Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients with Suspected Acute Nontraumatic Thoracic Aortic Dissection

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From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Nontraumatic Thoracic Aortic Dissection.

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is a revision of the 2015 Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients with Suspected Acute Nontraumatic Thoracic Aortic Dissection.[1] A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical question: "In adult patients presenting to the emergency department with suspected acute non-traumatic thoracic aortic dissection, can a clinical decision rule plus additional lab testing or imaging* (plain film or point of care ultrasound) identify a group of patients at very low risk for the diagnosis of thoracic aortic dissection?" Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Acute aortic syndromes (AAS) represent a spectrum of disease, including thoracic aortic dissections (AoD), intramural hematoma (IMH), penetrating aortic ulcers (PAU), and aortic rupture. PAU and IMH can both progress to aortic dissection. Among AAS, thoracic aortic dissection is the most common, occurring when the intima tears, allowing blood to pass into a false lumen. The dissection flap can spread proximally or distally and lead to significant morbidity and mortality. The mortality associated with ascending thoracic aortic dissection is estimated to be 1-2% per hour without appropriate treatment.[2] Although potentially lethal, the diagnosis of non-traumatic thoracic aortic dissection is rare, with an estimated two to four cases per 100,000 individuals.[3,4] Additionally, the clinical presentation of thoracic aortic dissection varies, often deviating from classic textbook descriptions. For example, “tearing” or “ripping” chest pain is uncommonly present and studies[5,6] have found negative likelihood ratios (LR-) between 0.41 to 1.26. While abrupt onset of pain is classic, it is not universally present. In fact, nearly one-third of patients present without chest pain and a minority of patients present with pulse deficits.[6,7] Further complicating the diagnostic evaluation is that the clinical presentation of thoracic aortic dissection overlaps with those of other disease processes such as stroke, acute coronary syndrome, and pulmonary embolism. As a result, missed diagnosis is common, with one Canadian study demonstrating a 12.5% miss rate between 2003-2018.[6]

The test of choice for diagnosing aortic dissection is computed tomography angiogram (CTA), given its excellent diagnostic performance, speed, and availability in emergency departments. Magnetic resonance imaging (MRI) and trans-esophageal echocardiogram (TEE) are also accurate and reasonable alternatives if CTA cannot be performed.[2] Unfortunately, readily available bedside imaging such as chest radiographs have not been found to be sufficiently sensitive nor specific for aortic dissection.[8] Point of care ultrasound may be more specific than chest radiograph but is inadequately sensitive for AoD. A 2023 study evaluated the performance of resident performed ultrasounds assessing for signs of AoD. These signs included the presence of a pericardial effusion, intimal flap or aortic outflow track diameter greater than 35 mm measured from the inner wall to inner wall within 20 mm of the aortic annulus during end-diastole on cardiac views and/or the presence of an undulating intimal flap suggesting Sanford type B dissection while visualizing the abdominal aorta. In 1,314 ultrasounds with an overall prevalence of 3.3%, the SPEED protocol demonstrated inadequate sensitivity (93.2%; 95% CI 81.3-98.6%); but good specificity (90.9% ;95% CI 89.2-92.5%) and positive LR of 10.2 (95% CI 8.5-12.5).[9]

The diagnostic yield of CTA for thoracic aortic dissection in the ED is low, with studies demonstrating 2-3% of CTAs as positive for thoracic aortic dissection, raising concerns for potential over-testing.[10,11] Emergency clinicians must balance the risks of over-testing for this rare disease process with the risks of missing a critical diagnosis and medicolegal concerns. Taken together, studies demonstrating low CTA yield for AoD and those demonstrating missed opportunities for diagnosis demonstrate clinicians may benefit from help in identifying patients who should undergo evaluation for AoD. As a result, there has been substantial interest in risk stratification of patients to determine which patients do not warrant further testing. Risk stratification in clinical emergency medicine generally relies on the premise of a test threshold – the balance between risks and benefits of testing and potentially missed diagnosis. Although there are well-established thresholds for pulmonary embolism and acute coronary syndrome, the rare but devastating nature of thoracic aortic dissection has resulted in a less well-defined test threshold.

