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

The ADvISED Prospective Multicenter Study

BACKGROUND: Acute aortic syndromes (AASs) are rare and severe cardiovascular emergencies with unspecific symptoms. For AASs, both misdiagnosis and overtesting 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 stand-alone test. Integration of pretest probability assessment with DD testing is feasible, but the safety and efficiency of such a 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 the differential diagnosis. The tool for pretest probability assessment was the aortic dissection detection risk score (ADD-RS, 0–3) per current guidelines. DD was considered negative (DD−) if <500 ng/mL. Final case adjudication was based on conclusive diagnostic imaging, autopsy, surgery, or 14-day follow-up. Outcomes were the failure rate and efficiency of a diagnostic strategy for ruling out AAS in patients with ADD-RS=0/DD− or ADD-RS ≤1/DD−.

RESULTS: A total of 1850 patients were analyzed. Of these, 438 patients (24%) had ADD-RS=0, 1071 patients (58%) had ADD-RS=1, and 341 patients (18%) had ADD-RS >1. Two hundred forty-one patients (13%) 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% confidence interval [CI], 93.6–98.6) and a specificity of 64% (95% CI, 61.6–66.4) for the diagnosis of AAS; 8 patients with AAS had DD−. In 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 an efficiency of 15.9% (95% CI, 14.3–17.6) for the ADD-RS=0/DD− strategy. In 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 an efficiency of 49.9% (95% CI, 47.7–52.2) for the ADD-RS ≤1/DD− strategy.

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

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Clinical Perspective

What Is New?

- The ADvISED international multicenter study (Aortic Dissection Detection Risk Score Plus D-Dimer in Suspected Acute Aortic Dissection) prospectively assessed the diagnostic performance of standardized strategies integrating pretest 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 pretest probability assessment, effectively stratified the risk of acute aortic syndrome (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 ≈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 overtesting.
- Patients at high probability of AAS (ie, ADD-RS >1) should proceed to computed tomography angiography or other conclusive imaging regardless of D-dimer levels.
- ADD-RS=0 plus D-dimer <500 ng/mL and 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 computed tomography angiography examinations in patients with suspected AAS.

Acute aortic syndromes (AASs), which include aortic dissection, intramural aortic hematoma, penetrating aortic ulcer, and aortic rupture, are life-threatening cardiovascular emergencies affecting 3 to 6 per 100 000 individuals a year.[1,2] AASs constitute a diagnostic challenge because their clinical presentation is highly unspecific.[3] Indeed, although key symptoms of AASs such as chest pain account for millions of emergency department (ED) visits worldwide every year, AAS is the responsible cause in only a small minority of patients.[4] Accordingly, the misdiagnosis rate of AAS is 14% to 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] Differences across centers notwithstanding, as few as 2.7% of CTA examinations performed for suspected AAS were positive in an ED-based series.[10] In addition, other advanced imaging methods such as transesophageal echocardiography (TEE) and aortic magnetic resonance angiography (MRA) are stress limited, potentially harmful, and costly, demanding careful patient selection. Therefore, algorithms helping physicians to reduce both misdiagnosis and overtesting for AAS are highly needed.

The aortic dissection detection (ADD) risk score (ADD-RS) is a tool allowing standardized assessment of the pretest probability AAS.[11] On the basis of the ADD-RS, patients can be classified in 3 (ADD-RS=0, ADD-RS=1, ADD-RS >1) or 2 (ADD-RS ≤1, ADD-RS >1) categories. 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] Because only very few cases of AAS are predicted to occur in patients at lower pretest probability also testing negative for DD, combined use of ADD-RS and DD testing could allow safe rule out of AAS without 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, analytical 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 (F.M.). For expanded methods, see the online-only Data Supplement.

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 http://www.clinicaltrials.gov (NCT02086136).

Patient Selection

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

Index Visit

Patients were evaluated by ≥1 physicians. 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 by physicians who were not blinded to the items for pretest probability assessment and to the DD test result.

