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ORIGINAL RESEARCH

Development and Validation of a Simplified Probability Assessment Score Integrated With Age-Adjusted D-Dimer for Diagnosis of Acute Aortic Syndromes

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BACKGROUND: When acute aortic syndromes (AASs) are suspected, pretest clinical probability assessment and D-dimer (DD) testing are diagnostic options allowing standardized care. Guidelines suggest use of a 12-item/3-category score (aortic dissection detection) and a DD cutoff of 500 ng/mL. However, a simplified assessment tool and a more specific DD cutoff could be advantageous.

METHODS AND RESULTS: In a prospective derivation cohort (n=1848), 6 items identified by logistic regression (thoracic aortic aneurysm, severe pain, sudden pain, pulse deficit, neurologic deficit, hypotension), composed a simplified score (AORTAs) assigning 2 points to hypotension and 1 to the other items. AORTAs≤1 and ≥2 defined low and high clinical probability, respectively. Age-adjusted DD was calculated as years/age × 10 ng/mL (minimum 500). The AORTAs score and AORTAs≤1/age-adjusted DD rule were validated in 2 patient cohorts: a high-prevalence retrospective cohort (n=1035; 22% AASs) and a low-prevalence prospective cohort (n=447; 11% AASs) subjected to 30-day follow-up. The AUC of the AORTAs score was 0.729 versus 0.697 of the aortic dissection detection score (P=0.005). AORTAs score assessment reclassified 16.6% to 25.1% of patients, with significant net reclassification improvement of 10.3% to 32.7% for AASs and −8.6 to −17% for alternative diagnoses. In both cohorts, AORTAs≥2 had superior sensitivity and slightly lower specificity than aortic dissection detection ≥2. In the prospective validation cohort, AORTAs≤1/age-adjusted DD had a sensitivity of 100%, a specificity of 48.6%, and an efficiency of 43.3%.

CONCLUSIONS: AORTAs is a simplified score with increased sensitivity, improved AAS classification, and minor trade-off in specificity, amenable to integration with age-adjusted DD for diagnostic rule-out.

Key Words: age ■ aorta ■ D-dimer ■ diagnosis ■ dissection ■ syndrome

Acute aortic syndromes (AASs) are deadly conditions involving the thoracic aorta and include acute aortic dissection (AAD), intramural hematoma, penetrating aortic ulcer, and spontaneous aortic rupture. AASs are rare in the general population (5–15 cases/100 000 individuals/y), present with unspecific symptoms, and lead to high morbidity and mortality.[1] Currently, highly accurate aortic biomarkers are not available, and conclusive diagnostic assessment requires contrast medium–enhanced computed tomography angiography (CTA). However, CTA uses radiation, may cause anaphylaxis and kidney injury, and is resource

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CLINICAL PERSPECTIVE

What Is New?

- The AORTAs is a simple noncategorical 6-item score estimating the pretest clinical probability of acute aortic syndromes (AASs).
- The AORTAs score was developed from a prospective multicenter cohort of patients with suspected AASs, aiming at integration with an age-adjusted D-dimer cutoff, already applied for rule-out of pulmonary embolism; preliminary validation of the AORTAs score was obtained in 2 independent emergency department cohorts, showing higher sensitivity, better AAS classification, and lower specificity compared with the aortic dissection detection score.
- For rule-out of AASs, the performance of AORTAs score plus age-adjusted D-dimer cutoff was similar to aortic dissection detection score plus D-dimer<500 ng/mL.

What Are the Clinical Implications?

- The AORTAs score can be applied at the bedside and ab initio to all patients with suspected AAS, independent of hemodynamic status.
- With AORTAs, hypotension or any combination of items defines a high clinical probability of AAS, thus reducing the risk of initial AAS misclassification and inappropriate use of D-dimer.
- Integration of AORTAs with age-adjusted D-dimer cutoff is practical and clinically meaningful, allowing improved single-cutoff rule-out at maximized specificity of both AASs and pulmonary embolism; further trial is needed for external multicenter validation.

Nonstandard Abbreviations and Acronyms

AAD	acute aortic dissection
AAS	acute aortic syndrome
ADD	aortic dissection detection
AltD	alternative diagnosis
CTA	computed tomography angiography
DD	D-dimer
DD_{500}	D-dimer cutoff of 500 ng/mL
$DD_{age-adj}$	age-adjusted D-dimer cutoff
NRI	net reclassification improvement

limited. Therefore, optimal patient selection for urgent CTA is challenging. Misdiagnosis may affect 1 in 3 to 7 AASs, leading to worse outcomes.[2,3] In the meantime, CTA overtesting and high variability in ordering are major issues, with diagnostic yields as low as 2% to 3%.[4,5]

To assist and standardize diagnostic decisions, pretest clinical probability assessment has been recommended, as for pulmonary embolism (PE). Guidelines have adopted the aortic dissection detection (ADD) score as a tool partitioning their diagnostic algorithms.[6,7] The ADD score was initially developed from a large international registry of AADs and has obtained external validation.[8,9] However, this tool has limitations.[10] First, categorizing and assignment of points with a 12-risk-factor/3-risk-category score may be difficult/impractical in busy emergency departments (EDs). Second, several risk factors are rarely encountered in everyday practice, and others have vague definitions. Third, hypotension and shock, representing key alerts, do not define per se a high pretest probability. Finally, presence of ≥2 risk factors in a single category does not affect ADD score defined probability.

D-dimer (DD), a plasma fibrin degradation product, is widely used as a rule-out biomarker of PE. DD levels almost invariably increase in AASs. Using a cutoff of 500 ng/mL (DD_{500}), DD has a sensitivity of 95% to 98% and low to moderate specificity for AASs.[11] Accordingly, low probability plus a negative DD can be used to safely avoid CTA in 15% to 50% of patients.[12] As the specificity of DD diminishes with aging, an age-adjusted DD cutoff ($DD_{age-adj}$) is suggested for PE rule-out as an alternative to DD_{500}, providing similar sensitivity but higher specificity.[13] Use of a single DD cutoff optimizing specificity to rule out both PEs and AASs may be practical and efficient. However, only few studies have evaluated $DD_{age-adj}$ for AASs so far.[12,14,15]

Herein, we developed a simplified clinical probability assessment tool amenable to dichotomic rule-out of AASs in combination with $DD_{age-adj}$. External validation was pursued in 2 independent patient cohorts, by comparison with current standard (ADD score and DD_{500}).

METHODS

The data, analytical methods and study materials will be made available to other researchers by contacting the corresponding author. For expanded methods, see Data S1. The study complies with the Declaration of Helsinki, the locally appointed ethics committees have approved the research protocol, and informed consent has been obtained from the participating subjects (or their legally authorized representative).

ADD Risk Score

The standard tool used to assess the pretest probability of AASs was the ADD score, based on 12 risk markers classified in 3 categories (Table S1): high-risk conditions (Marfan syndrome, family history of aortic disease, known aortic valve disease, recent aortic

manipulation, known thoracic aortic aneurysm), high-risk pain features (sudden, severe, ripping/tearing), and high-risk physical examination features (pulse deficit or systolic blood pressure differential, focal neurologic deficit, new aortic insufficiency murmur, hypotension/shock).

Derivation Cohort

The overall study design is shown in Figure 1. The derivation cohort was obtained from a previous multicenter, multinational, prospective diagnostic study.[16] Briefly, consecutive ED outpatients aged >18 years were enrolled in the presence of red-flag symptoms (chest/abdominal/back pain, syncope, perfusion deficit) lasting ≤14 days and a physician-defined clinical suspicion of AAS. Case adjudication was based on advanced imaging, surgery, autopsy, or 14-day follow-up data.

