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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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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Running title: ADD risk score plus D-dimer for aortic syndromes

ABSTRACT

Background—Acute aortic syndromes (AAS) are rare and severe cardiovascular emergencies with unspecific symptoms. For AAS, both misdiagnosis and over-testing are key concerns, and standardized diagnostic strategies may help physicians to balance these risks. D-dimer (DD) is highly sensitive for AAS, but is inadequate as a standalone test. Integration of pre-test probability assessment (PPA) with D-dimer (DD) testing is feasible, but the safety and efficiency of such diagnostic strategy are currently unknown.

Methods—In a multicenter prospective observational study involving 6 hospitals in 4 countries from 2014 to 2016, consecutive outpatients were eligible if they had ≥1 of the following: chest/abdominal/back pain, syncope, perfusion deficit, and if AAS was in differential diagnosis. The tool for PPA was the aortic dissection detection risk score (ADD-RS, 0 to 3), *per* current guidelines. DD was considered negative (DD-) if <500 ng/ml. Final case adjudication was based on conclusive diagnostic imaging, autopsy, surgery or on 14-day follow-up. The outcomes were the failure rate and efficiency of a diagnostic strategy ruling-out AAS in patients with ADD-RS=0/DD- or ADD-RS≤1/DD-.

Results—1850 patients were analyzed. 438 (24%) patients had ADD-RS=0, 1071 (58%) patients had ADD-RS=1, and 341 (18%) had ADD-RS>1. 241 (13%) patients had AAS: 125 had type A aortic dissection, 53 had type B aortic dissection, 35 had intramural aortic hematoma, 18 had aortic rupture, and 10 had penetrating aortic ulcer. A positive DD test result had an overall sensitivity of 96.7% (95% CI 93.6-98.6%) and a specificity of 64% (95% CI 61.6-66.4%) for diagnosis of AAS; 8 patients with AAS had DD-. Within 294 patients with ADD-RS=0/DD-, 1 case of AAS was observed. This yielded a failure rate of 0.3% (95% CI 0.1-1.9%) and efficiency of 15.9% (95% CI 14.3-17.6%) for the ADD-RS=0/DD- strategy. Within 924 patients with ADD-RS≤1/DD-, 3 cases of AAS were observed. This yielded a failure rate of 0.3% (95% CI 0.1-1%) and efficiency of 49.9% (95% CI 47.7-52.2%) for the ADD-RS≤1/DD- strategy.

Conclusions—Integration of ADD-RS (both =0 or ≤1) with DD may be considered to standardize diagnostic rule-out of AAS.

Clinical trial registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02086136

Keywords: aorta, dissection, syndrome, D-dimer

CLINICAL PERSPECTIVE

What's new?

> The ADvISED international multicenter study prospectively assessed the diagnostic performance of standardized strategies integrating pre-test probability assessment and D-dimer, in 1850 patients from the Emergency Department.

> The aortic dissection detection risk score (ADD-RS), a bedside clinical tool for standardized pre-test probability assessment, effectively stratified the risk of AAS.

> In patients with ADD-RS >1 and D-dimer <500 ng/mL, the rate of AAS was significant (1 in 22 cases).

> Rule-out strategies for AAS integrating ADD-RS =0 plus D-dimer <500 ng/mL or ADD-RS ≤1 plus D-dimer <500 ng/mL were found to miss around 1 in 300 cases of AAS.

What are the clinical implications?

> Integration of ADD-RS with D-dimer may help to standardize diagnostic decisions on advanced imaging for suspected AAS, balancing the risks of misdiagnosis and over-testing.

> Patients at high probability of AAS (*i.e.* ADD-RS>1) should proceed to computed tomography angiography (CTA) or other conclusive imaging irrespective of D-dimer levels.

> ADD-RS =0 plus D-dimer <500 ng/mL or ADD-RS ≤1 plus D-dimer <500 ng/mL are possible rule-out diagnostic strategies for AAS.

> The ADD-RS ≤1 plus D-dimer <500 ng/mL strategy may avoid up to 1 in 2 CTA exams in patients with suspected AAS.