Pretest Probability Assessment

The tool used to assess the pretest probability of AAS was the ADD-RS, based on 12 risk markers classified in 3 categories (Table I in the online-only Data Supplement).[11–13,21,22] The ADD-RS of each patient was automatically calculated as the number of categories (0–3) in which at least 1 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 the 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 with 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, and 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 2 expert physicians who independently reviewed the diagnostic data obtained during the index ED visit and during the 14-day follow-up period while blinded to the ADD-RS and to the DD test result. A case of AAS was predefined 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 2 diagnostic strategies ruling out AAS, 1 in patients with ADD-RS=0 and a negative DD test result (ADD-RS=0/DD−) and 1 in patients with 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 2 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 with mean and SD, median and interquartile range, and proportions and 95% confidence intervals (CIs). Univariate logistic regression models were used to assess the association (odds ratio) between AAS and selected categorical and continuous independent
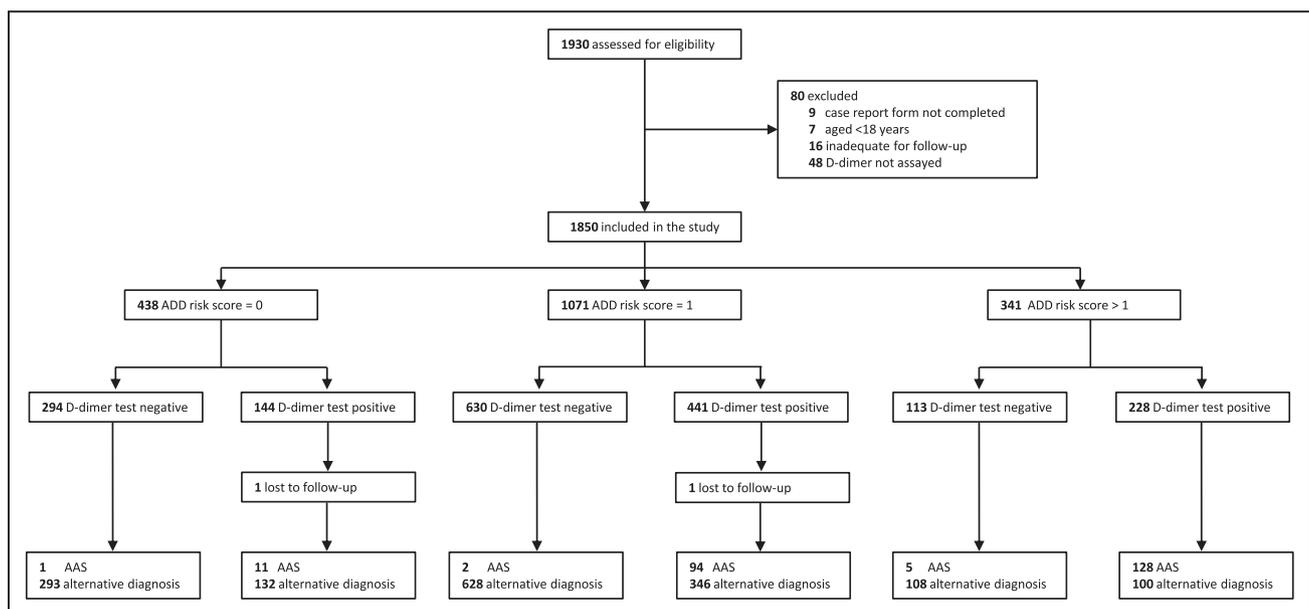
Figure 1. Study flow chart.
AAS indicates acute aortic syndrome; and ADD, aortic dissection detection.

variables. Statistical differences were compared with the 2-tailed Student 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 (1 sided) and type II error of 0.2, we estimated that at least 1767 patients needed to be included.

RESULTS

Patients

Prospective data were collected for 1930 patients (Figure 1). Because 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 Table II in the online-only Data Supplement. Four hundred thirty-eight patients (23.7%) had ADD-RS=0 and 1071 (57.9%) had ADD-RS=1; 1509 patients (81.6%) were classified at nonhigh risk of AAS (ADD-RS ≤1), and 341 patients (18.4%) had ADD-RS >1.

Overall, the DD test was positive (≥500 ng/mL) in 813 patients (43.9%). The DD test was positive in 144 patients (32.9%) with ADD-RS=0 and in 441 patients (41.2%) with ADD-RS=1. Hence, the DD test was positive in 585 patients (38.8%) with ADD-RS ≤1. The DD test was positive in 228 patients (66.9%) with ADD-RS >1 (P<0.001 versus ADD-RS ≤1).

Diagnostic Workup and Case Adjudication

For 865 study patients (46.8%), conclusive diagnostic data were obtained by CTA, TEE, MRA, surgery, or autopsy (Figure 2). The ADD-RS classification of these patients was as follows: ADD-RS=0 in 169 patients (38.9%), ADD-RS=1 in 439 (41%), and ADD-RS >1 in 257 (75.4%). Two patients were lost to follow-up, and 3 patients died without advanced imaging or surgery (all had positive DD; Tables III and IV in the online-only Data Supplement).

AAS was adjudicated in 241 patients (13%; Table V in the online-only Data Supplement): type A aortic dis-

Table 1. Demographic and Clinical Characteristics of the Study Patients

Characteristic	All Patients* (n=1850)	Acute Aortic Syndrome (n=241)	Alternative Diagnosis (n=1607)	Odds Ratio (95% CI)	P Value
Demographic data					
Age, y	62 (50–74)	67 (58–78)	61 (49–73)	1.51 (1.3–1.75)	<0.001
Female sex, n (%)	698 (37.7)	74 (30.7)	624 (38.8)	0.7 (0.52–0.93)	0.015
Medical history, n (%)					
Hypertension	1024 (55.4)	172 (72.3)	850 (52.9)	2.32 (1.72–3.13)	<0.001
Diabetes mellitus	251 (13.6)	19 (8)	231 (14.4)	0.52 (0.32–0.84)	0.007
Smoker	636 (34.5)	64 (26.9)	572 (35.6)	0.66 (0.49–0.9)	0.008
Illicit drug use	12 (0.8)	3 (1.3)	9 (0.7)	1.79 (0.48–6.66)	0.379
Coronary artery disease	337 (18.2)	20 (8.4)	316 (19.7)	0.37 (0.23–0.60)	<0.001
Abdominal aortic aneurysm	103 (5.6)	26 (10.9)	77 (4.8)	2.44 (1.53–3.89)	<0.001
Clinical presentation					
Time from onset, h	7.5 (2–30)	3 (2–14.5)	8 (3–48)	0.8 (0.67–0.95)	0.006
Anterior chest pain, n (%)	1403 (75.8)	159 (66)	1244 (77.4)	0.57 (0.42–0.76)	<0.001
Posterior chest pain, n (%)	506 (27.4)	104 (43.2)	401 (25)	2.28 (1.73–3.02)	<0.001
Abdominal pain, n (%)	287 (15.5)	60 (24.9)	226 (14.1)	2.03 (1.46–2.8)	<0.001
Lumbar pain, n (%)	123 (6.6)	29 (12)	93 (5.8)	2.23 (1.43–3.46)	<0.001
Any pain, n (%)	1711 (92.5)	224 (92.9)	1485 (92.4)	1.08 (0.64–1.83)	0.77
Syncope, n (%)	211 (11.4)	44 (18.3)	167 (10.4)	1.93 (1.34–2.77)	<0.001
Perfusion deficit, n (%)	147 (7.9)	53 (22)	94 (5.8)	4.54 (3.14–6.56)	<0.001
Clinical features					
Systolic blood pressure, mm Hg	140±26	131±39	139±28	0.69 (0.59–0.79)	0.001
Diastolic blood pressure, mm Hg	81±14	76±22	80±16	0.76 (0.66–0.87)	0.004
Pulse, bpm	78±18	78±23	78±18	0.98 (0.85–1.13)	0.838