Proposed tools to aid in risk stratification of patients with potential aortic dissection include risk scores, D-dimer, and point of care ultrasound. Several risk scores exist for acute aortic syndrome (AAS) including the aorta

simplified score (AORTAs) the Canadian score, and the Sheffield score.[12,13] Of these, aortic dissection detection risk score (ADD-RS) is the most systematically studied.

Aortic Dissection Detection Risk Score (ADD-RS)	
Any high-risk condition Marfan syndrome, family history of aortic disease, known aortic valve disease, recent aortic manipulation, or known thoracic aortic aneurysm	Yes (1) No (0)
Any high-risk pain feature Chest, back, or abdominal pain described as abrupt onset, severe intensity, or ripping/tearing	Yes (1) No (0)
Any high-risk exam feature Evidence of perfusion deficit (pulse deficit, systolic BP differential, or focal neuro deficit plus pain), new aortic insufficiency murmur (with pain), hypotension/shock	Yes (1) No (0)
Scoring system	
Score of ≤1 ("Low risk")	Proceed to D-dimer testing; if <500 ng/mL FEU, consider stopping evaluation for dissection, or if ≥500 ng/mL FEU, consider CTA
Score of 2 ("High risk")	Proceed directly to CTA

Studies used one of the following assays: HemosIL DD HS (Instrumentation Laborator, Bedford MA, USA, STA®-Liatest® D-Di (Diagnostica Stago, Asnières sur Seine Cedex, France), TriniLIA DD (TCOAG, Bray, Ireland), and INNOVANCE® DD (Siemens, Erlangen, Germany).

The 2015 clinical policy reviewed, separately, the use of clinical decision tools, a serum D-dimer, and transthoracic echocardiogram (TTE) to identify groups of patients at very low risk for the diagnosis of thoracic aortic dissection.[1] Since then, several studies have assessed the combination of risk stratification tools and lab tests and imaging to better identify ultra-low-risk patients.

This clinical policy will address the question of whether a clinical decision tool, in conjunction with additional lab testing or bedside imaging can identify a group of patients at very low risk for the diagnosis of thoracic aortic dissection.

METHODOLOGY

This ACEP clinical policy was developed by emergency physicians with input from medical librarians and a patient safety advocate; is based on a systematic review and critical, descriptive analysis of the medical literature; and is reported in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[14]

Search and Study Selection

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, Science Direct, Scopus, EMBASE, and the Cochrane Database of Systematic Reviews were performed by a librarian. Search terms and strategies were peer reviewed by a second librarian. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under the critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

Using Covidence (Covidence, Melbourne, Australia), 2 subcommittee members independently reviewed the identified abstracts to assess for possible inclusion. Of those identified for potential inclusion, each full-length text was reviewed for eligibility. Those identified as eligible were subsequently abstracted and forwarded to the committee's methodology group (emergency physicians with specific research methodological expertise) for methodological grading using a Class of Evidence framework (Appendix E1, available at http://www.annemergmed.com).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by 2 methodologists.

Design 1 represents the strongest possible study design to answer the critical question, which relates to whether the focus was therapeutic, diagnostic, or prognostic, or a meta-analysis. Subsequent design types (eg, Design 2 and Design 3) represent respectively weaker study designs. Articles are then graded on dimensions related to the study's methodological features and execution, including but not limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and potential for conflicts of interest.

Using a predetermined process that combines the study's design, methodological quality, and applicability to the critical question, 2 methodologists independently assigned a preliminary Class of Evidence grade for each article. Articles with concordant grades from both methodologists received that grade as their final grade. Any discordance in the preliminary grades was adjudicated through discussion which involved at least 1 additional

methodologist, resulting in a final Class of Evidence assignment as Class I, Class II, Class III, or Class X (Appendix E2, available at http://www.annemergmed.com). Studies identified with significant methodologic limitations and/or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of evidence. Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence for the critical question, the subcommittee drafted the recommendations and supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific certainty (eg, based on evidence from one or more Class of Evidence I or multiple Class of Evidence II studies that demonstrate consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from one or more Class of Evidence II studies or multiple Class of Evidence III studies that demonstrate consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty of effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations. When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allow adjustment when applying to patients with extremes of risk (Appendix E3, available at http://www.annemergmed.com).