INTRODUCTION

Acute aortic syndromes (AAS), which include aortic dissection, intramural aortic hematoma, penetrating aortic ulcer and aortic rupture, are life-threatening cardiovascular emergencies affecting 3-6 cases/100.000 individuals/year.[1, 2] AAS constitute a diagnostic challenge, because their clinical presentation is highly unspecific.[3] Indeed, while key symptoms of AAS such as chest pain, account for millions of Emergency Department (ED) visits worldwide every year, AAS is the responsible cause only in a small minority of patients.[4] Accordingly, the misdiagnosis rate of AAS is 14-39%, and represents a substantial concern.[5-7]

Chest and abdomen computed tomography angiography (CTA) can accurately diagnose AAS, but exposes patients to risks of radiation and contrast-induced anaphylaxis and nephropathy.[3, 8, 9] Notwithstanding differences across centers, as low as 2.7% of CTA exams performed for suspected AAS result positive in ED-based series.[10] Also other advanced imaging methods such as transesophageal echocardiography (TEE) and aortic magnetic resonance angiography (MRA) are stress limited, potentially harmful and costly resources demanding careful patient selection. Therefore, algorithms helping physicians to reduce both misdiagnosis and over-testing for AAS, are highly needed.

The aortic dissection detection risk score (ADD-RS) is a tool allowing standardized assessment of the pre-test probability AAS.[11] Based on the ADD-RS, patients can be classified in 3 (ADD-RS=0, ADD-RS=1, ADD-RS>1) or 2 categories (ADD-RS≤1, ADD-RS>1). This classification is adopted by international guidelines, and inspires the proposed diagnostic algorithms for AAS.[12, 13]

D-dimer (DD) is a well-established rule-out biomarker for pulmonary embolism.[14, 15] Several studies have shown that DD is also highly sensitive for AAS.[16, 17] However, a negative DD test result *per se* is insufficient for AAS rule-out in any patient.[18] As only very few cases of AAS are predicted to occur in patients at lower pre-test probability also testing negative for DD, combined use of ADD-RS and DD testing could allow safe rule-out of AAS without performing conclusive imaging.[13, 15, 17, 19-21] This approach has never been evaluated prospectively. We have performed a prospective multicenter

study assessing the accuracy and efficiency of a diagnostic strategy integrating ADD-RS with DD testing.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure, by contacting the corresponding author (FM). For expanded methods, see **supplemental materials**.

Study design and setting

This was a multicenter, multinational, prospective diagnostic accuracy observational study involving 6 hospitals and 150 physicians, in 4 countries. The Ethics Committees of the participating centers approved the study. Written informed consent of participants was obtained for inclusion. The study was registered on ClinicalTrials.gov (NCT02086136).

Patient selection

From 2014 to 2016, consecutive outpatients aged >18 years presenting to the ED were eligible if they experienced ≥1 of the following symptoms, dating ≤14 days: chest pain, abdominal pain, back pain, syncope, signs or symptoms of perfusion deficit. Patients were included only if AAS was considered in differential diagnosis by the attending physician, which defined a provider-determined need for rule-out of AAS. Subjects were enrolled 24 hours/7 days. Exclusion criteria were primary trauma and unwillingness or inadequacy to participate in the study.

Index visit

Patients were evaluated by ≥1 physician. After eligibility assessment, a case report form was completed and a DD test was ordered. Subsequent diagnostic and clinical decisions were based on

clinical judgment, not blinded to the items for pre-test probability assessment and to the DD test result.

Pre-test probability assessment

The tool used to assess the pre-test probability of AAS was the ADD-RS, based on 12 risk-markers classified in 3 categories (**supplemental table 1**).[11-13, 21, 22] The ADD-RS of each patient was automatically calculated as the number of categories (0 to 3) where at least one risk-marker was present.[12, 13]

D-dimer

Patients were subjected to venous sampling during the index visit. The samples were immediately sent to the local laboratory for automated DD assay. A DD test result was defined negative if <500 ng/ml fibrinogen equivalent units.[16, 17]

Diagnostic workup and follow-up

The following advanced imaging methods were considered conclusive for diagnosis of AAS: CTA, TEE and MRA. Patients not subjected to these tests, and without surgical or autopsy data confirming or excluding AAS, entered a 14-day clinical follow-up for case adjudication. For this purpose, patients or family members were interviewed by telephone using a structured questionnaire or underwent an outpatient visit, after 14 days from ED discharge. The following events were queried: diagnosis of AAS or any aortic disease, subsequent ED visit, hospital admission, death. Patients dismissed from the ED were instructed to return to the ED in case of new, worsening or recurrent symptoms. Hospital charts and dismissal documents of all enrolled patients were acquired and reviewed for case adjudication.