Categorical variables are presented as number (percent); age and time from onset are presented as median and 25th through 75th interquartile range; clinical features as presented as mean±SD. For continuous variables, odds ratios are referred to 1 SD.

CI indicates confidence interval.

*Includes 2 patients who were further lost to follow-up for whom final case adjudication was not possible.

section 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 patients (87%), 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-RS Classification

The classification of patients with AAS was ADD-RS=0 in 12 patients (5%), 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 ≥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 the diagnosis of AAS. The positive predictive value of ADD-RS ≥1 was 16.2% (95% CI, 14.3–18.3), the positive likelihood ratio was 1.29 (95% CI, 1.24–1.35), the negative predictive value was 97.3% (95% CI, 95.3–98.6), and the negative likelihood ratio was 0.19 (95% CI, 0.11–0.33).

D-Dimer

The median levels of DD were 5810 ng/mL (95% CI, 596–50983) in AAS and 370 ng/mL (95% CI, 98–5560) in alternative diagnoses (P<0.001; Figure I in the online-
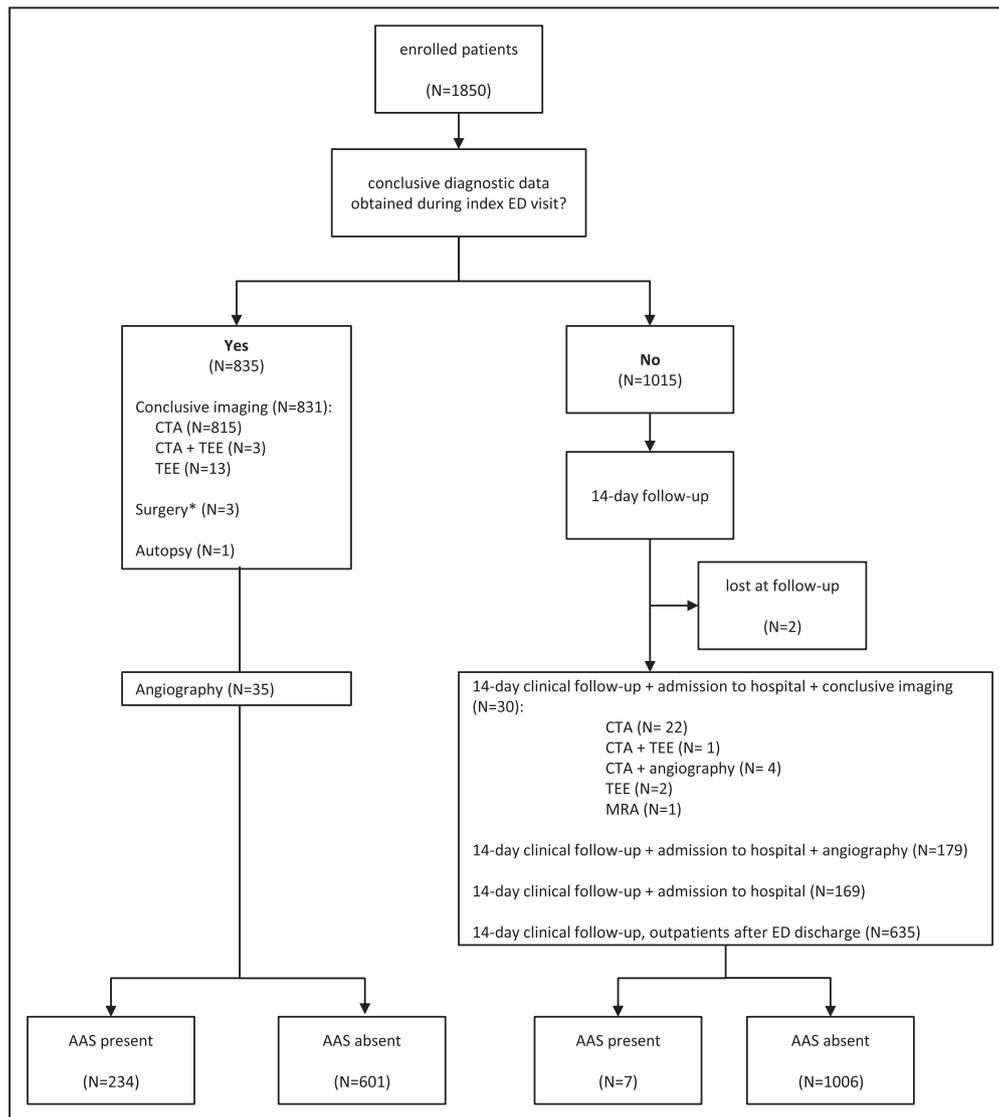
Figure 2. Flow chart summarizing diagnostic workup.
AAS indicates acute aortic syndrome; CTA, computed tomography angiography; ED, emergency department; MRA, magnetic resonance angiography; and TEE, transesophageal echocardiography. *Without previous conclusive imaging.

only Data Supplement). 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 the diagnosis of AAS. The positive predictive value was 28.7% (95% CI, 25.6–32); the positive likelihood ratio was 2.69 (95% CI, 2.51–2.88); the negative predictive value was 99.2% (95% CI, 98.5–99.7); and the negative likelihood ratio was 0.05 (95% CI, 0.03–0.1). Eight patients with AAS tested negative for DD (Table 2).