Evaluation and Review of Recommendations

Once drafted, the policy was distributed for internal review (by members of the entire committee) followed by external expert review and an open comment period for all ACEP membership. Comments were received during a 30-day open comment period with notices of the comment period sent electronically to ACEP members, published in *EM Today*, posted on the ACEP website, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy, although responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly.

Application of the Policy

This policy is not intended to be a complete manual on the evaluation and management of adult patients with suspected thoracic aortic dissection, but rather a focused examination of a critical question that has particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within the critical question.

It is the goal of the Clinical Policies Committee to provide evidence-based recommendations when the scientific literature provides sufficient quality information to inform recommendations for the critical question. In accordance with ACEP Resolution 56(21), ACEP clinical policies do not use race-based calculators in the formulation of recommendations. When the medical literature does not contain adequate empirical data to inform the critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to inform the critical question addressed in this policy. ACEP funded this clinical policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected acute non-traumatic thoracic aortic dissection.

Exclusion Criteria. This guideline is not intended for pediatric patients or pregnant patients.

CRITICAL QUESTION

In adult patients presenting to the emergency department with suspected acute non-traumatic thoracic aortic dissection, can a clinical decision rule plus additional lab testing or imaging* (plain film or point of care ultrasound) identify a group of patients at very low risk for the diagnosis of thoracic aortic dissection?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In adult patients who have an aortic dissection detection risk score (ADD-RS) of ≤ 1 (low risk) and a highly sensitive D-Dimer <500 ng/ml FEU emergency physicians can exclude acute non-traumatic aortic dissection without obtaining advanced imaging (i.e. CTA, MRI, or TEE).

Level C recommendations. In adult patients who have an aortic dissection detection risk score (ADD-RS) of ≤ 1 (low risk), emergency physicians can consider the use of focused cardiac point of care ultrasound as a secondary risk stratification tool. If emergency physicians trained in cardiac ultrasound identify direct signs of AAS, bypassing d-dimer testing should be considered, and patients should go directly to advanced imaging (i.e. CTA, MRI, or TEE).

Potential Benefit of Implementing the Recommendations:

- Ability to balance the risks of misdiagnosis and over testing
- Limit radiation exposure

Potential Harm of Implementing the Recommendations:

- Indiscriminate ordering of a D-dimer in patients who do not meet the appropriate clinical presentation for acute aortic dissection may lead to over testing.

Key words/phrases for literature searches:

Thoracic Aortic Dissection, Aortic Aneurysm, Acute Aortic Syndrome, Intimal Tear, Aortic Rupture, Clinical decision rules, Decision Support, Clinical Prediction Rule, Clinical decision aid, Risk prediction, Risk score, Predictive Model, Algorithm, Aortic Dissection Detection Risk Score (ADD-RS), Aorta Simplified Score (AORTAs), d-dimer, Fibrinogen, White blood cell, Imaging, Chest X-Ray, Plain Film x-ray, Point of Care Ultrasound, POCUS, Sonography, Emergency Medicine, Emergency Department, Emergency Room

Study Selection: Three thousand nine hundred and seventy-seven articles were identified in the searches. Twenty-six were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, 0 Class I studies and 2 Class II studies study were included for this critical question (Appendix E4, available at http://www.annemergmed.com). Appendix E6 lists the 23 articles graded for methodological rigor but were ultimately found to not meet methodological criteria for inclusion.