Case definition and adjudication

The definition of AAS included: Stanford type A or B aortic dissection, aortic intramural hematoma, penetrating aortic ulcer and aortic rupture. Case adjudication was performed by two expert physicians, who independently reviewed the diagnostic data obtained during the index ED visit and during the 14-day follow-up period, blinded to the ADD-RS and to the DD test result. A case of AAS was pre-defined by evidence of AAS on CTA, TEE, MRA, surgery or autopsy. For deaths occurring in patients without conclusive imaging, surgery or autopsy, adjudication was clinical. Case adjudication was dichotomic: AAS present or absent. In patients without AAS, an alternative diagnosis was indicated.

Outcomes

The primary outcome was the failure rate of a diagnostic strategy ruling out AAS in patients with: (1) ADD-RS=0 and a negative DD test result (ADD-RS=0/DD-), and (2) ADD-RS≤1 and a negative DD test result (ADD-RS≤1/DD-). The failure rate was computed as the number of adjudicated AAS diagnoses, divided by the number of patients with negative DD within a risk category. The secondary outcome was the efficiency in ruling-out AAS of the two diagnostic strategies. This was computed as the number of patients with negative DD within a risk category, divided by the number of enrolled patients.

Statistical analysis

General characteristics were assessed using mean and standard deviation, median and interquartile range, proportions and 95% confidence interval (95% CI). Univariate logistic regression models were used to assess the association (odds ratio) between AAS and selected categorical and continuous independent variables. Statistical differences were compared using two-tail Student's *t*-test for independent samples or χ^2 test. *P*-values were considered significant if <0.05.

The present study was powered to test the null hypothesis that the failure rate of the indicated diagnostic rule-out strategies exceeds 2%. This was based on previous estimates that the threshold

clinical probability of AAS above which the benefits of testing outweigh its risks is 3% for CTA.[23] Using

a type I error of 0.05 (one sided) and type II error of 0.2, we estimated that at least 1.767 patients

needed to be included.

RESULTS

Patients

Prospective data were collected for 1930 patients (**figure 1**). As 80 patients had exclusion

criteria, 1850 patients were enrolled in the study (**table 1**). The prevalence of the ADD-RS risk-markers

is presented in **supplemental table 2**. 438 (23.7%) patients had ADD-RS=0 and 1071 (57.9%) had ADD-

RS=1; 1509 (81.6%) patients classified at non-high risk of AAS (ADD-RS≤1). 341 (18.4%) patients had

ADD-RS>1.

Overall, the DD test resulted positive (≥500 ng/mL) in 813 (43.9%) patients. The DD test was

positive in 144 (32.9%) patients with ADD-RS=0, and in 441 (41.2%) with ADD-RS=1. Hence, the DD

test resulted positive in 585 (38.8%) patients with ADD-RS≤1. The DD test was positive in 228 (66.9%)

patients with ADD-RS>1 (*P*<0.001 versus ADD-RS≤1).

Diagnostic workup and case adjudication

For 865 (46.8%) study patients, conclusive diagnostic data were obtained by CTA, TEE, MRA,

surgery or autopsy (**figure 2**). The ADD-RS classification of these patients was: ADD-RS=0 in 169

patients (38.9%), ADD-RS=1 in 439 (41%), and ADD-RS>1 in 257 (75.4%). 2 patients were lost to follow-

up, and 3 patients died without advanced imaging or surgery (all had positive DD, **supplemental tables

3-4**).

AAS was adjudicated in 241 (13%) patients (**supplemental table 5**): type A aortic dissection in

125 (6.8%), type B dissection in 53 (2.9%), intramural aortic hematoma in 35 (1.9%), aortic rupture in

18 (1%), and penetrating aortic ulcer in 10 (0.5%). In 1607 (87%) patients, AAS was adjudicated as

absent. The alternative diagnoses were: muscle-skeletal chest pain (485 patients, 26.2%), acute

coronary syndrome (244, 13.2%), gastrointestinal disease (191, 10.3%), syncope (78, 4.2%), pleuritis or pneumonia (57, 3.1%), pericarditis (54, 2.9%), uncomplicated aortic aneurysm (53, 2.9%), pulmonary embolism (30, 1.6%), stroke (15, 0.8%), limb ischemia (2, 0.1%), and other diagnoses (398, 21.5%).