Validation Cohorts

Validation of the simplified score and rule was sought in 2 independent study cohorts: a retrospective high-prevalence cohort and a prospective lower-prevalence cohort.

Retrospective Validation Cohort

As a high-prevalence population, we used a retrospective cohort, detailed elsewhere.[17] Briefly, this study enrolled outpatients presenting to 2 EDs of urban teaching hospitals from 2008 to 2013. Inclusion criteria were chest pain, back pain, abdominal pain, syncope, or symptoms of perfusion deficit, in conjunction with the absence of an obvious alternative diagnosis after the first medical evaluation. Clinical suspicion of AAS was high enough to have all patients undergo a CTA for final diagnosis. ADD score and DD test results were available for all patients.

Prospective Validation Cohort

As a cohort representative of Western ED practice at lower prevalence of AASs, outpatients with suspected AAS were prospectively enrolled in 2 urban teaching hospitals in a new study, from January 2018 to November 2019. Inclusion criteria were (1) presence of at least 1 red-flag symptom among truncal (chest, abdominal, or back pain) pain, syncope, neurological deficit, and limb ischemia; (2) symptom(s) lasting for ≤14 days; and (3) AASs considered as meaningful differential diagnoses by the attending physician. Exclusion criteria were age <18 years, primary trauma, and an established diagnosis of AAS.

Patient Management

During the ED visit, a case report form including probability assessment was filled out by the attending physician or resident, before availability of blood test results and imaging exams. The recommended standard of care was represented by the European Society of Cardiology 2014 guidelines.[7] However, physicians were free to derogate from guideline indications, and clinical decisions were independent from patient's participation in the study. Advanced imaging exams (CTA, transesophageal echocardiography, or magnetic resonance angiography) were performed and interpreted

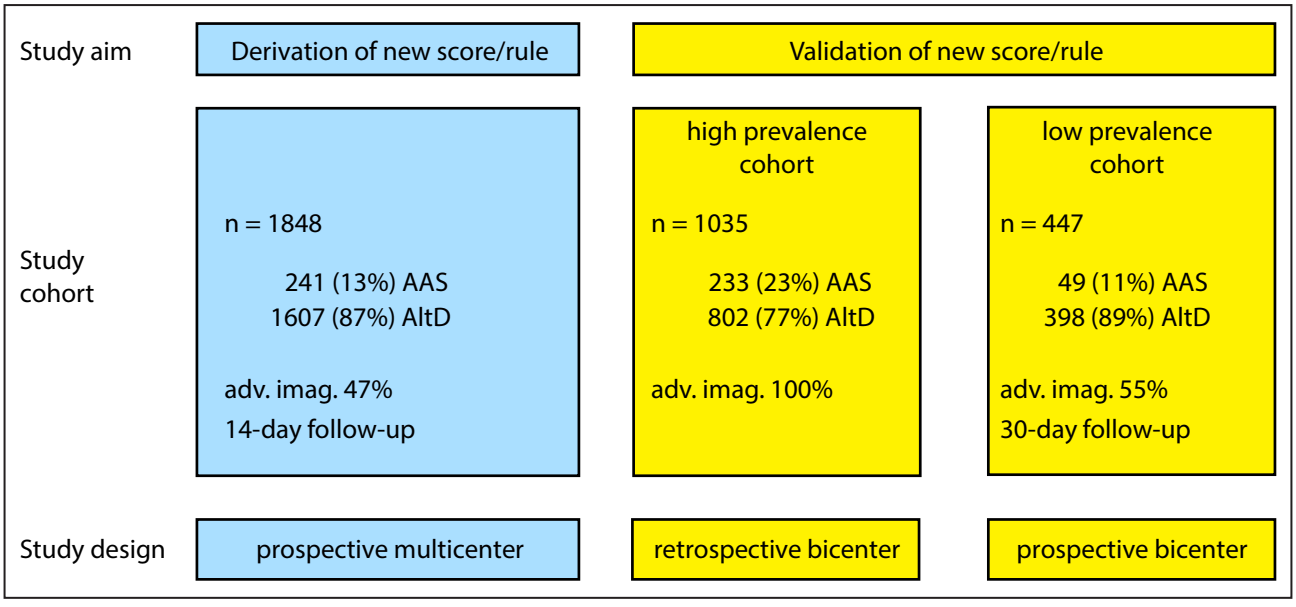

Figure 1. Overall study design.
AAS indicates acute aortic syndrome; adv. imag., advanced imaging; and AltD, alternative diagnosis.

by specialized physicians not involved in the study. Discharged patients were instructed to return to the ED in case of new, worsening, or recurrent symptoms.

D-dimer

Samples obtained during the visit were sent to the local laboratory for urgent processing. DD assays were the STA-Liatest D-Di assay (Stago, Asnières sur Seine, France) and HemosIL D-Dimer HS (Instrumentation Laboratory, Bedford, MA, USA). We planned to analyze the DD test results on the basis of 2 different cutoffs: 500 ng/mL fibrinogen equivalent units and an age-adjusted cutoff (DD_{adj}). DD_{adj}, already applicable for the rule-out of PE, was calculated as follows: age (years) × 10 ng/mL (with a minimum of 500 ng/mL for patients aged ≤50 years; e.g., 500 ng/mL for a patient aged 40 years, 600 ng/mL for a patient aged 60 years, 750 ng/mL for a patient aged 75 years).[13,14] The attending physicians were not blinded to the DD test results.

Case Adjudication

Case adjudication was performed by 2 expert physicians who independently assessed ED chart, blood test results (excluding DD), imaging data, and 30-day follow-up data. The latter included results of a structured telephone interview evaluating subsequent diagnosis of any aortic disease, ED visits and admissions to hospital, and hospital database search for additional ED visits and hospital admissions within 30 days. For ED visits and hospital admissions, medical charts, surgical reports, autopsy reports (if applicable), imaging, and blood test results were obtained and reviewed. For patients lost to follow-up, vital status was checked in the local public registries. In case of discordant adjudication, discussion between the 2 reviewers was planned for final decision.

Statistical Analysis

Age was assessed with mean and SD, and tested with Student's t test. The variable "hours from symptom onset," which was not normally distributed, was assessed with median and interquartile range, and tested with the Mann–Whitney *U* test. Categorical variables were assessed with proportion and 95% CI, and tested using the χ^2 or Fisher's exact test.

Multivariate logistic regression analysis was used to identify independent predictors among ADD score items plus DD, and the natural logarithm of their odds ratios was used to weight each predictor. Contingency tables were built, including the number of true-positive, false-positive, false-negative, and true-negative patients. Standard diagnostic performance measures were sensitivity, specificity, and positive/negative likelihood ratio. The failure rate was calculated as false negative/(false negative + true negative), which corresponds to (1 – negative predictive value), as previously.[18] This measure indicates the number of AAS cases mistakenly ruled out with the diagnostic rule-out protocol. The rule-out efficiency was calculated as (true negative + false negative) / (true positive + false positive + true negative + false negative). For contingency tables containing cells with a 0 value, CIs were calculated using a bootstrap method.[19] Sensitivities and specificities were compared using an exact binomial method.[20] Likelihood ratios were compared using a regression model approach.[21]

The diagnostic performance of different strategies was assessed using receiver operating characteristic (ROC) curve analysis, McNemar test and net reclassification improvement (NRI). In ROC analysis, the areas under the curves (AUCs) were compared using DeLong's test for paired AUCs. Improvement in risk prediction was assessed with NRI, which was split for patients with AASs and alternative diagnoses (AltDs).[22] A positive NRI value indicates improvement in risk prediction. The Pauker and Kassirer decision threshold model was applied to calculate 2 theoretical thresholds: a testing threshold and a test-treatment threshold.[23]