The ADvISED (Aortic Dissection Detection Risk Score Plus D-Dimer in Suspected Acute Aortic Dissection) prospective, multicenter Class II study assessed the combined diagnostic accuracy of the aortic dissection risk score (ADD-RS) and a negative (<500 ng/mL FEU) D-dimer (DD) for identifying acute aortic syndrome (AAS) in 1,850 adult ED patients. D-dimer assays varied by site.[15] All but one assay were highly sensitive quantitative D-dimer assays (HemosIL DD HS (Instrumentation Laboratory, Bedford MA, USA), STA®-Liatest® D-Di (Diagnostica Stago, Asnières sur Seine Cedex, France), and INNOVANCE® DD (Siemens, Erlangen, Germany)). The TriniLIA DD (TCOAG, Bray, Ireland) is a polystyrene microparticle agglutination assay (not approved for use in the US). Patients were enrolled in the study if their differential diagnosis included AAS and the patient had one or more of the following symptoms within the past 14 days: chest pain, abdominal pain, back pain, syncope or signs or symptoms of perfusion deficit. The prevalence of AAS in the overall cohort was 13%. Of the 141 patients with an AAS, most had a type A aortic dissection (N=125), followed by type B aortic dissection (N=53), IMH (N=35), aortic rupture (N=18), and PAU (N=10). The prevalence was 2.7% in patients with ADD-RS=0, 9% in patients with ADD-RS=1, and 39% in patients with ADD-RS>1. In the 294 patients with an ADD-RS=0 (low risk) plus a negative DD, 1 case of Stanford type B aortic dissection was observed, yielding a failure rate (proportion of dissections that would have been missed using the strategy) of 0.3% (95% CI 0.1-1.9%) for the ADD-RS=0/DD- strategy. This equates to 1 missed case in 294 patients and an LR- of 0.02 (95% CI 0.003-0.16). In 924 patients with an ADD-RS$\leq$1 plus a negative DD, one Stanford type B and two Stanford type A aortic dissections were observed yielding a failure rate of 0.3% (95% CI 0.1-1) for the ADD-RS$\leq$1(low risk)/DD- strategy. The LR- for this strategy was 0.02 (95% CI 0.01-0.07). The failure rate for ADD-RS>1(high risk)/DD- was 4.4 (95% CI 1.9-9.9) with 5 cases of AAS observed. Investigators also evaluated the efficiency of the rule-out strategy. For low-risk patients, the efficiency in ruling out AAS was 15.9% (95% CI 14.3-17.6), corresponding to sparing 1 in 6 patients conclusive imaging examinations. The conclusive diagnosis of acute aortic syndrome was made by diagnostic imaging, autopsy and surgery for approximately half of the patients and the remainder was made by case adjudication at 14-day follow-up.

In a 2019 Class III study, investigators performed a separate pre-specified analysis of the ADvISED multicenter prospective study evaluating the integration of transthoracic focused cardiac ultrasound (FoCUS) into the diagnostic algorithm described above for 839 patients in whom acute non-traumatic AAS was in the attending physician's differential diagnosis.[16] FoCUS was performed by either a cardiologist (20.3%), emergency medicine or internal medicine physician (79.7%) before any advanced imaging or surgery looking for direct and indirect ultrasound signs of AAS. A poor acoustic window was reported in 74 (8.8%) patients and these cases were included in the analysis. Direct sonographic signs include presence of an intimal flap separating two aortic lumens, presence of an intramural aortic hematoma (crescentic thickening of the aortic wall > 5 mm) and penetrating aortic ulcer (crater-like outpouching with jagged edges in the aortic wall). Indirect sonographic signs of AAS include thoracic aortic dilatation (diameter $\geq$ 4cm), pericardial effusion or tamponade, and aortic valve regurgitation (AR) noted on color Doppler. Direct FoCUS signs of AAS were detected in 84 (10%) patients. Any FoCUS sign of AAS was detected in 307 (36.6%) patients. FoCUS findings except AR were independent positive predictors of AAS. Receiver operator characteristic curve (ROC) analysis demonstrated that the integration of FoCUS with the clinical probability assessment with ADD-RS increased the diagnostic accuracy for AAS. A combination of ADD-RS$\leq$1 and absence of any FoCUS signs of AAS had a sensitivity of 93.8% (95% CI 88.6-97.1), an AUC-ROC of 80.9% and failure rate of 1.9% (95% CI 0.9-3.6%). Including DD in the rule out strategy with ADD-RS$\leq$1 and FoCUS signs negative had a sensitivity of 100%, an AUC-ROC of 74.2%, and failure rate of 0. The two patients with an ADD-RS >1 and a D-dimer <500 ng/mL FEU both had indirect signs of AAS on FoCUS. Although sensitivities were comparable for any sonographic sign of AAS when performed by cardiologists and non-cardiologists, sensitivity was much higher for direct signs when performed by cardiologists (70%; 95% CI 45.7-88.1%) compared with non-cardiologists (41.3%; 95% CI 32.6-50.4%). This suggests that training may play a role in identification of signs of AoD.

Brief Summary

The use of ADD-RS $\leq$ 1 in conjunction with a quantitative D-dimer <500 ng/mL FEU can aid emergency medicine physicians in identifying patients with very low risk of aortic dissection who do not

require imaging. This approach could minimize unnecessary advanced imaging and risk of radiation exposure.