Integration of ADD-RS With DD

We estimated the performance of 2 rule-out strategies for AAS: ADD-RS=0/DD– and ADD-RS ≤1/DD– (Table 3 and Table VI in the online-only Data Supplement). In patients with ADD-RS=0, 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. In patients with ADD-RS ≤1, DD was negative in 924 individuals (50%). 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.

In patients with ADD-RS >1, DD was negative in 113 individuals (33.1%), 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 (ie, ADD-RS=0) testing negative for DD, the rate of AAS diagnosis was ≈1 missed case in 300 patients. Application of this rule may potentially spare ≈3 in 5 conclusive imaging examinations in this patient category and 1 in 6 conclusive imaging examinations in all patients with suspected AAS. Another key finding is that in patients presenting with a high pretest probability of AAS (ie, 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. Finally, in the large group of patients at nonhigh pretest probability of AAS (ie, ADD-RS≤1) testing negative for DD, the rate of AAS diagnosis was also ≈1 missed case in 300 patients. Application of this rule may potentially spare ≈3 in 5 conclusive imaging examinations in this patient category and 1 in 2 conclusive imaging examinations 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, in which the prevalence of AAS in patients with ADD-RS=1 was only 9%, the failure rate was low for both the ADD-RS=0/DD– and ADD-RS ≤1/DD– strategies. The likely cause lies in the systematic application of the ADD-RS, which led 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]

Table 2. Clinical Details of Study Patients With an AAS Testing Negative for DD

Patient No.	Clinical Description	Time From Symptom Onset	ADD Risk Factors	ADD-RS	Chest X-Ray	AAS Type
1	78-y-old woman; history of hypertension, diabetes mellitus, smoking; posterior chest pain, high blood pressure at visit	7 d	None	0	Enlarged mediastinum	B-AD
2	72-y-old man; history of hypertension, CAD; anterior chest pain, syncope	2 h	Sudden, severe, ripping pain	1	Normal mediastinum	A-AD
3	34-y-old man; silent history; anterior and posterior chest pain, syncope	2 h	Sudden, severe, ripping pain	1	Enlarged mediastinum	A-AD
4	40-y-old man; silent history; anterior chest pain	1 h	Sudden pain; family history of AAS	2	Normal mediastinum	A-AD
5	75-y-old man; history of hypertension, diabetes mellitus, CAD; anterior and posterior chest pain	24 h	Sudden, severe, ripping pain; pulse deficit	2	Normal mediastinum	IMH
6	59-y-old man; history of hypertension; anterior and posterior chest pain	2 h	Known TAA; sudden, severe pain	2	Not done	IMH
7	54-y-old man; history of AAS; anterior and posterior chest pain	23 h	Sudden pain; pulse deficit	2	Normal mediastinum	Spontaneous aortic rupture
8	46-y-old man; history of smoking; anterior chest and abdominal pain	7 d	Sudden, severe pain; diastolic murmur	2	Not done	A-AD

A-AD indicates Stanford type A aortic dissection; AAS, acute aortic syndrome; ADD, aortic dissection detection; ADD-RS, aortic dissection detection risk score; B-AD, Stanford type B aortic dissection; CAD, coronary artery disease; DD, D-dimer; IMH, intramural aortic hematoma; and TAA, thoracic aortic aneurysm.

Table 3. Diagnostic Variables of the ADD-RS Integrated With DD Testing for Diagnosis or Rule Out of AAS in 1848 Included Patients

Diagnostic Variable	Diagnostic Strategy (95% CI)	
	ADD-RS=0 Plus DD <500 ng/mL	ADD-RS ≤1 Plus DD <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)

AAS indicates acute aortic syndrome; ADD-RS, aortic dissection detection risk score; CI, confidence interval; DD, D-dimer; LR, likelihood ratio; NPV, negative predictive value; and PPV, positive predictive value.

In a previous study, the threshold clinical probability of AAS above which the benefits of testing outweigh its risks was 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 showing that the misdiagnosis rate of AAS reaches 40% and that only 2.7% of CTA examinations requested for possible AAS turn out positive.[5–7,10]

The present study has limitations. First, although the symptoms triggering screening were prespecified, 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 (International Registry of Acute Aortic Dissection Substudy on Biomarkers).[13,26] This likely affected 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 this has not been validated. Among patients with a negative DD in follow-up, none were lost to follow-up, none died without a clear cause, and 7 cases of AAS were identified during the specified follow-up period, which strengthen our findings. Clinical follow-up data were also supported
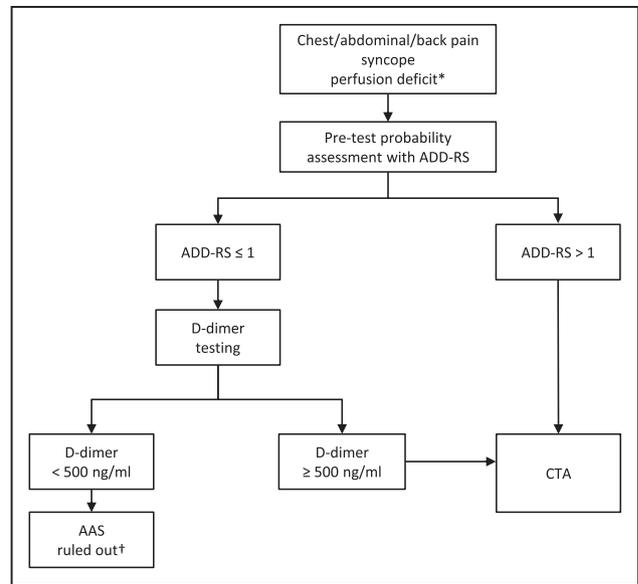
Figure 3. Proposed diagnostic algorithm based on pre-test probability assessment and D-dimer.
AAS indicates acute aortic syndrome; ADD-RS, aortic dissection detection risk score; and CTA, computed tomography angiography. *AAS in differential diagnosis. †Caution in patients with early presentation (≤2 hours) or long-lasting symptoms (≥1 week; see Table 2).

