

Critical Review Form

Meta-analysis

PGY-1

[Asha SE, Miers JW. A Systematic Review and Meta-analysis of D-dimer as a Rule-out Test for Suspected Acute Aortic Dissection. Ann Emerg Med. 2015 Oct;66\(4\):368-78.](#)

Objectives: “to determine the sensitivity, specificity, and positive and negative likelihood ratios of the D-dimer test for the diagnosis of acute aortic dissection,” and “to discuss how the results of the his meta-analysis could be used as part of an algorithm to evaluate patients with suspected acute aortic dissection.” (p. 2)

Methods: A literature search was performed in July 2014, including MEDLINE and EMBASE through OVID SP (with no limits), Medion, and Google scholar. After articles meeting inclusion and exclusion criteria were identified, Web of Science was used to identify publications that had cited these articles. Reference lists of articles meeting inclusion and exclusion criteria and all systematic reviews and meta-analyses identified were searched for additional articles.

Articles were included if they reported original research of cross-sectional design in which patients with suspected acute aortic dissection (duration of symptoms < 14 days) were identified prospectively, were enrolled before confirmation of the diagnosis, had D-dimer levels measured, had their diagnosis confirmed or refuted with an appropriate reference standard (aortic angiography, CT aortic angiography, MRI, or transesophageal echocardiography), and if the studies reported absolute numbers to form two by two contingency tables.

Two reviewers independently evaluated articles for inclusion and independently extracted data. Study quality was assessed using the [standards for reporting of diagnostic accuracy \(STARD\)](#) statement to evaluate study reporting, and the [quality assessment of diagnostic accuracy studies \(QUADAS\)](#) tool to evaluate study design and conduct.

Five studies meeting all inclusion and exclusion criteria were identified. Of the 25 items in the STARD criteria, 11 items could be found in 2 studies, 15 items could be found in 2 studies, and 20 items could be found in 1 study. With regards to the QUADAS tool, of 14 items described, 9 could be answered yes in 2 studies, 10 could be answered yes in 2 studies, and 1 could be answered yes in 1 study. Only 4 of the studies used a D-dimer cut-off of 0.50 µg/mL, and these were combined in a meta-analysis. These 4 studies comprised 1557 participants.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes. The authors sought to evaluate the diagnostic accuracy of D-dimer for acute aortic dissection, and to determine if an algorithm could be devised to use the results of D-dimer in such patients. The use of a screening test such as D-dimer for the evaluation of patients with suspected aortic dissection, but felt to be low risk, could potentially reduce unnecessary radiation exposure, reduce contrast exposure, and reduce the time necessary to exclude aortic dissection in a substantial number of patients.
2.	Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched MEDLINE, EMBASE, Medion, Google scholar, Web of Science, and searched the reference lists of included articles and any systematic reviews and meta-analyses identified. They did not search conference abstracts or “grey literature.”
3.	Were the primary studies of high methodological quality?	Yes. While reporting was poor to moderate, study quality was moderate to high, with the majority of answers to the QUADAS checklist questions being “yes,” and minority being “unclear.” All patients received a reference standard, and the same reference standard was used regardless of D-dimer test results, limiting potential verification bias .
4.	Were the assessments of the included studies reproducible?	Yes. The authors used two well-known checklists, STARD and QUADAS , to evaluate the quality of both reporting and study design.
II.	<i>What are the results?</i>	
1.	What are the overall results of the study?	The overall diagnostic characteristics in the 4 studies included in the meta-analysis are as follows: Sensitivity 98.0% (95% CI 96.3% to 99.1%; $I^2 = 0.0\%$) Negative LR 0.05 (95% CI 0.03 to 0.09; $I^2 = 0.0\%$) Specificity 41.9% (95% CI 39.0% to 44.9%; $I^2 = 95.1\%$) Positive LR 2.11 (95% CI 1.46 to 3.05; $I^2 = 94.5\%$)
2.	How precise are the results?	See above. Overall, the 95% CI’s are narrow. For the negative LR, the upper bound of the 95% CI is 0.09, which would still indicate a significant reduction in the probability of disease with a negative result.
3.	Were the results similar from study to study?	For the sensitivity and negative LR, the results were quite similar, with an I^2 value of 0.0%. For specificity and positive LR, the I^2 values were > 90% suggesting a great deal of heterogeneity.
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?	These results suggest that a D-dimer level less than 0.50 µg/mL in patients being evaluated for acute aortic dissection results in a substantial reduction in the probability of disease. In patients with low risk of disease, such as those identified using the acute aortic dissection risk score (in which low risk patients had a prevalence of 6%), a negative D-dimer would result in a low post-test probability (0.3% using pre-test probability of 6% and a LR- of 0.05). As the authors point out, outcome studies still need to be performed to validate the safety of this rule-out strategy.
2.	Were all patient important outcomes considered?	Yes. The authors of this meta-analysis were only concerned with the diagnostic accuracy of the D-dimer in acute aortic dissection, and did not specifically address clinical outcomes (which will still need to be assessed).
3.	Are the benefits worth the costs and potential risks?	Uncertain. As pointed out, studies evaluating the safety of such a rule-out strategy in low risk patients still need to be performed prior to implementation of such strategies.

Limitations:

- 1. The largest study included in the review used data from a registry not originally intended to answer this clinical question, and nearly a third of participants were excluded due to lack of a D-dimer test result ([selection bias](#)).**
- 2. The overall quality of reporting in the included studies was poor, allowing for potential bias to go undetected.**
- 3. There was significant [heterogeneity](#) between studies with regards to specificity and positive likelihood ratios.**
- 4. The authors do not provide a calculation of a [test threshold \(Pauker and Kassirer 1980\)](#) for definitive testing in patients with suspected acute aortic dissection.**

Bottom Line:

The results of this meta-analysis suggest that a negative D-dimer in patients being evaluated for acute aortic dissection, but deemed to be low risk, effectively rules out the disease, with a very low miss rate. While the authors did not calculate a specific test threshold for definitive testing in such patients, it is likely that the post-test probability in these patients would fall well below such a threshold. The safety of such a rule-out strategy should ideally be evaluated in prospective studies prior to implementations.