Future Research

There are multiple opportunities for future investigation on this topic. First, should the D-dimer cut-off be adjusted based on age? Given there are various D-dimer assays available, it would be important to understand how they perform in patients in whom one is concerned about acute AoD. Another area for research is identifying a well-delineated testing threshold similar to what has been developed for pulmonary embolism. Lastly, one has to wonder how the diagnostic algorithm incorporating ADD-RS and D-dimer fares when the prevalence of acute AoD is low.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

Relevant industry relationships are those relationships with companies associated with products or services that significantly influence the specific aspect of disease addressed in the critical question.

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Appendix E1. Literature classification schema.*

Design/ Class	**Therapy**†	**Diagnosis**‡	**Prognosis**§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix E2. Approach to downgrading strength of evidence.

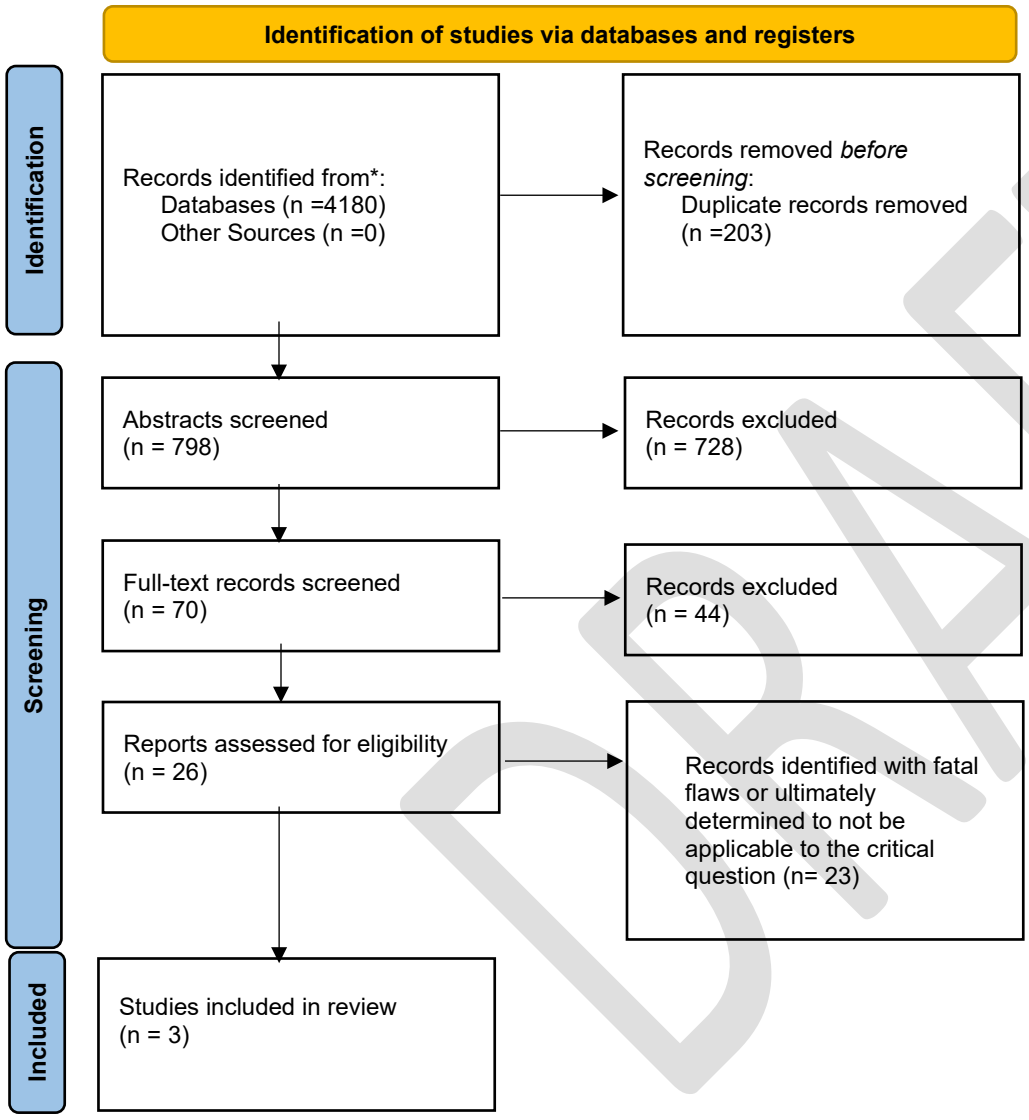
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix E3. Likelihood ratios and number needed to treat.*