ADD risk score classification

The classification of patients with AAS was: ADD-RS=0 in 12 (5%) patients, ADD-RS=1 in 96 (39.8%), and ADD-RS>1 in 133 (55.2%). The prevalence of AAS was 2.7% in patients with ADD-RS=0, 9% in patients with ADD-RS=1, and 39% in patients with ADD-RS>1.

Presence of ADD-RS$\geq$1 had a sensitivity of 95% (95% CI 91.5-97.4%) and a specificity of 26.4% (95% CI 24.3-28.7%) for diagnosis of AAS. The positive predictive value (PPV) of ADD-RS$\geq$1 was 16.2% (95% CI 14.3-18.3%), the positive likelihood ratio (LR+) was 1.29 (95% CI 1.24-1.35), the negative predictive value (NPV) was 97.3% (95% CI 95.3-98.6%) and the negative likelihood ratio (LR-) was 0.19 (95% CI 0.11-0.33).

D-dimer

The median levels of DD were 5810 ng/mL (95% CI 596-50983 ng/mL) in AAS and 370 ng/mL (95% CI 98-5560 ng/mL) in alternative diagnoses (*P*<0.001; **supplemental figure 1**). A positive DD test (≥500 ng/mL) had an overall sensitivity of 96.7% (95% CI 93.6-98.6%) and a specificity of 64% (95% CI 61.6-66.4%) for diagnosis of AAS. The PPV was 28.7% (95% CI 25.6-32%), the LR+ was 2.69 (95% CI 2.51-2.88), the NPV was 99.2% (95% CI 98.5-99.7%), and the LR- was 0.05 (95% CI 0.03-0.1). There were 8 patients with AAS testing negative for DD (**table 2**).

Integration of ADD risk score with D-dimer

We estimated the performance of two rule-out strategies for AAS: ADD-RS=0/DD- and ADD-RS≤1/DD- (**table 3** and **supplemental table 6**). Within ADD-RS=0 patients, DD was negative in 294 individuals. In this low-risk subgroup, 1 case of AAS was observed. This yielded for the ADD-RS=0/DD-

strategy, a failure rate of 0.3% (95% CI 0.1-1.9%), corresponding to 1 missed case in 294 patients. The efficiency in ruling-out AAS was 15.9% (95% CI 14.3-17.6%), corresponding to 1 in 6 patients. Within ADD-RS≤1 patients, DD was negative in 924 (50%) individuals. In this non-high-risk subgroup, 3 cases of AAS were observed. This yielded for the ADD-RS≤1/DD- strategy, a failure rate of 0.3% (95% CI 0.1-1%), corresponding to 1 missed case in 312 patients. The efficiency in ruling-out AAS was 49.9% (95% CI 47.7-52.2%), corresponding to 1 in 2 patients.

Within ADD-RS>1 patients, DD was negative in 113 (33.1%) individuals, and 5 cases of AAS were observed. This yielded a failure rate of 4.4% (95% CI 1.9-9.9%), corresponding to 1 missed case in 22 patients.

DISCUSSION

The present study is the first to obtain direct prospective evidence that in patients without risk factors for AAS (*i.e.* ADD-RS=0) testing negative for DD, the rate of AAS diagnosis was about 1 missed case in 300 patients. Application of this rule may potentially spare about 3 in 5 conclusive imaging exams in this patient category, and 1 in 6 conclusive imaging exams in all patients with suspected AAS. Another key finding is that in patients presenting with a high pre-test probability of AAS (*i.e.* ADD-RS>1), the rate of AAS was significant (4%) even if the DD tested negative, thus confirming that this approach is not suitable in this patient group. Last and importantly, in the large group of patients at non-high pre-test probability of AAS (*i.e.* ADD-RS≤1) testing negative for DD, the rate of AAS diagnosis was also about 1 missed case in 300 patients. Application of this rule may potentially spare about 3 in 5 conclusive imaging exams in this patient category, and 1 in 2 conclusive imaging exams in all patients with suspected AAS. It was previously hypothesized that only the ADD-RS=0/DD- strategy should be considered for AAS rule-out.[17] In the present study, where the prevalence of AAS in patients with ADD-RS=1 was only 9%, the failure rate was low both for the ADD-RS=0/DD- and the ADD-RS≤1/DD- strategy. The likely cause lies in the systematic application of the ADD-RS, which lead to better identification of risk factors for AAS.

