Critical Review Form
Diagnostic Test

Diagnosis of Acute Aortic Dissection by D-Dimer: The International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) Experience
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Objective: **"To evaluate "the diagnostic performance of D-dimer in acute AD (aortic dissection) in a population suspected of having the disease". (p. 2702)**

Methods: **Very little methodological details are provided by the investigators. Consenting patients presenting within 24 hours of symptom onset were prospectively enrolled from 14 centers in Europe, Japan, and the United States. "The suspicion of AD had to be high enough to cause the evaluating physician to order an imaging test to identify the presence of AD." (p. 2703). Blood plasma was drawn on presentation and D-dimer measured using the Triage D-dimer test (Biosite, San Diego, CA). Diagnostic test characteristics were analyzed using Analyze – It software.**

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. Consenting patients with symptom onset < 24 hours prior and sufficient clinical concern for the physician to order imaging to exclude aortic dissection (AD).
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group? (Confirmation Bias)**	Uncertain since investigators fail to report how AD was ascertained (CT, MRI, TEE, angiography, autopsy) or whether the Radiologist/Pathologist was blinded to the D-dimer result.
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	Generally all subjects had both D-dimer and definitive AD imaging though investigators do not clearly state this fact.
II.	**What are the results?**	

A.	**What likelihood ratios were associated with the range of possible test results?**	• 220 enrolled with 87 cases of radiographically proven AD (prevalence 40%). Of the 87 AD cases 61% were male, 64 (74%) were Type A dissections and 23 (26%) were Type B. Of the 133 non-AD cases most (83 or 62%) were MI or angina. • D-dimer levels mean were higher for Type A (3213 ng/mL) and Type B (3574 ng/mL) than for MI (1459 ng/mL) angina (760 ng/mL) or PE (2452 ng/mL). • Using a cut-off of 500 ng/mL, D-dimer displayed the following diagnostic test characteristics

Condition	Sen (95% CI)	Spec (95% CI	LR-	AUC
All AD vs. All Controls	96.6 (90.3-99.3)	46.6 (37.9-55.5)	0.07	0.84
All AD vs. MI	96.6	39.1 (25-55)	0.09	0.81
All AD vs. Angina	96.6	62.2 (45-78)	0.06	0.93
All AD vs. PE	96.6	20.0 (0.5-71.6)	0.17	0.65
Type A vs. All controls	96.9 (89.2-99.6)	46.6 (37.9-55.5)	0.07	
Type B vs. All controls	95.7 (78.1-99.9)	46.6 (37.9-55.5)	0.09	

• Analysis of D-dimer diagnostic performance within the first 6-hours of symptom onset revealed AUC 0.94 (95% CI 0.84-1.00) for diagnosing any AD.

• Within 6-hours of symptom onset D-dimer > 1600 ng/mL showed positive LR 12.8 for AD.

• Analysis by false lumen patency revealed a slight trend for false lumen patency to be associated with higher levels of D-dimer, but this was not statistically significant". (p. 2705).

III.	How can I apply the results to patient care?	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes, these results are consistent with a dozen other trials and two meta-analyses (Sodeck, Marill). May have less external validity between less specialized non-tertiary centers.
B.	**Are the results applicable to the patients in my practice?**	Yes. " The present prospective multicenter study was unique in that the entry criterion for all patients, including control subjects, was suspicion of AD, which allowed better estimation of assay performance in the clinical setting." (p. 2705)
C.	**Will the results change my management strategy?**	Yes. "Accumulated evidence is now sufficient to suggest that routine use of D-dimer testing is helpful in risk- stratifying patients with suspected acute AD." (p. 2706)
D.	**Will patients be better off as a result of the test?**	Because of its relative rarity but high lethality, AD remains a highly litigated disease with accusations of malpractice against treating physicians and hospitals. History, physical exam, and plain film imaging cannot rule in or rule out the diagnosis of AD so a readily available blood test would be beneficial and perhaps cost-effective". A D-dimer blood test could assist the clinician when stratifying patients presenting with chest pain within 24-hours or onset to rule out both PE and AD to decide whether to subject the patient to further diagnostic testing". (p. 2706). However, before advocating routine use of D-dimer in EM one would need to assess the clinician reliability in identifying "low-risk" AAD patients and the resulting impact on definitive test ordering in a randomized controlled trial.

Limitations

1) **Poor description of criterion standard. What imaging modality was used? What was experience of Radiologist outcome assessors? Were Radiologists blinded to D-dimer result and study objectives? In general diagnostic studies should follow STARD reporting guidelines.**
2) **Poor description of who the suspicious clinicians were (EP? General Practice? Thoracic Surgeons?)**
3) **Poor description of patients presenting complaint. Chest pain? Syncope? Back pain?**
4) **Limited external validity to patient populations in non-tertiary centers.**

Bottom Line

Because of its relative rarity but high lethality, AD remains a highly litigated disease with accusations of malpractice against treating physicians and hospitals. History, physical exam, and plain film imaging cannot rule in or rule out the diagnosis of AD so a readily available blood test would be beneficial and perhaps cost-effective. On appropriately low-risk subsets, D-dimer blood testing could potentially assist the clinician when stratifying patients presenting with suspected acute aortic dissection within 24-hours or onset to rule out both PE and AD without further diagnostic testing. However, without a validated decision-aid to reliably identify low-risk subsets appropriate for D-dimer screening, premature acceptance of this test as a valid screening tool could paradoxically increase expensive, time-consuming, risky diagnostic testing for the elusive aortic dissection diagnosis without improving diagnostic accuracy.