in 37% of the patients by hospitalization data after the index visit. Nonetheless, we cannot exclude with certainty that in 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 a 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 in Figure 3. Expert evaluation and debate in the medical community are needed to define whether these strategies meet safety and efficiency criteria for their recommendation in clinical practice.

APPENDIX

The ADvISED Study (Aortic Dissection Detection Risk Score Plus D-Dimer in Suspected Acute Aortic Dissection) Investigators

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DISCLOSURES

None.

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FOOTNOTES

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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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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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SUPPLEMENTAL MATERIAL

CONTENTS

EXPANDED METHODS

Study design and setting

This was a multicenter, multinational, prospective diagnostic accuracy observational study involving 6 hospitals and 150 physicians, in 4 countries (Brazil, Germany, Italy, Switzerland). All participating hospitals are referral centers for AAS and other cardiovascular emergencies, and their EDs have an average annual census of 65000 visits. The Ethics Committees of the participating centers approved the study. Written informed consent was obtained for inclusion in the study. The study was registered on ClinicalTrials.gov (No.: NCT02086136).

Patient selection

From September 2014 to December 2016, consecutive outpatients older than 18 years presenting to the ED were eligible if they experienced one or more of the following symptoms, dating no more than 14 days: chest pain, abdominal pain, back pain, syncope, signs or symptoms of perfusion deficit. Patients were included in the study only if AAS was considered in differential diagnosis by the attending physician. These criteria defined a provider-determined need for rule-out of AAS.

Subjects were enrolled 24 hours a day, 7 days per week. Exclusion criteria were the following: primary trauma, unwillingness or inadequacy to participate in the study. Also inability to prospectively collect clinical data or to obtain a DD test result, determined patient exclusion.

Index visit

During the index visit in the ED, patients were evaluated and managed by one or more emergency physician. The patient eligibility was established by the attending physician during his standard evaluation, which included complete physical exam comprehensive of vital sign collection with blood pressure measurement at both arms and ECG recording. After assessing that a patient was eligible for the study, the attending physician or a medical researcher completed a case report form

(CRF) and ordered a DD test. The CRF was completed blinded to the DD test result and to the results of conclusive imaging methods.

Subsequent diagnostic and clinical decisions, including decision to perform conclusive imaging methods, surgery and autopsy, and disposition for the patient's hospitalization or ED dismissal, were determined by the attending physicians based on their clinical judgment and in compliance with local protocols, not blinded to the items collected during the pre-test probability assessment and to the DD test result.

Data collection and pre-test probability assessment

Structured data collection for pre-test probability assessment was performed prospectively during the index ED visit by the attending physician or a medical researcher. For each patient, a standardized CRF was filled, which recorded pre-specified variables from medical history, presenting signs/symptoms, and risk factors of AAS. If CRF data could not be recorded, the patient was excluded from the study. If only limited data was unavailable during the index ED visit, lacking data was defaulted to negative. CRF data were subsequently inputted into an electronic database.

The tool used to assess the pre-test probability of AAS was the ADD-RS, endorsed by international guidelines on aortic diseases.[1-5] The ADD-RS is based on presence or absence of 12 risk factors, classified in 3 categories (**supplemental table 1**). 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.[1, 2]

Within ADD-RS factors, aortic valve disease included also any previous surgical/endovascular repair or graft replacement for aortic valve disease. Thoracic aortic aneurysm was defined as known aortic enlargement, or any previous surgical or endovascular graft repair of thoracic aortic aneurysm. Recent aortic manipulation was defined as coronary or aortic angiography, intra-aortic balloon pump, aortic surgery, coronary artery bypass surgery or aortic valve surgery performed within the last month. Pain intensity was judged at the pain peak, based on patient-defined numeric rating scale (0 to 10).

Pain was considered severe if >6. Systolic blood pressure differential was defined by >20 mmHg between extremities. Neurologic deficits included any motor, sensory or cranial nerve deficit or coma state. Hypotension was defined by systolic blood pressure ≤90 mmHg.

D-dimer

Patients were subjected to venous sampling during the index ED visit. Patients in whom a venous sample for DD testing was not collected during the index ED visit, and patients in whom a DD test result was not available due to technical issues, were excluded from the study. The venous samples were immediately sent to the local laboratory for an automated DD assay. Diagnostic tests were site-specific and included: HemosIL DD HS (Instrumentation Laboratory, 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 laboratory technicians were unaware of clinical data. A DD test result was defined negative if lower than 500 ng/ml fibrinogen equivalent units. This cutoff has been validated for DD use in venous thromboembolic disease, and has shown high sensitivity for AAS in several studies and metanalyses.[6, 7]

Diagnostic imaging

The primary conclusive imaging method allowing conclusive diagnosis of AAS was chest and abdomen contrast-enhanced multi-detector CTA (≥64 row-detectors). Other imaging methods accepted for conclusive diagnosis of AAS were TEE and MRA. Instruments used for imaging were site-specific. These exams were performed and interpreted by specialized radiologists, cardiologists or cardiac surgeons not involved in the present study.