The acceptable failure rate of a rule-out strategy for AAS is not yet established. Similar algorithms have been considered safe for pulmonary embolism if the upper limit of the 95% CI around the failure was <3%.[14, 24, 25] In a previous study, the threshold clinical probability of AAS above which the benefits of testing outweigh its risks is 3% for CTA.[23] In the present study, the upper limit of the 95% CI around the failure rate was 1.9% for the ADD-RS=0/DD- strategy, and 1% for the ADD-RS≤1/DD- strategy. Empirical judgment on these rule-out strategies needs to strongly consider the current disappointing data from clinical practice, where the misdiagnosis rate of AAS reaches 40% and only 2.7% of CTA exams requested for possible AAS turn out positive.[5-7, 10]

The present study has limitations. First, although the symptoms triggering screening were pre-specified, the entry criterion was a provider-determined need for rule-out of AAS, which is hard to standardize. In this respect, results from urban teaching hospitals may not be generalized. In clinical practice, the actual failure and efficiency of the diagnostic strategies ultimately depend on the number and type of patients receiving testing, and inappropriate DD testing may paradoxically increase the number of patients undergoing CTA. Second, attending physicians were not blinded to ADD-RS data and to DD test results, for clinical and ethical reasons, as in the IRAD-Bio study.[13, 26] This likely impacted on their decision to perform conclusive imaging.

Third, about half of study patients were not subjected to conclusive diagnosis with CTA, TEE, MRA, surgery or autopsy, and their case adjudication was based on 14-day clinical follow-up data only. This follow-up approach was tailored on the assumption that individuals with undiagnosed AAS would experience major clinical events leading to repeated medical evaluation and conclusive diagnosis within 14 days from the ED visit, but has not been previously validated. The fact that, among patients with a negative DD in follow-up, none was lost to follow-up and none died without a clear cause, and identification of 7 cases of AAS during the specified follow-up period, strengthen our findings. Clinical follow-up data was also supported in 37% of the patients by hospitalization data following the index visit. Nonetheless, we cannot exclude with certainty that within 731 study patients with ADD-RS≤1/DD- and a negative 14-day follow-up, few cases of AAS with mild or atypical manifestations

might have been missed. Such clinical scenario is hardly compatible with type A dissections, and may essentially derive from intramural hematomas, ulcers, or short type B dissections.

A flowchart summarizing the proposed diagnostic approach to suspected AAS in the ED is presented (**Figure 3**). Expert evaluation and debate in the medical community are needed to define if these strategies meet safety and efficiency criteria for their recommendation in clinical practice.

DISCLOSURES

Nothing to disclose.

FIGURE LEGENDS

Figure 1. Study flowchart. ADD: aortic dissection detection; AAS: acute aortic syndrome.

Figure 2. Flowchart summarizing diagnostic workup. AAS: acute aortic syndrome; CTA: computed tomography angiography; ED: Emergency Department; MRA: magnetic resonance angiography; TEE: transesophageal echocardiography. *without previous conclusive imaging.

Figure 3. Proposed diagnostic algorithm based on pre-test probability assessment and D-dimer. AAS: acute aortic syndrome; ADD-RS: aortic dissection detection risk score; CTA: computed tomography angiography. *AAS in differential diagnosis. †Caution in patients with early presentation (≤2 hours) or long-lasting symptoms (≥1 week; see table 2).

TABLES

Table 1. Demographic and clinical characteristics of the study patients.

Characteristic	All patients*	Acute aortic syndrome	Alternative diagnosis	Odds Ratio	P Value
	(N = 1850)	(N = 241)	(N = 1607)		
Demographic data					
Age – yr	62 (50-74)	67 (58-78)	61 (49-73)	1.51 (1.3-1.75)	<0.001
Female sex – no (%)	698 (37.7%)	74 (30.7%)	624 (38.8%)	0.7 (0.52-0.93)	0.015
Medical history					
Hypertension – no (%)	1024 (55.4%)	172 (72.3%)	850 (52.9%)	2.32 (1.72-3.13)	<0.001
Diabetes – no (%)	251 (13.6%)	19 (8%)	231 (14.4%)	0.52 (0.32-0.84)	0.007
Smoke – no (%)	636 (34.5%)	64 (26.9%)	572 (35.6%)	0.66 (0.49-0.9)	0.008
Illicit drug use – no (%)	12 (0.8%)	3 (1.3%)	9 (0.7%)	1.79 (0.48-6.66)	0.379
Coronary artery disease – no (%)	337 (18.2%)	20 (8.4%)	316 (19.7%)	0.37 (0.23-0.60)	<0.001
Abdom. aortic aneurism – no (%)	103 (5.6%)	26 (10.9%)	77 (4.8%)	2.44 (1.53-3.89)	<0.001
Clinical presentation					