LR (+)	**LR (–)**	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix E4. PRISMA flow diagram. (Page 2021)



Appendix E5. Literature Searches

Search Date	Database	Search Strings	Filters
3/7/2023	PubMed	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome OR Intimal Tear OR Aortic Rupture OR "Aortic Aneurysm, Thoracic"[Mesh] OR "Aortic Aneurysm"[Mesh] OR "Acute Aortic Syndrome"[Mesh] OR "Dissection, Ascending Aorta"[Mesh] OR "Aortic Dissection"[Mesh]) AND (Clinical decision rules OR Decision Support OR Clinical Prediction Rule OR Clinical decision aid OR Risk prediction OR Risk score OR Predictive Model OR Algorithm OR Aortic Dissection Detection Risk Score OR (ADD-RS) OR Aorta Simplified Score OR "Clinical Decision Rules"[Mesh] OR "Decision Support Techniques"[Mesh] OR "Clinical Decision-Making"[Mesh] OR "Risk" [Mesh]) AND ("Emergency Medicine" OR "Emergency Department" OR "Emergency Room" OR "Emergency Medicine"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Hospitalization"[Mesh])	English, Human, 2012-Current
3/7/2023	PubMed	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome OR Intimal Tear OR Aortic Rupture OR "Aortic Aneurysm, Thoracic"[Mesh] OR "Aortic Aneurysm"[Mesh] OR "Acute Aortic Syndrome"[Mesh] OR "Dissection, Ascending Aorta"[Mesh] OR "Aortic Dissection"[Mesh]) AND (d-dimer OR Fibrinogen OR White blood cell OR "Biomarkers" [Mesh] OR "Fibrin Fibrinogen Degradation Products" [Mesh] OR "fibrin fragment D" [Supplementary Concept] OR "Hematologic Tests"[Mesh]) AND ("Emergency Medicine" OR "Emergency Department" OR "Emergency Room" OR "Emergency Medicine"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Hospitalization"[Mesh])	English, Human, 2012-Current
3/7/2023	PubMed	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome OR Intimal Tear OR Aortic Rupture OR "Aortic Aneurysm, Thoracic"[Mesh] OR "Aortic Aneurysm"[Mesh] OR "Acute Aortic Syndrome"[Mesh] OR "Dissection, Ascending Aorta"[Mesh] OR "Aortic Dissection"[Mesh]) AND (Imaging OR Chest X-Ray OR Plain Film x-ray OR Point of Care Ultrasound OR POCUS OR Sonography OR "Diagnostic Imaging"[Mesh] OR "Ultrasonography"[Mesh] OR "Radiography, Thoracic"[Mesh]) AND ("Emergency Medicine" OR "Emergency Department" OR "Emergency Room" OR "Emergency Medicine"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Hospitalization"[Mesh])	English, Human, 2012-Current
3/7/2023	PubMed	("Aortic Aneurysm, Thoracic/diagnosis"[Mesh] OR "Aortic Aneurysm/diagnosis"[Mesh] OR "Acute Aortic Syndrome/diagnosis"[Mesh]	English, Human, 2012-Current