Follow-up

Given the severity of AAS in untreated patients, we assumed that individuals with undiagnosed AAS would experience major clinical events leading to repeated medical evaluation and conclusive

diagnosis, or would decease within 14 days from the ED visit. Therefore, in all patients for whom

conclusive diagnostic data was not obtained during the index ED visit by conclusive imaging (CTA, TEE,

MRA), surgery or autopsy, entered a 14-day follow-up to allow accurate case adjudication. The

timeline of the follow-up (14 days) was tailored on the acute phase of AAS, based on the classic

definition and guidelines: the mortality of untreated AAS is 1-2% per hour from symptom onset, and

complications are frequent in the first days after symptom onset.[1, 8, 9]

Patients dismissed after the ED visit without conclusive diagnostic data were instructed to

return to the ED in case of new, worsening or recurrent symptoms. Patients or family members were

interviewed by telephone using a structured questionnaire, or underwent an outpatient visit, after 14

days. The following health-related events since ED discharge were queried for all patients in follow-

up: diagnosis of AAS or any aortic disease, subsequent ED visit, subsequent admission to hospital,

death. Hospital charts and dismissal documents of all enrolled patients were acquired and reviewed

for final case adjudication.

Case definition and adjudication

The following etiological entities were considered in the definition of AAS: Stanford type A or

B aortic dissection, intramural aortic 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, if applicable, during the 14-day follow-up period, blinded

to the ADD-RS and to the DD test result at recruitment. For all patients admitted to hospital after the

ED visit or with novel ED visits, medical records with diagnostic data were reviewed. Case adjudication

was dichotomic: AAS present or AAS absent. In case of discordance, the case was adjudicated after

discussion.

A case of AAS was pre-defined by evidence of AAS on conclusive imaging (CTA, TEE, MRA),

surgery or autopsy. For deaths occurring in patients without conclusive diagnostic data by advanced

imaging, surgery or autopsy, adjudication was clinical, based on all available *pre-mortem* data. In these

cases, AAS was adjudicated as present if any direct or indirect sign of AAS was detected at transthoracic echocardiography (intimal flap, intramural aortic hematoma, aortic ulcer, aortic dilatation or aneurysm, pericardial effusion or tamponade) or chest radiography (mediastinal enlargement), and if alternative death causes were confidently ruled out by both reviewers. The diagnostic data used for case adjudication were annotated.

In patients where adjudication was AAS absent, an alternative diagnosis to AAS was also indicated based on available data. Pre-specified alternative diagnoses were the following: acute coronary syndrome, gastrointestinal disease, pleuritis or pneumonia, pericarditis, pulmonary embolism, stroke not related to AAS, limb ischemia not related to AAS, syncope not related to AAS, uncomplicated aortic aneurysm, muscle-skeletal pain and other diagnoses.

Outcomes

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

Statistical analysis

General characteristics were assessed using mean and standard deviation or median and interquartile range for continuous variables, and proportions with 95% confidence interval (95% CI) for categorical variables. The Wilson score method without continuity correction was used to compute the 95% CI around estimated proportions. The CI for the likelihood ratios were estimated based on a generalized linear model. 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 (continuous variables), or χ^2 test (proportions). *P*-values were considered significant if lower than 0.05.

The diagnostic performance of D-dimer was assessed by Receiver Operated Characteristic (ROC) analysis, estimating the area under the curve (AUC). The diagnostic variables of the ADD-RS/DD diagnostic strategies (**table 3** and **supplemental table 6**) were calculated as follows. Sensitivity was calculated as the percent of patients with AAS who did not satisfy the ADD-RS/DD diagnostic rule-out strategy. Specificity was calculated as the percent of patients without AAS who satisfied the ADD-RS/DD diagnostic rule-out strategy. The positive predictive value (PPV) was calculated as the percent of patients with AAS within all patients who did not satisfy the ADD-RS/DD diagnostic rule-out strategy. The positive likelihood ratio (LR+) was calculated as: sensitivity/(1-specificity). The negative predictive value (NPV) was calculated as the percent of patients without AAS within all patients who satisfied the ADD-RS/DD diagnostic rule-out strategy. The negative likelihood ratio (LR-) was calculated as: (1-sensitivity)/specificity.

Statistical computations were conducted with SPSS software ver. 20 (IBM).

Sample size calculation

In contrast with therapeutic or intervention studies, formal sample size calculations based on power assumptions for diagnostic or prognostic modeling cohort studies are controversial. Nonetheless, we aimed at including enough patients to provide accurate estimates of the primary outcome. In our previous study, evaluating only patients subjected to ADI, the prevalence of AAS was 6% in patients with ADD-RS=0 and 18% in patients with ADD-RS≤1, and the negative likelihood ratio of DD was 0.05, which was further confirmed in the metanalysis by Asha *et al*.[4, 6] We assumed that the point estimates of the failure rate would be: (1) 0.3% for a diagnostic strategy ruling out AAS in patients with ADD-RS=0/DD-, and (2) 0.8% in patients with ADD-RS≤1/DD-. The present study was powered to test the null hypothesis that the failure rate of these diagnostic 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 are 2% for MRA, 3% for CTA and 9% for TEE.[10] Using a type I error of 0.05 (one sided) and type II error of 0.2, we needed to include about 265 participants with ADD-RS=0/DD-, and about 793 participants with ADD-RS≤1/DD-, to reject the null hypothesis. Hypothesizing that individuals with ADD-RS=0/DD- and with ADD-RS≤1/DD- would be around 15% and 40% respectively of total patients with suspected AAS, we estimated that at least 1.767 patients needed to be included.