The prospective validation study was powered for comparison between the sensitivity of a high-probability

Table 1. Logistic Regression Analysis for Simplified Score Development

Clinical Item	OR (95% CI)	*P*	Ln (OR)	AORTAs Score Points
Known thoracic aortic aneurysm	3.52 (2.18–5.66)	<0.001	1.26	1
Severe pain	2.72 (1.86–3.98)	<0.001	1.00	1
Sudden-onset pain	2.98 (2.07–4.29)	<0.001	1.09	1
Pulse deficit	3.77 (2.24–6.33)	<0.001	1.33	1
Neurologic deficit	2.77 (1.41–5.42)	0.003	1.02	1
Hypotension/shock	5.79 (3.38–9.93)	<0.001	1.76	2
Known aortic valve disease	0.89 (0.44–1.79)	0.743	—	—
Ripping/tearing pain	1.02 (0.66–1.56)	0.936	—	—
D-dimer>500 ng/mL	37.67 (18.23–77.82)	<0.001	—	—

OR indicates odds ratio.

definition obtained with the new score and the sensitivity of the standard high-probability definition (ADD ≥2), for diagnosis of AASs. Using a type I error of 0.05 (2 sided) and a power rate of 80% and assuming a prevalence of 10% of AASs, we estimated that at least 430 patients needed to be included.

P values were considered significant if <0.05. Statistical analysis was carried out using SPSS software version 25.0 (IBM Corp, Armonk, NY), except for ROC curve analysis, bootstrap CI, and diagnostic accuracy measure comparison (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Development of a New Simplified Risk Score and Dichotomic Rule

The derivation cohort included 1848 ED patients with suspected AAS (Figure 1). Demographic and clinical characteristics are described elsewhere.[16] To create a parsimonious model, ADD items with a prevalence <5% (Marfan syndrome, family history, new diastolic murmur, respectively, 0.3%, 1.7%, and 2.7%) were removed. In multivariable logistic regression analysis (Table 1), 6 items were found as independent predictors of AAS diagnosis: thoracic aortic aneurysm, severe pain, sudden-onset pain, pulse deficit, neurologic deficit, and hypotension/shock. These variables were used to develop a simplified noncategorical assessment tool, amenable to integration with $DD_{age\text{-}adj}$. Based on the odds of AAS diagnosis weighted on a logarithmic scale, we assigned a score of 2 to hypotension/shock and a score of 1 to the other variables. The sum was called the aorta simplified (AORTAs) score. AORTAs ≤1 (associated with a disease probability of 4.6%; 95% CI, 3.6%–6%), defined low pretest clinical probability and AORTAs ≥2 defined high probability (Figure S1).

Compared with the ADD score, the AORTAs score had superior AUC (*P*<0.001; Figure S2a) and reclassified 23.7% of patients (Table S2), with significant NRI for both AASs (22.4%; *P*<0.001) and AltDs (–16.2%, *P*<0.001). AORTAs ≥2 was more sensitive and less specific than ADD ≥2 (Table 2). In the derivation cohort, the AORTAs ≤1/$DD_{age\text{-}adj}$ rule reclassified 16.9% of patients (Table S3), with a significant NRI for AltDs (–5.4%; *P*<0.001), and was less specific than the ADD ≤1/DD_{500} rule (Table 3).

External Validation of the Simplified Score

As summarized in Figure 1, external validation of the new score and integrated rule was conducted in 2 independent cohorts of patients with suspected AAS from 2 EDs: a high-prevalence retrospective cohort

Table 2. Diagnostic Performance of the AORTAs Score in the Study Cohorts

Diagnostic Variable	Study Cohorts								
	Derivation Cohort (n=1848)			Validation Cohorts					
				High Prevalence Cohort (n=1035)			Low Prevalence Cohort (n=447)		
	AORTAs≥2	ADD≥2	*P* Value	AORTAs≥2	ADD≥2	*P* Value	AORTAs≥2	ADD≥2	*P* Value
Sensitivity	77.6% (71.8%–82.7%)	55.2% (48.7%–61.6%)	<0.001	54.1% (48.1%–60.5%)	34.8% (29.2%–40.8%)	<0.001	71.4% (56.7%–83.4%)	38.8% (25.2%–53.8%)	<0.001
Specificity	70.8% (68.5%–73%)	87.1% (85.3%–88.7%)	<0.001	75.9% (72.8%–78.8%)	84.5% (81.9%–87%)	<0.001	72.1% (67.4%–76.5%)	89.1% (85.6%–92%)	<0.001
LR+	2.66 (2.40–2.94)	4.26 (3.60–5.06)	<0.001	2.25 (1.89–2.67)	2.25 (1.77–2.86)	1.0	2.56 (2.02–3.25)	3.55 (2.26–5.58)	0.13
LR-	0.32 (0.25–0.40)	0.52 (0.45–0.59)	<0.001	0.61 (0.52–0.70)	0.77 (0.70–0.85)	<0.001	0.40 (0.25–0.62)	0.69 (0.12–0.86)	0.009

95% CI in parentheses. ADD indicates aortic dissection detection; and LR, likelihood ratio.

Table 3. Diagnostic Performance of the Integrated AORTAs ≤1/$DD_{age-adj}$ Rule in the Study Cohorts

Diagnostic Variable	Study Cohorts								
	Derivation Cohort (n=1848)			Validation Cohorts					
				High Prevalence Cohort (n=1035)			Low Prevalence Cohort (n=447)		
	AORTAs≤1/$DD_{age-adj}$	ADD≤1/DD_{500}	*P* Value	AORTAs≤1/$DD_{age-adj}$	ADD≤1/DD_{500}	*P* Value	AORTAs≤1/$DD_{age-adj}$	ADD≤1/DD_{500}	*P* Value
Sensitivity	99.2% (97%–99.9%)	98.8% (96.4%–99.7%)	1.0	98.3% (95.7%–99.5%)	99.1% (96.9%–99.9%)	0.63	100% (92.7%–100%)	98% (89.3%–99.6%)	1.0
Specificity	51.9% (49.4%–54.4%)	57.3% (54.9%–59.8%)	<0.001	30% (26.9%–33.4%)	30.2% (27%–33.5%)	1.0	48.7% (43.8%–53.7%)	52.8% (47.9%–57.7%)	0.08
LR+	2.06 (1.96–2.17)	2.31 (2.18–2.45)	<0.001	1.41 (1.34–1.47)	1.42 (1.35–1.49)	0.58	1.95 (1.74–2.14)	2.08 (1.86–2.33)	0.12
LR-	0.02 (0–0.06)	0.02 (0.01–0.07)	0.67	0.06 (0.02–0.15)	0.03 (0.01–0.11)	0.33	0 (0–0.12)*	0.04 (0–0.14)	0.95

95% CI in parentheses. ADD indicates aortic dissection detection; $DD_{age-adj}$, age-adjusted d-dimer cutoff; and LR, likelihood ratio.
*To allow LR comparison, a false-negative unit was added in the corresponding cell.