		OR "Dissection, Ascending Aorta/diagnosis"[Mesh] OR "Aortic dissection/diagnosis"[Mesh]) AND ("Emergency Medicine" OR "Emergency Department" OR "Emergency Room" OR "Emergency Medicine"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Hospitalization"[Mesh])	
3/7/2023	PubMed	("Aortic Aneurysm, Thoracic/diagnostic imaging"[Mesh] OR "Aortic Aneurysm/diagnostic imaging"[Mesh] OR "Acute Aortic Syndrome/diagnostic imaging"[Mesh] OR "Dissection, Ascending Aorta/diagnostic imaging"[Mesh] OR "Aortic Dissection/diagnostic imaging"[Mesh]) AND ("Emergency Medicine" OR "Emergency Department" OR "Emergency Room" OR "Emergency Medicine"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Hospitalization"[Mesh])	English, Human, 2012-Current
3/7/2023	EMBASE	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome OR Intimal Tear OR Aortic Rupture OR 'thoracic aorta aneurysm') AND (Emergency Medicine OR Emergency Department OR Emergency Room OR 'Emergency ward' OR 'Emergency Health Service') AND (Clinical decision rules OR Decision Support OR Clinical Prediction Rule OR Clinical decision aid OR Risk prediction OR Risk score OR Predictive Model OR Algorithm OR Aortic Dissection Detection Risk Score OR (ADD-RS) OR Aorta Simplified Score OR 'clinical decision rule' OR 'decision support system')	English, Human, 2012-Current
3/7/2023	EMBASE	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome OR Intimal Tear OR Aortic Rupture OR 'thoracic aorta aneurysm') AND (Emergency Medicine OR Emergency Department OR Emergency Room OR 'Emergency ward' OR 'Emergency Health Service') AND (d-dimer OR Fibrinogen OR White blood cell OR 'biological marker' OR 'blood examination')	English, Human, 2012-Current
3/7/2023	EMBASE	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome OR Intimal Tear OR Aortic Rupture OR 'thoracic aorta aneurysm') AND (Emergency Medicine OR Emergency Department OR Emergency Room OR 'Emergency ward' OR 'Emergency Health Service') AND (Imaging OR Chest X-Ray OR Plain Film x-ray OR Point of Care Ultrasound OR POCUS OR Sonography OR 'Echography' OR 'radiography')	English, Human, 2012-Current
3/7/2023	Science Direct	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND ("Emergency Medicine" OR "Emergency Department") AND (Clinical decision rules OR Clinical Prediction Rule OR decision support system)	2012 to Present, English, Human, Research Articles, Review Articles
3/7/2023	Science Direct	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND ("Emergency Medicine" OR "Emergency Department")	2012 to Present, English, Human, Research Articles, Review Articles

		AND (d-dimer OR Fibrinogen OR White blood cell OR 'biological marker' OR 'blood examination')	
3/7/2023	Science Direct	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (Chest X-Ray OR Point of Care Ultrasound OR Sonography OR radiography)	2012 to Present, English, Human, Research Articles, Review Articles
3/7/2023	Scopus	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (Clinical decision rules OR Clinical Prediction Rule OR decision support system)	English, Human, 2012-Current
3/7/2023	Scopus	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (d-dimer OR Fibrinogen OR White blood cell OR 'biological marker' OR 'blood examination')	English, Human, 2012-Current
3/7/2023	Scopus	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (Chest X-Ray OR Point of Care Ultrasound OR Sonography OR radiography)	English, Human, 2012-Current
3/7/2023	Cochrane	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (Clinical decision rules OR Clinical Prediction Rule OR decision support system)	English, Human, 2012-Current
3/7/2023	Cochrane	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (d-dimer OR Fibrinogen OR White blood cell OR 'biological marker' OR 'blood examination')	English, Human, 2012-Current
3/7/2023	Cochrane	(Thoracic Aortic Dissection OR Aortic Aneurysm OR Acute Aortic Syndrome) AND (“Emergency Medicine” OR “Emergency Department”) AND (Chest X-Ray OR Point of Care Ultrasound OR Sonography OR radiography)	English, Human, 2012-Current

Appendix F. Evidentiary Table.

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nazerian 2018[15]	II	Prospective, observational, multicenter	Consecutive patients > 18 years of age with ≥1 symptom within ≤14	N=1,850 with a prevalence of 13% (241/1,850) for AAS. ADD-RS=0 in 12 patients (5%), ADD-RS=1 in	High prevalence of AAS.