Supplemental figure 1
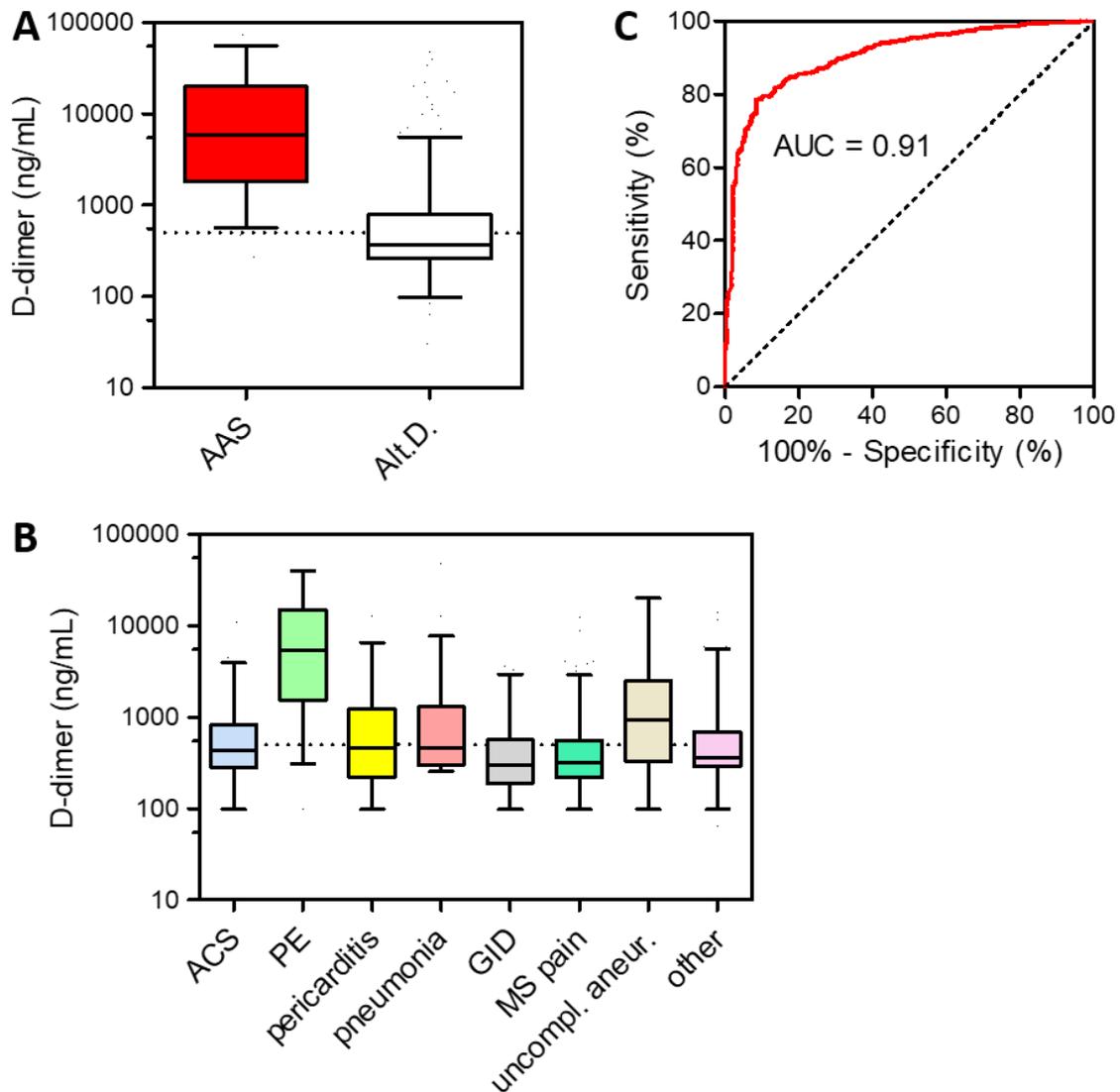
Supplemental figure 1 legend. A. Box-plot of D-dimer levels in patients with final diagnosis of acute aortic syndrome (AAS) or an alternative diagnosis (Alt.D.). D-dimer levels are represented on a log (10) scale. **B.** Box-plot of D-dimer levels in patients with different alternative diagnoses to AAS. D-dimer levels are represented on a log (10) scale. ACS: acute coronary syndrome. PE: pulmonary embolism; GID: gastrointestinal disease; MS: muscle-skeletal; uncompl. aneur.: uncomplicated aortic aneurysm. **C.** ROC curve of D-dimer for diagnosis of AAS. AUC indicates the area under the curve.

Supplemental table 1. Aortic dissection risk score (ADD-RS) for assessment of the pre-test clinical probability of acute aortic syndrome.

Risk categories	Risk factors	Points*
Predisposing conditions	Marfan syndrome or other connective tissue disease	1
	Family history of aortic disease	
	Known aortic valve disease	
	Known thoracic aortic aneurysm	
	Recent aortic manipulation	
Pain features	Abrupt pain	1
	Severe pain	
	Ripping or tearing pain	
Physical findings	Pulse asymmetry or systolic blood pressure differential	1
	Focal neurological deficit	
	New diastolic murmur of aortic insufficiency	
	Shock state or hypotension	

*For each risk category, one point is assigned if one or more risk factors is present. The ADD-RS can therefore vary from 0 to 3.