(applying advanced imaging adjudication for all patients) and a low-prevalence prospective cohort (applying clinical follow-up adjudication). The clinical and demographic characteristics of the former cohort (n=1035) are detailed elsewhere.[17] The latter cohort (Figure 2) included 447 patients, whose characteristics and diagnostic data are summarized in Table S4 and Figure S3. Advanced aortic imaging was performed in 245 (54.8%) patients; 161 (36.3%) patients were hospitalized, and 4 (0.9%) were lost at follow-up (clinical details in Table S5). An AAS was adjudicated in 49 (11.1%) patients: type-A AAD (n=31), type-B AAD (n=7), and intramural aortic hematoma (n=11). AltDs were musculoskeletal pain (n=119), gastrointestinal disease (60), acute coronary syndrome (39), non–AAS-related syncope (30), uncomplicated aortic aneurysm (30), pneumonia (23), pericarditis (21), PE (10), and other diagnoses (62). AORTAs ≤1 was associated with a disease prevalence of 4.7% (95% CI, 2.8%–7.7%; Figure 3).

In composite ROC analysis of the validation cohorts, the AORTAs score had superior AUC versus the ADD score (*P*=0.005; Figure 4A, Figure S2B–S2C). Compared with the ADD score, the AORTAs score reclassified 16.6% (*P*<0.001) and 25.1% (*P*<0.001) of patients in the high- and low-probability cohort, respectively. In the high-prevalence cohort (Table S6), the AORTAs score reclassified 172 patients, including 55 with AASs (n=50 low to high *P*, n=5 high to low *P;* NRI, 19.3%; *P*<0.001) and 117 with AltDs (n=93 low to high *P*, and n=24 high to low *P;* NRI –8.6%; *P*<0.001). In the low-prevalence cohort (Table S7), the AORTAs score reclassified 111 patients, including 18 with AASs (n=17 low to high *P*, n=1 high to low *P;* NRI 32.7%; *P*<0.001) and 93 with AltDs (n=80 low to high *P*, and n=13 high to low *P;* NRI –17%; *P*<0.001). AORTAs ≥2 was more sensitive and less specific than ADD ≥2 for diagnosis of AASs in both validation cohorts (Table 2).

External Validation of the Integrated Rule

In composite ROC analysis of the validation cohorts, the AORTAs ≤1/$DD_{age-adj}$ and the ADD ≤1/DD_{500} rule had similar AUCs (*P*=0.18; Figure 4B). Compared with the ADD ≤1/DD_{500} rule, the AORTAs ≤1/$DD_{age-adj}$ rule reclassified 9% (*P*=0.91) and 17.4% (*P*=0.53) of patients in the high- and low-prevalence cohort, respectively. However, the NRI of the AORTAs≤1/$DD_{age-adj}$ rule was not significant for both AASs and AltDs and in both cohorts (Tables S8–S9).

The diagnostic performance of the AORTAs ≤1/$DD_{age-adj}$ and the ADD ≤1/DD_{500} rules was similar in both validation cohorts (Table 3). Integration of AORTAs ≤1 with DD_{500}, instead, was less specific than both the AORTAs ≤1/$DD_{age-adj}$ and the ADD ≤1/DD_{500} rule (Table S10). In the prospective validation cohort, there was 1 false-negative case with the ADD≤1/DD_{500} rule. This

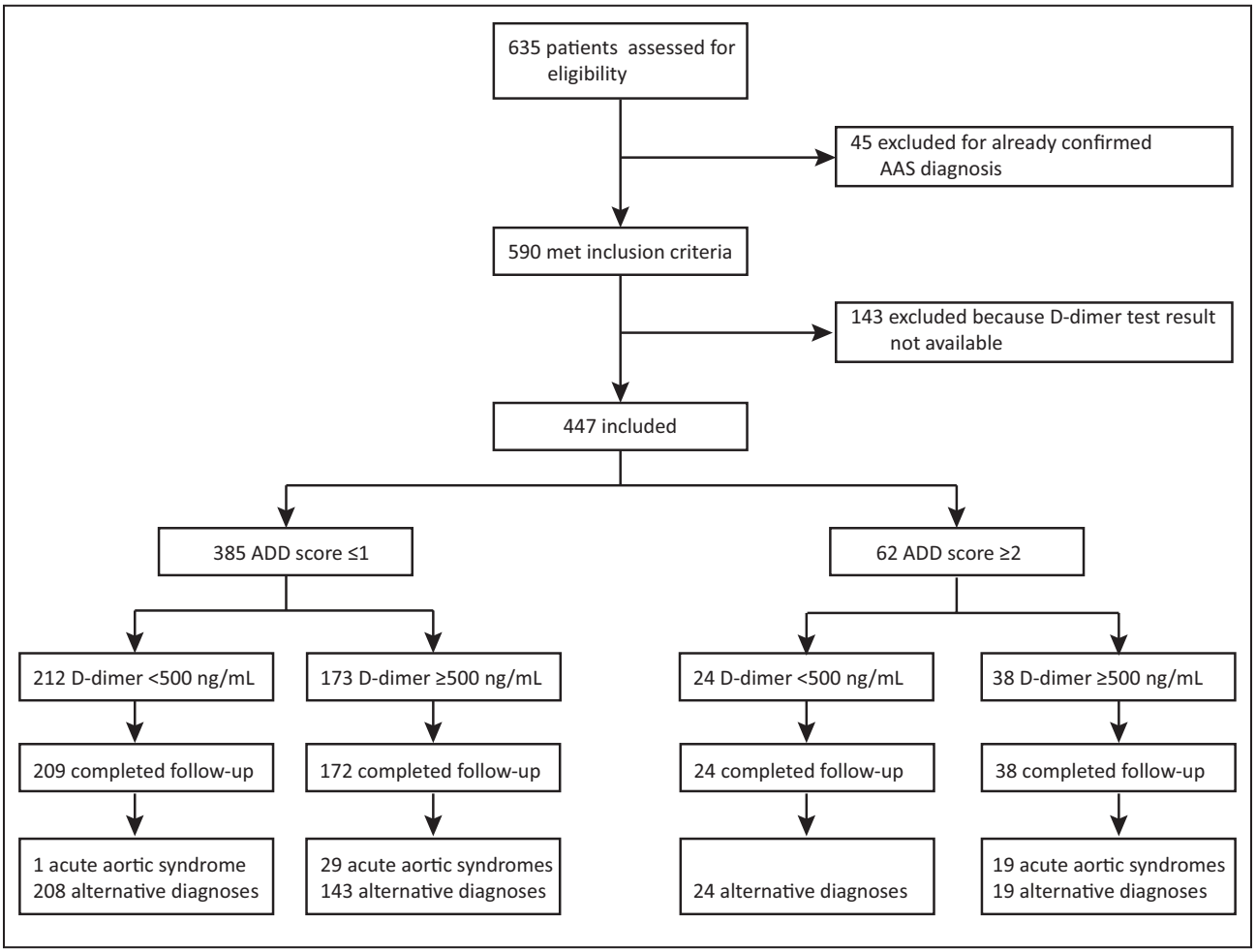

Figure 2. Flow diagram of the prospective low-prevalence validation cohort study.

was a 54-year-old woman with a type B intramural aortic hematoma presenting with severe and sudden anteroposterior thoracic pain radiating to the abdomen. The DD level was 493 ng/mL. With the AORTAs score, this patient was classified as high probability and was ruled in. In the prospective cohort, the failure rate was 0% (0%–2%) for the AORTAs ≤1/$DD_{age\text{-}adj}$ rule and 0.5% (0.01%–2.7%) for the ADD ≤1/DD_{500} rule. Potential computed tomography scans avoided per 100 patients were 43 (95% CI, 39–48) for AORTAs ≤1/$DD_{age\text{-}adj}$ and 47 (95% CI, 42–52) for ADD ≤1/DD_{500} (P=0.53).

According to the Pauker-Kassirer decision threshold model,[23–26] the AORTAs ≤1/$DD_{age\text{-}adj}$ rule could be applied if the probability of AAS is 1.1% to 46.3%, while the ADD≤1/DD_{500} rule could be applied if the probability is 1% to 32.6% (Figure 5).