		cohort study from 2014 to 2016 6 hospitals in 4 countries	days: chest pain, abdominal pain, back pain, syncope, or signs or symptoms of perfusion deficit. ADD-RS was calculated based on physician case report form and D-dimer was ordered. D-dimer was considered negative if <500 ng/mL FEU using one of the following assays: HemosIL DD HS (Instrumentation Laborator, Bedford MA, USA, STA®-Liatest® D-Di (Diagnostica Stago, Asnières sur Seine Cedex, France), TriniLIA DD (TCOAG, Bray, Ireland), and INNOVANCE® DD (Siemens, Erlangen, Germany). Outcome: failure rates of (1) ADD-RS=0 and negative D-dimer (2) ADD-RS ≤1 and negative D-dimer. For diagnosis of acute aortic syndrome (AAS) – type A or B aortic dissection (AoD), penetrating aortic ulcer, aortic intramural	96 patients (39.8%) and ADD-RS>1 in 133 (55.2%). Diagnostic characteristics of ADD-RS=0 and negative D-dimer: Sensitivity 99.6% (95% CI 97.7-100), Specificity 18.2% (95% CI 16.4-20.2), Positive LR 1.22 (95% CI 1.19-1.25), Negative LR 0.02 (95% CI 0.003-0.16) Diagnostic characteristics of ADD-RS≤1 and negative D-dimer: Sensitivity 98.8% (95% CI 96.4-99.7), Specificity 57.3% (95% CI 54.9-59.7), Positive LR 2.31 (95% CI 2.18-2.45), Negative LR 0.02 (95% CI 0.01-0.07)	Gold standard data only obtained in 46.8% of cases (n=865).7 cases of AAS were identified in patients who did not initially receive gold standard imaging This study assessed operating characteristics for a variety of AAS, not just thoracic aortic dissection.

			hematoma, and aortic rupture		
Nazerian 2019[16]	III	Prespecified subanalysis of the Nazerian 2018 prospective multicenter study from 6 hospitals in 4 countries	Consecutive patients > 18 years of age with ≥1 symptom within ≤14 days: chest pain, abdominal pain, back pain, syncope, or signs or symptoms of perfusion deficit, AAS on differential diagnosis by attending physician and focused cardiac ultrasound (FoCUS) was performed. FoCUS was performed prior to advanced aortic imaging by a cardiologist, internal medicine or emergency physician. Outcome: Diagnostic performance of ADD-RS≤1—in diagnosis of AAS	N=839 patients with a prevalence of 17.4% (N=146) for AAS. 10.1% (N=85) had a Type A AoD, 3.2% (N=27) had a Type B AoD, 2.4% (N=20) had a intramural hematoma, 1.3% (n=11) had a spontaneous aortic rupture, and 0.4% (N=3) had a penetrating aortic ulcer. Diagnostic performance of FoCUS for AAS: Diagnostic performance of ADD-RS≤1, direct FoCUS signs absent, and D-dimer <500 ng/mL: Sensitivity 100% (95% CI 97.3-100), Specificity 58.7% (95% CI 55-62.4%), Positive LR 2.42 (95% CI 2.2-2.64), Negative LR 0.0 (95% CI 0-0.1). AUC-ROC 79.4% Diagnostic performance of ADD-RS≤1, FoCUS negative, and D-dimer <500 ng/mL: Sensitivity 100% (95% CI 97.3-100), Specificity 48.4% (95% CI 44.6-52.1), Positive LR 1.94 (95% CI 1.79-2.08), Negative LR 0.0 (95% CI 0-0.12). AUC-ROC 74.2%.	There were 5 cases of AAS identified in 14-day clinical follow up in patients who did not initially receive conclusive imaging. 20% of FoCUS exams performed by cardiologists who demonstrated higher sensitivity for direct signs of AAS.

Appendix E6. Articles graded for methodological rigor but ultimately found to be fatally flawed.

Bima P, Pivetta E, Nazerian P, Toyofuku M, Gorla R, Bossone E, Erbel R, Lupia E, Morello F. Systematic Review of Aortic Dissection Detection Risk Score Plus D-dimer for Diagnostic Rule-out Of Suspected Acute Aortic Syndromes. Acad Emerg Med. 2020 Oct;27(10):1013-1027. doi: 10.1111/acem.13969. Epub 2020 Apr 21.

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Morello F, Santoro M, Fargion AT, Grifoni S, Nazerian P. Diagnosis and management of acute aortic syndromes in the emergency department. *Intern Emerg Med*. 2021;16(1):171-181. doi:10.1007/s11739-020-02354-8

Morello F, Bima P, Pivetta E, et al. Development and Validation of a Simplified Probability Assessment Score Integrated With Age-Adjusted d-Dimer for Diagnosis of Acute Aortic Syndromes. *J Am Heart Assoc*. 2021;10(3):e018425. doi:10.1161/JAHA.120.018425

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