aortic dissection by pooling data from all relevant series, and to assess the potential of the serum D-dimer as a test for patients who present with a low likelihood of acute aortic dissection". (p. 368)**

Methods: **One investigator, the author, conducted an electronic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials using the terms "aortic dissection" and "D-dimer". Only English-language publications of consecutive case series of acute aortic dissection and a measured D-dimer were included. Study quality was reported using the STARD, MOOSE, and QUADAS check lists. All data were abstracted by a single unblinded investigator.**

From each study the following measurements were abstracted: method of D-dimer assay; average D-dimer value; number of patients with acute aortic dissection above the threshold (0.5 µg/mL); symptom duration, dissection type; number of subjects with a patent or thrombosed lumen. The author conducted a sensitivity analysis of the test sensitivity that included only those studies in which all acute aortic dissection patients had a D-dimer test.

Inter-study heterogeneity was assessed prior to pooling results. Specificity was not combined due to heterogeneous control groups. A fixed- effects model was used for the meta-analytic model, weighting each study by sample size. Publication bias was assessed by funnel plot.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Can D-dimer exclude patients with suspected acute aortic dissection with sufficient sensitivity to begin using clinically?
2.	Was the search for relevant studies details and exhaustive?	No. The author used only two search terms and three electronic engines and no hand-search was performed. Studies were limited to English-language. No attempt to assess scientific abstracts or contact industry for white papers.

3.	Were the primary studies of high methodological quality?	In tables 2 and 3 (p 370 – 372) the author succinctly reports accepted attributes of quality in diagnostic reports. Generally, the available studies were small, lacked a control group, did not blind outcome assessors to D-dimer results, used four different assays with variable cut-off points, and did not consistently report the number of patients ruled out for acute aortic dissection.
4.	Were the assessments of the included studies reproducible?	Only one author abstracted data and no kappa analysis was possible. However, he used valid reproducible checklists from STARD and QUADAS.
II.	***What are the results?***	
1.	What are the overall results of the study?	• 21 studies were identified, 11 included in this meta-analysis. • Funnel plot (p.373) suggested publication bias was likely since the majority of smaller studies had sensitivity estimates greater than the two larger studies. • Statistical heterogeneity was identified for both sensitivity and specificity, but the p-value was an insignificant 0.39 for sensitivity after removal of only one study. Specificity remained heterogeneous ($p < 0.0001$) so results not pooled. • Pooled sensitivity 327/349 (94%, 95% CI 91% -96%) for D-dimer ≥ 0.5 µg/mL. Including only those studies in which all acute aortic dissection patients had the D-dimer test, sensitivity 183/192 (95%, 95% CI 91% - 98%). • Specificity ranged from 40% to 100%. • Assuming sensitivity 94% and specificity 40% negative likelihood ratio (LR) 0.15 and positive LR 1.6. Given these values negative D-dimer in high-risk (2% pre-test probability) would reduce post-test probability to 0.3%. • If use less conservative estimates of 94% sensitivity 100% specificity then LR- = 0.06 and post-test probability would be reduced to 0.1%. • 22 aortic dissections would have been missed by D-dimer < 0.5 µg/mL. Hazui's logistic regression suggested the following features were associated with a false-negative D-dimer: completely thrombosed dissection lumen; shorter length of dissection; and younger age. Longer duration dissections may be more thrombosed leading to ↑ false-negative rates.

2.	How precise are the results?	Tight CI's described above would not dissuade one from using D-dimer to risk-stratify patients for aortic dissection as long as the factors leading to increased false-negative rates are understood.
3.	Were the results similar from study to study?	No. See Figure 2 (p.373) Forest plots. Sensitivity estimates hovered tightly around 92% – 100% sensitive, but significant spread of specificity estimates (40%, 54%, 67%, 69%, 80%, 100%).
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	D-dimer is a sensitive, non-specific screening tool for acute aortic dissection. Since history, physical examination and chest x-ray cannot rule out acute aortic dissection alone (Klompas), D-dimer may be most useful for screening low-probability patients. Von Kodolitsch previously described that the absence of acute tearing or ripping pain, pulse or blood pressure differentials, or mediastinal or aortic widening on CXR reduced the aortic dissection risk from 50% to 7%. D-dimer might be used in conjunction with these findings or a yet-to-be developed CDR to optimize benefit to patients. Patients at moderate or high risk of acute aortic dissection would probably not benefit from D-dimer since they would require further testing regardless of the D-dimer result.
2.	Were all patient important outcomes considered?	No – only the D-dimer diagnostic accuracy for aortic dissection.
3.	Are the benefits worth the costs and potential risks?	Yes, if validated in prospective fashion on a consecutive sampling of uniformly tested, treated, and followed up ED patients with suspected aortic dissection. Since currently available aortic dissection definitive diagnostics (CT, TEE, MRI, aortography, autopsy) are expensive, uncomfortable, risky, and not always readily available. D-dimer could enhance the EP's diagnostic toolbox.

Limitations

1) **Incomplete search strategy – only three electronic engines, two search terms, and English-language bias, could have missed non-English, research abstracts, or industry data.**
2) **Data abstractor not blinded to hypothesis so ascertainment bias possible and reproducibility of search and conclusions uncertain.**
3) **Inconsistent D-dimer cut-points and myriad assays described (Latex agglutination, turbidimetric, ELISA).**

4) **Small studies with small total number of aortic dissections.**
5) **Publication bias likely by funnel plot analysis.**
6) **Inconsistent presence of control or no-dissection group with statistically significant specificity heterogeneity prohibiting complete understanding of diagnostic test characteristics and increasing risk of spectrum bias.**

Bottom Line

Based on a few small studies employing different D-dimer assays and cut-points, a D-dimer < 0.5 µg/mL is a sensitive (94%), non-specific (40% - 100%) tool to exclude acute aortic dissection probably best employed in low-risk populations. Future research should assess validated CDR's to identify low-risk populations and then prospectively assess the additional benefit D-dimer offers in sensitivity, specificity, reliability and impact on test-ordering. For now, D-dimer for aortic dissection is where D-dimer for pulmonary embolism was 10-years ago.