DISCUSSION

We describe development and validation of a simplified score assessing the clinical probability of AASs and of a rule integrating this score with an age-adjusted DD cutoff for diagnostic rule-out. In the latest guidelines, pretest clinical probability has received a class I/level B recommendation, and integrated DD rule-out a IIa/B recommendation.[7]

Proposals to modify ADD score–based classification and diagnostic flowchart have clinical, methodological, and pragmatic motivations. In clinical terms, the ADD score contradicts clinical gestalt when approaching patients with hemodynamic instability, typically caused by cardiac tamponade, myocardial ischemia, or aortic rupture. Per ADD score, hypotension/shock in the absence of risk factors in the other 2 categories (e.g., pain not severe, sudden, or tearing; unknown aortic aneurysm) defines low probability (European Society of Cardiology) or intermediate risk (American Heart Association/American College of Cardiology) of AAS.[6,7] Because of the categorical structure of the ADD score, such underestimation persists even with perfusion deficit or aortic regurgitation in conjunction with hypotension/shock. Similar patients, however, are clinically unsuitable for

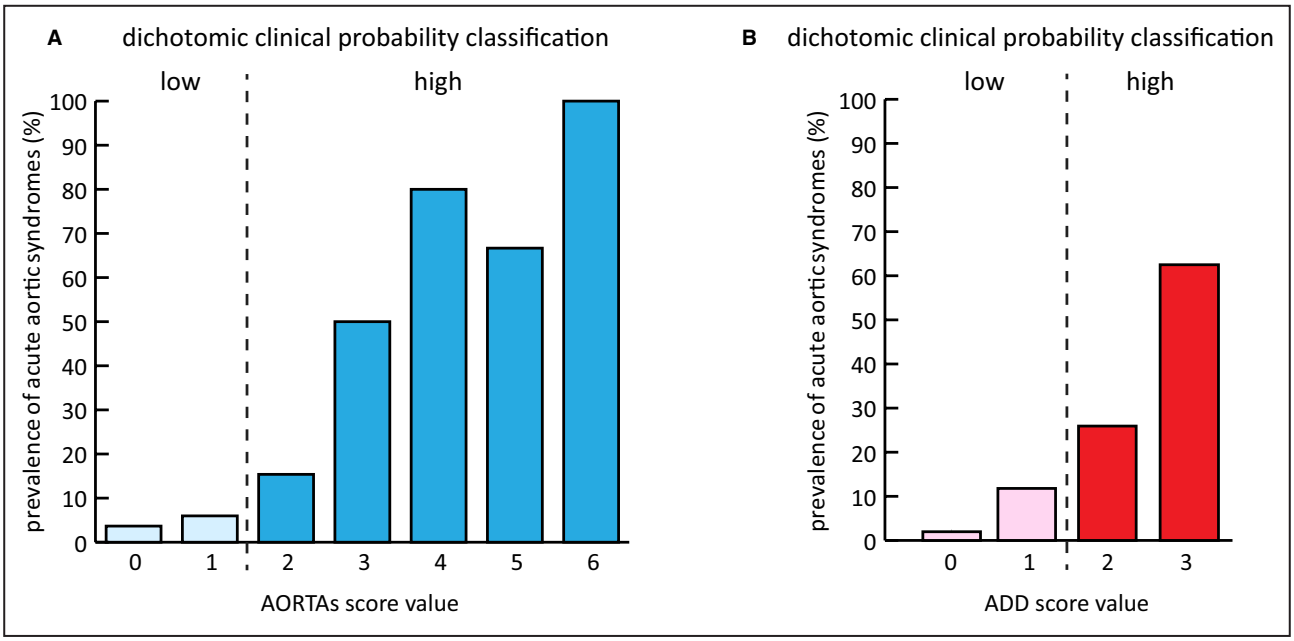

Figure 3. Prevalence of acute aortic syndromes associated with (A) AORTAs score and (B) ADD score values, in the prospective low-prevalence validation cohort.
ADD indicates aortic dissection detection.

integrated rule-out and require urgent advanced aortic imaging.

The AORTAs score overcomes this contradiction by defining hypotension as a major predictor (2 points) leading per se to high pretest probability. Thus, AORTAs can be applied ab initio to all patients with suspected AAS independent of hemodynamic status and in keeping with clinical reasoning. Second, the AORTAs score attributes a high-probability tag to all patients presenting with >1 item. For instance, patients with severe and sudden pain, or patients with neurological deficit and pulse deficit, are defined with AORTAs at high probability of AAS, thus

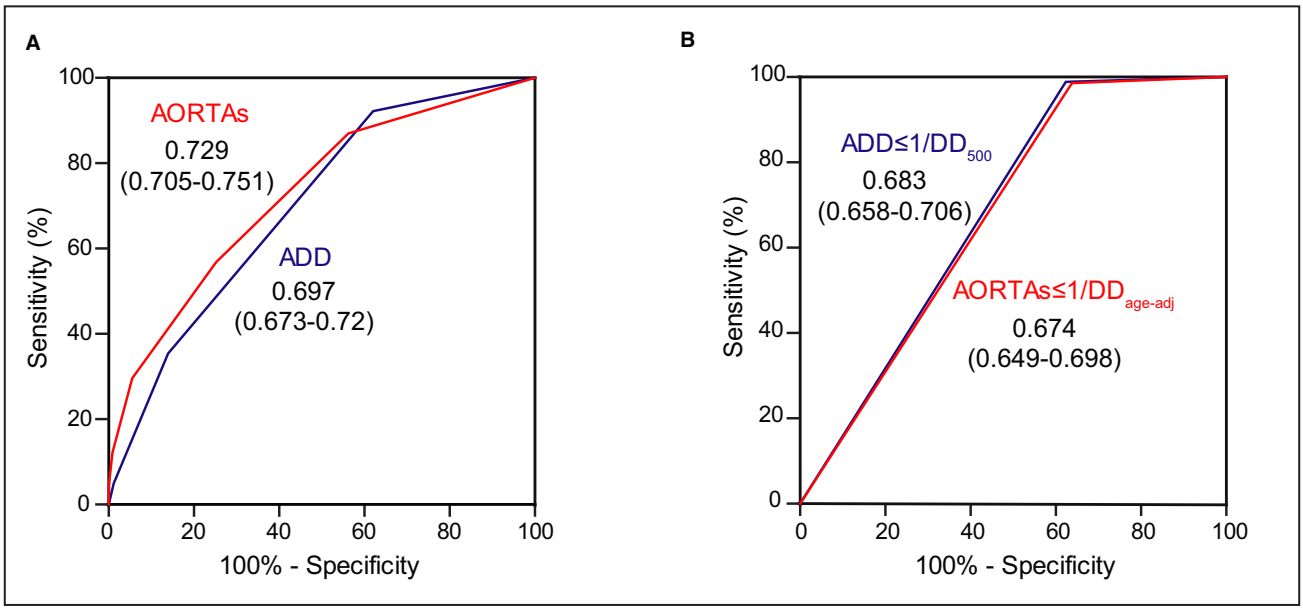

Figure 4. ROC curves of (A) AORTAs versus ADD score, and (B) AORTAs ≤1/$DD_{age-adj}$ vs ADD≤1/DD_{500} rule, in the validation cohorts.
AUC values are presented in insets. N=1478 (282 with acute aortic syndromes, 1196 with alternative diagnoses). ADD indicates aortic dissection detection; $DD_{age-adj}$, age-adjusted d-dimer cutoff; and DD_{500}, d-dimer cutoff of 500 ng/mL.