Time from onset – hours	7.5 (2-30)	3 (2-14.5)	8 (3-48)	0.8 (0.67-0.95)	0.006
Anterior chest pain – no (%)	1403 (75.8%)	159 (66%)	1244 (77.4%)	0.57 (0.42-0.76)	<0.001
Posterior chest pain – no (%)	506 (27.4%)	104 (43.2%)	401 (25%)	2.28 (1.73-3.02)	<0.001
Abdominal pain – no (%)	287 (15.5%)	60 (24.9%)	226 (14.1%)	2.03 (1.46-2.8)	<0.001
Lumbar pain – no (%)	123 (6.6%)	29 (12%)	93 (5.8%)	2.23 (1.43-3.46)	<0.001
Any pain – no (%)	1711 (92.5%)	224 (92.9%)	1485 (92.4%)	1.08 (0.64-1.83)	0.77
Syncope – no (%)	211 (11.4%)	44 (18.3%)	167 (10.4%)	1.93 (1.34-2.77)	<0.001
Perfusion deficit – no (%)	147 (7.9%)	53 (22%)	94 (5.8%)	4.54 (3.14-6.56)	<0.001
Clinical features					
Syst. blood pressure – mmHg	140 ± 26	131 ± 39	139 ± 28	0.69 (0.59-0.79)	0.001
Diastolic blood pressure – mmHg	81 ± 14	76 ± 22	80 ± 16	0.76 (0.66-0.87)	0.004
Pulse – beats per minute	78 ± 18	78 ± 23	78 ± 18	0.98 (0.85-1.13)	0.838

*Includes 2 patients who were further lost to follow-up, for whom final case adjudication was not possible. Categorical variables are presented as number and percent value; age and time from onset are presented as median and 25th-75th interquartile range; clinical features as presented as mean ± standard deviation (SD). For continuous variables, Odds Ratios are referred to 1 SD.

Table 2. Clinical detail of study patients with an acute aortic syndrome testing negative for D-dimer.

Patient number	Clinical description	Time from symptom onset	ADD risk factors	ADD risk score	Chest X-ray	AAS type
1	78-year old woman; history of hypertension, diabetes, smoke; posterior chest pain, high blood pressure at visit	7 days	none	0	enlarged mediastinum	B-AD
2	72-year old man; history of hypertension, CAD; anterior chest pain and syncope	2 hours	sudden, severe, ripping pain	1	normal mediastinum	A-AD
3	34-year old man; silent history; anterior and posterior chest pain, syncope	2 hours	sudden, severe, ripping pain	1	enlarged mediastinum	A-AD
4	40-year old man; silent history; anterior chest pain	1 hour	sudden pain family history of AAS	2	normal mediastinum	A-AD
5	75-year old man; history of hypertension, diabetes, CAD; anterior and posterior chest pain	24 hours	sudden, severe, ripping pain pulse deficit	2	normal mediastinum	IMH

6	59-year old man; history of hypertension; anterior and posterior chest pain	2 hours	known TAA sudden, severe pain	2	not done	IMH
7	54-year old man; history of previous AAS; anterior and posterior chest pain	23 hours	sudden pain pulse deficit	2	normal mediastinum	spontaneous aortic rupture
8	46-year old man; history of smoke; anterior chest and abdominal pain	7 days	sudden, severe pain diastolic murmur	2	not done	A-AD

A-AD: Stanford type A aortic dissection; AAS: acute aortic syndrome; ADD: aortic dissection detection; B-AD: Stanford type B aortic dissection; CAD: coronary artery disease; IMH: intramural aortic hematoma; TAA: thoracic aortic aneurysm.

Table 3. Diagnostic variables of the aortic dissection detection risk score combined with D-dimer testing, for diagnosis or rule-out of acute aortic syndrome, in 1848 included patients.