Supplemental table 2. Aortic dissection detection (ADD) risk-markers in study patients.

Characteristic	All patients* (N = 1850)	Acute aortic syndrome (N = 241)	Alternative diagnosis (N = 1607)	Odds Ratio	P Value
Risk conditions					
Marfan syndrome – no (%)	15 (0.8%)	2 (0.8%)	13 (0.8%)	1.04 (0.23-4.63)	0.960
Family history of AAS – no (%)	50 (2.7%)	12 (5%)	38 (2.4%)	2.19 (1.13-4.26)	0.018
Aortic valve disease – no (%)	100 (5.4%)	17 (7.1%)	83 (5.2%)	1.41 (0.82-2.43)	0.208
Recent aortic manipulation – no (%)	22 (1.2%)	4 (1.7%)	18 (1.1%)	1.51 (0.51-4.5)	0.457
Thoracic aortic aneurism – no (%)	167 (9%)	52 (21.8%)	115 (7.2%)	3.63 (2.53-5.21)	<0.001
Any risk condition – no (%)	293 (15.8%)	72 (29.9%)	221 (13.8%)	2.68 (1.96-3.65)	<0.001
Pain features					
Sudden pain – no (%)	749 (40.6%)	159 (66%)	590 (36.8%)	3.33 (2.51-4.43)	<0.001
Severe pain – no (%)	886 (47.9%)	172 (71.4%)	713 (44.4%)	3.13 (2.32-4.2)	<0.001
Ripping/tearing pain – no (%)	338 (18.3%)	56 (23.2%)	282 (17.5%)	1.42 (1.03-1.97)	0.033

Any pain feature – no (%)	1207 (65.2%)	200 (83%)	1006 (62.6%)	2.92 (2.05-4.14)	<0.001
Physical findings					
Pulse deficit – no (%)	116 (6.3%)	50 (20.7%)	66 (4.1%)	6.11 (4.1-9.09)	<0.001
Neurologic deficit – no (%)	92 (5%)	27 (11.2%)	65 (4%)	2.99 (1.87-4.79)	<0.001
New aortic murmur – no (%)	32 (1.7%)	17 (7.1%)	15 (0.9%)	8.06 (3.97-16.36)	<0.001
Hypotension/shock – no (%)	94 (5.1%)	53 (22%)	41 (2.6%)	10.77 (6.97-16.63)	<0.001
Any physical finding – no (%)	285 (15.4%)	112 (46.5%)	173 (10.8%)	7.21 (5.35-9.71)	<0.001

*Includes 2 patients who were further lost at follow-up, for and whom final case adjudication was not possible. Variables are presented as number and percent value. AAS: acute aortic syndrome.

Supplemental table 3. Clinical detail of patients lost to follow-up (n=2).

Patient number	Clinical description	ADD risk score	D-dimer test result	Chest radiography	Diagnosis at ED discharge
1	63-year old male; history of hypertension; abdominal and lumbar pain	0	positive	normal mediastinum	muscle-skeletal pain
2	72-year old man; history of hypertension, diabetes, CAD; posterior chest pain	1	positive	normal mediastinum	gastrointestinal disease

ADD: aortic dissection detection; CAD: coronary artery disease; ED: Emergency Department

Supplemental Table 4. Clinical detail of patients who died without available *pre-mortem* advanced diagnostic imaging or surgical data (n=3).

Patient number	Clinical description	ADD risk score	D-dimer test result	Diagnostic findings	Autopsy data	Case adjudication
1	62 year-old man; primary evaluation in ED for syncope and shock state	1	positive	bedside ultrasonography: cardiac tamponade	available	AAS (aortic rupture)
2	88 year-old woman; history of hypertension, diabetes; abdominal pain, syncope, suspected perfusion deficit	1	positive	bedside ultrasonography: intimal flap, aortic dilatation and pericardial effusion	not available	AAS (Stanford type A aortic dissection)
3	72-year old woman; history of smoke; anterior chest pain	1	positive	chest radiography: normal mediastinum	not available	sepsis (AAS absent)

AAS: acute aortic syndrome; ADD: aortic dissection detection

Supplemental table 5. Diagnostic data available for patients with acute aortic syndrome adjudication

(n=241).

Diagnostic data	n (%)
CTA	234 (97.1%)
CTA + TEE	4 (1.7%)
Cardiac surgery	119 (49.4%)
TEVAR	13 (5.4%)
Autopsy	1 (0.4%)
Death, clinical adjudication*	1 (0.4%)

CTA: computed tomography angiography of chest and abdomen; TEE: transesophageal echocardiography; TEVAR: thoracic aorta endovascular repair. *In this patient, who died in-hospital during clinical follow-up, there was *pre-mortem* evidence of intimal flap, aortic dilatation and pericardial effusion with bedside transthoracic echocardiography.

Supplemental table 6. Diagnostic variables of the aortic dissection detection risk score combined with D-dimer testing, for diagnosis or rule-out of acute aortic syndrome, in the subgroup of patients (n=865) subjected to conclusive diagnosis by CTA, TEE, MRA, surgery or autopsy.

	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	9.8% (7.6-12.4%)	30.4% (26.8-34.2%)
PPV	29.8% (26.6-33.1%)	35.3% (31.7-39%)
LR+	1.1 (1.07-1.13)	1.42 (1.34-1.5)
NPV	98.4% (91.3-100%)	98.4% (95.5-99.7%)
LR-	0.04 (0.01-0.31)	0.04 (0.01-0.13)

Variables are presented as percent and 95% confidence interval (in brackets). ADD: aortic dissection detection. LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value PPV: positive predictive value.

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APPENDIX

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