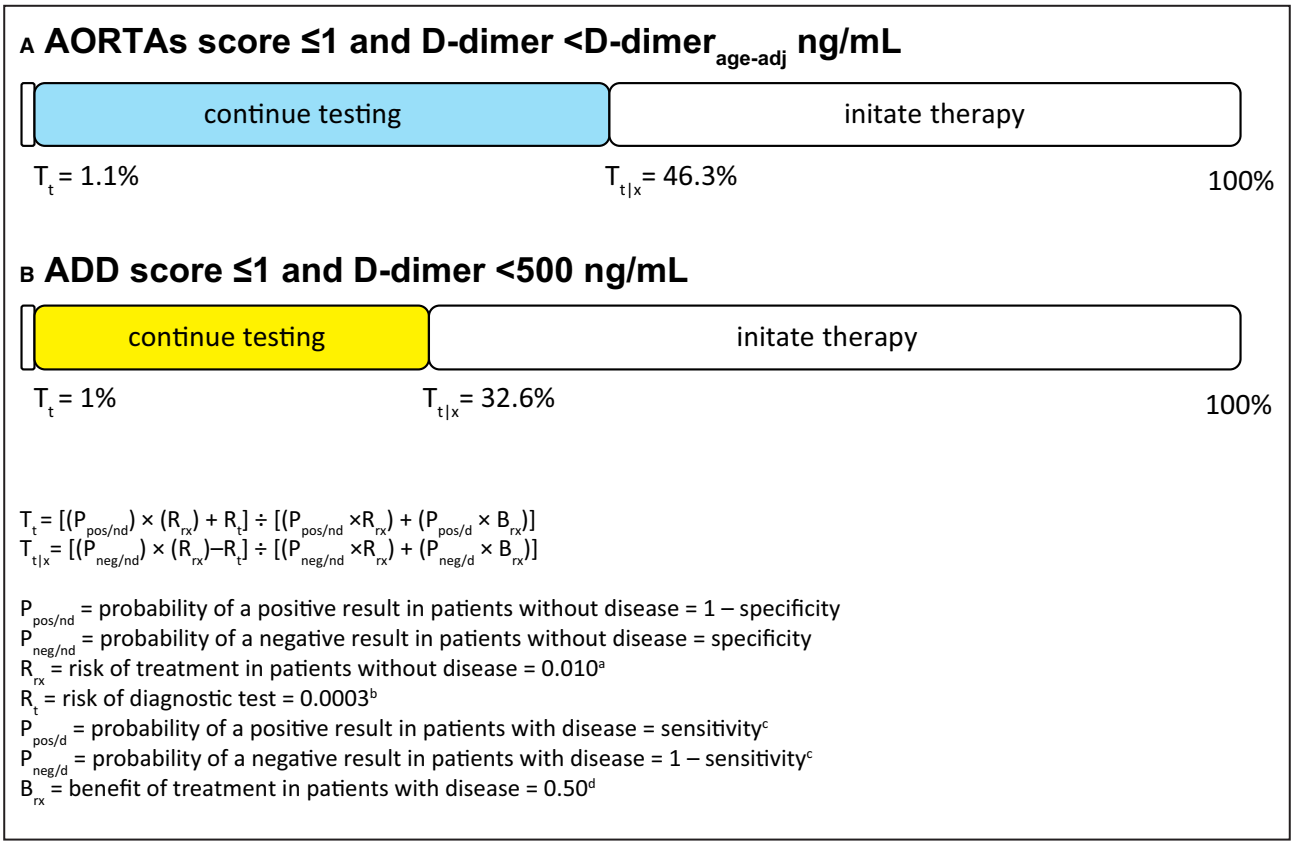

Figure 5. Test-treatment threshold analysis based on the prospective validation cohort study data.
(**A**) Based on Taylor and Iyer[25]; (**B**) based on Cochran[26]; (**C**) the sensitivity of AORTAs ≤1/$DD_{age-adj}$ was computed as 99%; (**D**) estimated form mortality of treated and untreated acute aortic dissection.[25] ADD indicates aortic dissection detection; $DD_{age-adj}$, age-adjusted d-dimer cutoff; T_t, testing threshold; and $T_{t|x}$, test-treatment threshold.

excluding DD rule-out. Accordingly, the main advantage of the AORTAs score is represented by increased sensitivity (consistently shown in 3 study cohorts), ideally providing increased safety and earlier diagnosis of AASs. A minor trade-off in specificity slightly increases the false-positive rate within patients at high probability undergoing urgent CTA. However, integration with a higher DD cutoff (providing per se higher specificity[12,15]) was not associated with a significant change in specificity and efficiency for rule-out in the validation cohorts.

Under a methodological point of view, the ADD score was developed from the IRAD database, a large international case series of AADs with minor representation of intramural aortic hematomas and penetrating aortic ulcers.[8,24] Formal derivation methods of the ADD score are unknown, and several issues regarding its development, refinement, validation, implementation, and dissemination remain open.[10] Most importantly, the IRAD database does not allow any estimate of the diagnostic accuracy of the ADD score as a screening or diagnostic tool, and so far, external validation has been attempted in few retrospective and only 1 prospective study.[9] In methodological terms, the AORTAs score is developed instead through a bottom-up approach, taking advantage of a diagnostic prospective multicenter trial.[16] Preliminary external validation is provided herein in a large retrospective cohort and in a novel prospective cohort of ED outpatients. The decision threshold analysis also indicates that the AORTAs-based rule-out strategy could be applied to a wider range of disease probabilities.

Pragmatic considerations indicate that the AORTAs score may provide additional advantages. First, the AORTAs score uses only half of the items of the ADD score, which may ease applicability to busy EDs. Similar simplification processes have been done for commonly used scores such as the simplified Wells and Geneva scores for PE.[13] Second, application of a single higher-specificity cutoff for both AAS and PE rule-out appears convenient and practical.

This study has limitations. First, validation was performed in 2 patient cohorts, which were indeed fully independent but recruited in the same participating centers, potentially limiting external validity. Second, the retrospective nature of the first validation cohort has limits in score assignment through chart review because of potential underreporting of risk markers. Third, in the derivation and prospective validation

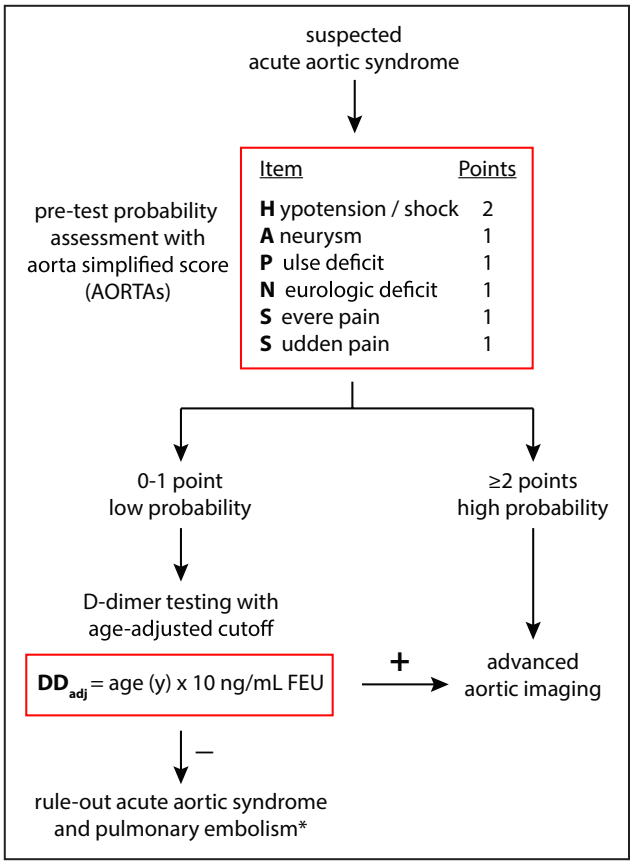

Figure 6. Summary of the aorta simplified score (AORTAs) and the proposed diagnostic algorithm based on study results.
*If the probability of pulmonary embolism is non-high.

cohorts, case adjudication was based on follow-up, which might lead to potential slight underestimation of patients affected by AAS (differential verification bias). Finally, the study was powered to evaluate the diagnostic accuracy of the AORTAs score, and not for statistical comparison of different scores/DD integrations. A larger multicenter trial is needed for this purpose.