	Diagnostic strategy	
Diagnostic variables	**ADD risk score = 0** **plus D-dimer < 500 ng/ml**	**ADD risk score ≤ 1** **plus D-dimer < 500 ng/ml**
Sensitivity	99.6% (97.7-100%)	98.8% (96.4-99.7%)
Specificity	18.2% (16.4-20.2%)	57.3% (54.9-59.7%)
PPV	15.4% (13.7-17.3%)	25.8% (23-28.7%)
LR+	1.22 (1.19-1.25)	2.31 (2.18-2.45)
NPV	99.7% (98.1-100%)	99.7% (99.1-99.9%)
LR-	0.02 (0.003-0.16)	0.02 (0.01-0.07)

Variables are presented as percent and 95% confidence interval (in brackets).

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APPENDIX

The ADvISED Study Investigators

Co-Principal Investigators: Fulvio Morello (Città della Salute e della Scienza, Torino, Italy), Peiman Nazerian (Careggi University Hospital, Firenze, Italy)

Investigators: Elisa Capretti, Matteo Castelli, Stefano Grifoni, Simona Gualtieri, Federica Trausi, Simone Vanni (Careggi University Hospital, Firenze, Italy); Stefania Battista, Paolo Bima, Federica Carbone, Francesca Giachino, Enrico Lupia, Emanuele Pivetta, Maria Tizzani, Maria G. Veglio (Città della Salute e della Scienza, Torino, Italy); Patrick Badertscher, Jasper Boeddinghaus, Karin Grimm, Christian Mueller, Thomas Nestelberger, Raphael Twerenbold (University Hospital, Basel, Switzerland); Múcio T. Oliveira Jr., Alexandre de M. Soeiro (University of São Paulo, Brazil); Bernd A. Leidel (Charité – Universitätsmedizin Berlin, Germany); Sibilla A. T. Salvadeo (Policlinico San Matteo, Pavia, Italy).

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                    ┌─────────────────────┐
                    │  enrolled patients  │
                    │                     │
                    │     (N=1850)        │
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────────┐
                    │  conclusive diagnostic   │
                    │  data obtained during    │
                    │   index ED visit?        │
                    └─────────────────────────┘
```

Yes
(N=835)

Conclusive imaging (N=831):
  CTA (N=815)
  CTA + TEE (N=3)
  TEE (N=13)

Surgery* (N=3)

Autopsy (N=1)

Angiography (N=35)

No
(N=1015)

14-day follow-up

lost at follow-up

(N=2)

14-day clinical follow-up + admission to hospital + conclusive imaging (N=30):

  CTA (N= 22)
  CTA + TEE (N= 1)
  CTA + angiography (N= 4)
  TEE (N=2)
  MRA (N=1)

14-day clinical follow-up + admission to hospital + angiography (N=179)

14-day clinical follow-up + admission to hospital (N=169)

14-day clinical follow-up, outpatients after ED discharge (N=635)

AAS present

(N=234)

AAS absent

(N=601)

AAS present

(N=7)

AAS absent

(N=1006)

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                    ┌─────────────────────────────┐
                    │  Chest/abdominal/back pain   │
                    │           syncope            │
                    │      perfusion deficit*      │
                    └──────────────┬──────────────┘
                                   │
                                   ▼
                    ┌─────────────────────────────┐
                    │     Pre-test probability     │
                    │    assessment with ADD-RS    │
                    └──────────────┬──────────────┘
                    ┌──────────────┴──────────────┐
                    ▼                              ▼
          ┌──────────────────┐          ┌──────────────────┐
          │    ADD-RS ≤ 1    │          │    ADD-RS > 1    │
          └────────┬─────────┘          └────────┬─────────┘
                   │                              │
                   ▼                              │
          ┌──────────────────┐                    │
          │     D-dimer      │                    │
          │     testing      │                    │
          └────────┬─────────┘                    │
         ┌─────────┴──────────┐                   │
         ▼                    ▼                    │
  ┌──────────────┐    ┌──────────────┐             │
  │   D-dimer    │    │   D-dimer    │             ▼
  │  < 500 ng/ml │    │  ≥ 500 ng/ml │───────►┌──────────┐
  └──────┬───────┘    └──────────────┘        │   CTA    │
         │                                     └──────────┘
         ▼
  ┌──────────────┐
  │     AAS      │
  │  ruled out†  │
  └──────────────┘
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