UAMS Journal Club Summary
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D-dimer as a Screening Tool for Aortic Dissection

Critical Bottom Line

By itself, a D-dimer <500 is not sufficient to rule out aortic dissection but with the use of the ADD-RS, it could be used to help guide workup in the ED. The ADD-RS has been validated, but ADD-RS with D-dimer (the ADvISED study algorithm) has not been externally validated and should be used with caution.

PICO

P - Patients presenting to ED, in whom aortic dissection is in the differential diagnosis
I – D-dimer as screening test to detect aortic dissection, with or without ADD-RS
C – Gold standard of CTA
O – Diagnosis of aortic dissection

Background

Aortic dissection is a dangerous disease with high morbidity and mortality. Unfortunately the presentation of patients with aortic dissection can be widely varied, so clinicians must have a high index of suspicion to avoid missing the diagnosis. CT angiography is the gold standard of diagnosis, but this modality can be expensive, time consuming, exposes the patient to radiation and is not available at all ERs. These two studies investigate D-dimer as a potential biomarker to help screen for aortic dissection in the ER.

Trial 1

Yao, J., Bai, T., Yang, B. *et al.* The diagnostic value of D-dimer in acute aortic dissection: a meta-analysis. *J Cardiothorac Surg* **16**, 343 (2021). https://doi.org/10.1186/s13019-021-01726-1

PubMed link: The diagnostic value of D-dimer in acute aortic dissection: a meta-analysis - PubMed (nih.gov)

Validity Rating: moderate to low validity, with high heterogeneity

The Basics:

This meta-analysis included 16 studies, including 1135 cases to evaluate the sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio and negative likelihood ratio of D-dimer in diagnosis of aortic dissection.

Inclusion Criteria:
(1) AAD was diagnosed; (2) D-dimer level was measured; (3) Human study; (4) The results of true positives, true negatives, false positives, and false negatives were reported or can be calculated.

Exclusion Criteria:
(1) Articles of review, case report, animal experiment research and comment type; (2) Repeated publications (only the research with the most complete data was selected); (3) Articles with only abstract or with insufficient important information such as P value, 95% confidence interval information or the diagnostic sensitivity and specificity cannot be extracted.

Primary Outcomes:
Sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (−LR), diagnostic odds ratio (DOR), summary receiver operating characteristic (SROC) curve and area under the curve (AUC)

Secondary Outcomes:
Heterogeneity

Results:
In the detection of aortic dissection, D-dimer had a pooled sensitivity of 0.96 (95% CI of 0.91-0.98), the pooled specificity of 0.70 (95% CI 0.57-0.81), the pooled diagnostic odd's ratio of 56.57 (95% CI 25.11-127.44), the pooled +LR of 3.25 (95% CI 2.18-4.85) and the pooled –LR of 0.06 (95% CI 0.03- 0.12). Heterogeneity was high with I^2 value of 97.1% for sensitivity, 98.66% for specificity, 93.99% for diagnostic odd's ratio, 98.52% for +LR, and 96.21% for –LR.

Limitation/Bias:
This was a large, meta-analysis with fairly exhaustive inclusion of articles. Although at first, it appears that the sensitivity of D-dimer in detecting aortic dissection is high at 96%, the lower end of the 95% confidence interval is 91%, meaning that by using D-dimer alone as a

screening test, up to 9% of dissections could be missed. There is also high heterogeneity in this meta-analysis, indicating that the included studies differed drastically in their results. Cochrane Handbook, section 9.5.3 recommends that if there is high heterogeneity, there are three options: (1) use a random-effects model rather than fixed-effects, (2) do not pool data using meta-analysis, or (3) investigate heterogeneity using subgroup analysis or meta-regression using *pre-planned* subgroups. This study investigated causes of heterogeneity with meta-regression and subgroup analysis, but with subgroups which were not pre-planned.

Trial 2

Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes

The ADvISED Prospective Multicenter Study

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link: **https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.029457**
Basics:

The Basics: Although d-dimer is highly sensitive for AAS, it alone is insufficient as a rule-out stand-alone test. This trial sought to examine the validity of adding a decision rule to d-dimer, the ADD-RS. The trail was designed as a multi center prospective observational study that analyzed 1850 patients over two years at 6 hospitals in 4 countries. D-dimer was considered negative if was less than 500 ng/mL. A final decision for each patient was based on diagnostic imaging, autopsy, surgery, or 14-day follow-up.

Inclusion Criteria: Patients were eligible if they had ≥1 of: chest/abdominal/back pain, syncope, perfusion deficit, and if AAS was in the differential diagnosis. Specifically AAS had to have been determined by the provider to need to be ruled-out for the patient.

Exclusion Criteria: patients were excluded for primary trauma and unwillingness or inadequacy to participate in the study.

Results: 1930 patients were screened. 80 were excluded. So a total of 1850 patients were enrolled. ADD-RS ≤1 were considered “non-high risk for AAS and totaled 1509 (81.6%). 341 patients (18.4%) had ADD-RS >1. In the foregoing groups the D-dimer was >500 “positive” in 813 patients (43.9%). This broke down to D-dimer being positive in 144 (32.9%) patients in the ADD-RS=0, 441 (41.2%) patients in the ADD-RS=1 and 228 patients (66.9%) in the ADD-RS >1. Overall 585 patients (38.8%) from combined ADD-RS ≤1 had a positive D-dimer. ($P<0.001$ versus ADD-RS>1).

Limitations/Bias:

The study only included patients for which an attending had included AAS in the differential and decided it required rule-out. This decisions was not necessarily made in an objective way and may have introduced selection bias and makes the results less generalizable. External validation is needed.