As with other similar tools, the AORTAs score is meant to aid in diagnostic decisions and to standardize clinical practice but not to substitute for clinical reasoning. Since study results were obtained in patients with a clinical suspicion of AAS (leading to a relatively high prevalence of AASs), results may not be generalized to unselected patients presenting to the ED (e.g., with chest pain). Therefore, clinical gestalt should be applied by treating physicians for proper selection of patients suitable for standardized probability assessment and rule-in/out protocols. Even posttest, a case-by-case diagnostic decision is always warranted.

In conclusion, we provide bottom-up development of a simplified 6-item noncategorical score for standardized assessment of the pretest probability of AASs, amenable to integration with an age-adjusted DD assay for rule-out applications (Figure 6). This score is easily applicable in the framework of current guidelines and clinical practice. In 3 independent cohorts, this score consistently showed higher sensitivity, better AAS classification and lower specificity compared with the ADD score, representing the current standard. Results also indicate comparable rule-out performance when integrated with $DD_{age-adj}$. Further external validation is needed to evaluate clinical applicability.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1-S10
Figures S1-S3

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Case adjudication

Disease types defining an AAS were non-traumatic AAD, IMH, PAU or SAR, either type A or B based on Stanford classification. Case adjudication was dichotomic: AAS present or absent. In patients without AAS, an alternative clinical diagnosis was indicated. Pre-specified alternative diagnoses were: 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.

A case was pre-defined by evidence of AAS in advanced imaging, surgery or autopsy data, obtained within 30 days from the index visit. For deaths occurring in patients without autopsy data and not subjected to advanced imaging or surgery, an AAS was adjudicated as possible if a reasonable alternative diagnosis was not found. For patients lacking advanced imaging/surgery data, an AAS was excluded if they had an uncomplicated clinical course, or if an AltD was made after a subsequent ED visit or hospital admission during the follow-up period.

Statistical analysis

General characteristics were assessed with median and interquartile range for continuous variables, with proportion and 95% confidence interval (CI) for categorical variables. Statistical differences were compared using the Mann-Whitney U test for continuous variables and using the χ^2 or the Fisher's exact test for proportions.

Multivariate logistic regression analysis was used to identify independent predictors among ADD score items plus D-dimer, and their odds ratios were used to weight each predictor for the new score. Contingency tables were used to calculate diagnostic performance measures: sensitivity, specificity, positive, positive/negative likelihood ratio (LR+/-). The failure rate was calculated as FN/(FN+TN), *i.e.* number of patients with AASs satisfying rule-out criteria divided by the total number of patients satisfying rule-out criteria. The rule-out efficiency was calculated as (TN+FN)/(TP+FP+TN+FN), *i.e.* number of patients ruled-out by each integrated strategy divided by total number of patients tested. For contingency tables containing cells with a 0 value, CIs were calculated using a bootstrap method.[19] Sensitivities and specificities were compared using an exact binomial method, which tests the null hypothesis that the difference between the two scores is equal to zero.[20] LRs were confronted according to a regression model approach which tests the null hypothesis that the ratio of the LRs between the two scores is equal to one.[21]

The diagnostic performance of different strategies was assessed using ROC curve analysis, McNemar test and net reclassification improvement (NRI). In ROC analysis, the AUCs were compared using DeLong's test for paired AUCs. The McNemar test for paired data was used to test marginal homogeneity of two

diagnostic strategies. In order to assess patient reclassification with the new diagnostic tool and rule, improvement in risk prediction was assessed with NRI, which was split for patients with AASs and AltDs. A positive NRI value indicates improvement in risk prediction: for AASs, this is represented by reclassification from low to high probability; for AltDs, this is represented by reclassification from high to low probability. A negative NRI value indicates worsening in risk prediction: for AASs, this is represented by reclassification from high to low probability; for AltDs, this is represented by reclassification from low to high probability.

The Pauker and Kassirer decision threshold model was applied to calculate two theoretical thresholds: a testing threshold (*i.e.* the probability of AAS at which there is no difference between performing the test and withholding the treatment) and a test-treatment threshold (*i.e.* the probability of AAS at which there is no difference between performing the test and administering the treatment).[23]

The prospective validation study was powered to allow comparison between the sensitivity ($sens_1$) of a high-probability definition obtained with the new diagnostic tool and the sensitivity ($sens_0$) of the standard high-probability definition (ADD score ≥2), for diagnosis of AASs. Sensitivity was chosen as the primary outcome, to focus on the safety and rule-out potential of the new score. The values of $sens_1$ and $sens_0$ were obtained from the prospective derivation cohort data. Using a type I error of 0.025 (1 sided), a type II error of 0.2 and assuming a prevalence of 10% of AASs, we estimated that at least 430 patients needed to be included.

P-values were considered significant if <0.05. Statistical analysis was carried out using the SPSS software version 25.0 (IBM Corp.), except for ROC curve analysis, bootstrap CI and diagnostic accuracy measure comparison, which were performed using the R packages pROC, bootLR and DTComPair (R version 3.6.0; https://www.R-project.org/).

Table S1. Aortic dissection detection (ADD) score items. For each risk category, one point is assigned if one or more risk factors is present. The ADD sore can therefore vary from 0 to 3.

High-risk conditions	High-risk pain features	High-risk exam features
• Marfan syndrome or other connective tissue disease • Family history of aortic disease • Known aortic valve disease • Recent aortic manipulation • Known thoracic aortic aneurysm	Chest, back, or abdominal pain described as: • Abrupt in onset • Severe in intensity • Ripping or tearing in quality	• Pulse deficit or systolic blood pressure differential • Focal neurologic deficit (with pain) • Murmur of aortic insufficiency (new, with pain) • Hypotension or shock state

Table S2. Cross-tabulation of low/high probability classification based on ADD and AORTAs score in the derivation cohort. The AORTAs score reclassified 438 (23.7%) patients (*P*<0.001), including 72 with AASs (n=63 low to high-*P*, n=9 high to low-*P;* NRI 22.4%, *P*<0.001) and 366 with AltDs (n=313 low to high-*P*, and n=53 high to low-*P;* NRI -16.2%, *P*<0.001).

		AORTAs score		
		≤1 **low *P***	**≥2** **high *P***	
ADD score	**≤1** **low *P***	1131 *45 AASs* *1086 AltDs*	376 *63 AASs* *313 AltDs*	1507 (81.5%) 108 (44.8%) *AASs* 1399 (87.1%) *AltDs*
	≥2 **high *P***	62 *9 AASs* *53 AltDs*	279 *124 AASs* *155 AltDs*	341 (18.5%) 133 (55.2%) *AASs* 208 (12.9%) *AltDs*
Total		1193 (64.6%) 54 (22.4%) *AASs* 1139 (70.9%) *AltDs*	655 (35.4%) 187 (77.6%) *AASs* 468 (29.1%) *AltDs*	1848 (100%) 241 *AASs* 1607 *AltDs*

AASs: acute aortic syndromes; AltDs: alternative diagnoses; *P*: probability.

Table S3. Cross-tabulation of rule-in/out classification based on ADD≤1/DD_{500} and AORTAs≤1/$DD_{age\text{-}adj}$ rules in the derivation cohort. Compared to ADD≤1/DD_{500}, the AORTAs≤1/$DD_{age\text{-}adj}$ rule reclassified 312 (16.9%) patients (*P*<0.001), including 3 with AAS (n=2 rule-out to rule-in, *n*=1 rule-in to rule-out; NRI 0.4%, *P*=0.56) and 309 AltDs (n=198 rule-out to rule-in, n=111 rule-in to rule-out; NRI -5.4%, *P*<0.001).

		AORTAs ≤1/$DD_{age\text{-}adj}$		
		Rule-out	**Rule-in**	
ADD ≤1/DD_{500}	**Rule-out**	724 1 AAS 723 AltDs	200 2 AASs 198 AltDs	924 (50%) 3 (1.2%) AASs 921 (57.3%) AltDs
	Rule-in	112 1 AAS 111 AltDs	812 237 AASs 575 AltDs	924 (50%) 238 (98.8%) AASs 686 (42.7%) AltDs
Total		836 (45.2%) 2 (0.8%) AASs 834 (51.9%) AltDs	1012 (54.8%) 239 (99.2%) AASs 773 (48.1%) AltDs	1848 (100%) 241 AASs 1607 AltDs

AASs: acute aortic syndromes; AltDs: alternative diagnoses.

Table S4. Characteristics of patients in the prospective low-prevalence validation cohort.

	All patients (n=443)	**AltDs** (n=394)	**AASs** (n=49)	***P*-value**
	N (%)	N (%)	N (%)	
General characteristics				
gender (F)	152 (33.3%)	136 (34.5%)	16 (32.6%)	0.80
age (years)	63 (16)	62 (16)	70 (12)	0.005
Hypertension	228 (51.5%)	194 (49.2%)	34 (69.4%)	0.008
Diabetes	52 (11.7%)	48 (12.2%)	4 (8.2%)	0.41
Smoke	114 (25.7%)	97 (24.6%)	17 (34.7%)	0.13
Drug use	3 (0.7%)	2 (0.5%)	1 (2%)	0.30
Coronary artery disease	55 (12.4%)	53 (13.5%)	2 (4.1%)	0.06
Presenting symptoms				
Hours from onset	5 (2-24)	5 (2-24)	2 (1-8)	0.006
Anterior chest pain	305 (68.8%)	272 (69%)	33 (67.3%)	0.81
Posterior chest pain	153 (34.5%)	131 (33.2%)	22 (44.9%)	0.11
Abdominal pain	84 (19%)	74 (18.8%)	10 (20.4%)	0.78
Lumbar pain	27 (6.1%)	23 (5.8%)	4 (8.2%)	0.52
Syncope	51 (11.5%)	47 (11.9%)	4 (8.2%)	0.44
Perfusion deficit	20 (4.5%)	15 (3.8%)	5 (10.2%)	0.06
ADD score factors				
Marfan syndrome	1 (0.2%)	1 (0.3%)	0 (0%)	1.00
Family history of AAS	5 (1.1%)	5 (1.3%)	0 (0%)	1.00
Known aortic valve disease	25 (5.6%)	18 (4.6%)	7 (14.3%)	0.013
Recent aortic manipulation	4 (0.9%)	3 (0.8%)	1 (2%)	0.38
Known thoracic aortic aneurysm	45 (10.2%)	34 (8.6%)	11 (22.9%)	0.009
Severe pain	198 (44.7%)	164 (41.6%)	34 (69.4%)	<0.001
Sudden-onset pain	168 (37.9%)	134 (34%)	34 (69.4%)	<0.001
Ripping/tearing pain	37 (8.4%)	26 (6.6%)	11 (22.4%)	0.001
Pulse deficit	18 (4.1%)	11 (2.8%)	7 (14.3%)	0.002
Neurological deficit	14 (3.2%)	9 (2.3%)	5 (10.2%)	0.013
New aortic murmur	1 (0.2%)	1 (0.3%)	0 (0%)	1.00
Hypotension/shock	13 (2.9%)	4 (1%)	9 (18.4%)	<0.001

AAS: acute aortic syndrome; AltD: alternative diagnosis.

Table S5. Characteristics of the patients lost at follow-up in the prospective low-prevalence validation cohort.

Pt N	Clinical characteristics	Time from onset	ADD score	AORTAs score	Blood test results	CXR	FoCUS	Discharge diagnosis	Vital status*
1	58 y.o. male, presented with sudden and severe abdominal pain	12 hours	1	2	DD 454 ng/mL, TnT 4 (normal range < 14), WBC 8.04x10^3/μL, creatinine 0.83 mg/dL	Normal	-	Unspecific GI pain	Alive
2	62 y.o. female with hypertension, presented for syncope	3 hours	0	0	DD 275 ng/mL, TnT 11 ng/L, WBC 6.18 x10^3/μL, creatinine 0.81 mg/dL	Normal	-	Non cardiac syncope, poorly controlled hypertension	Alive
3	71 y.o. male with hypertension and smoke habit, presented with severe abdominal and lumbar pain	6 hours	1	1	DD 741 ng/mL, TnT 18 ng/L, WBC 10.22 x10^3/μL, creatinine 1.12 mg/dL	Normal	Normal aortic root and abdominal aorta diameters	Unspecific GI pain, self-discharged from the ED	Alive
4	73 y.o male with hypertension, diabetes, TAA, presented with syncope	24 hours	1	1	DD 36 ng/mL, TnT 11 ng/L, WBC 6.49 x10^3/μL, creatinine 1.02 mg/dL	-	Aortic root 42 mm, no direct/indirect signs of AAS	Non cardiac syncope, poorly controlled hypertension	Alive

CXR: chest x-ray; FOCUS: focus cardiac ultrasound; DD: d-dimer; GI: gastro-intestinal; TnT: troponin T; TAA: thoracic aorta aneurysm; WBC: white blood cells count. *vital status was checked in the local public registries on 30th March 2020.

Table S6. Cross-tabulation of low/high probability classification based on ADD and AORTAs score in the retrospective high-prevalence validation cohort.

		AORTAs score		
		≤1 **low *P***	**≥2** **high *P***	
ADD score	**≤1** **low *P***	687 *102 AASs* *585 AltDs*	143 *50 AASs* *93 AltDs*	830 (80.2%) 152 (65.2%) *AASs* 678 (84.5%) *AltDs*
	≥2 **high *P***	29 *5 AASs* *24 AltDs*	176 *76 AASs* *100 AltDs*	205 (19.8%) 81 (34.8%) *AASs* 124 (15.5%) *AltDs*
Total		716 (69.2%) 107 (45.9%) *AASs* 609 (75.9%) *AltDs*	319 (30.8%) 126 (54.1%) *AASs* 193 (24.1%) *AltDs*	1035 (100%) 233 AASs 802 *AltDs*

AASs: acute aortic syndromes; AltDs: alternative diagnoses; *P*: probability.

Table S7. Cross-tabulation of low/high probability classification based on ADD and AORTAs score in the prospective low-prevalence validation cohort.

		AORTAs score		
		≤1 **low *P***	**≥2** **high *P***	
ADD score	**≤1** **low *P***	284 13 AASs 271 AltDs	97 17 AASs 80 AltDs	381 (86%) 30 (61.2%) AASs 351 (89.1%) AltDs
	≥2 **high *P***	14 1 AAS 13 AltDs	48 18 AASs 30 AltDs	62 (14%) 19 (38.8%) AASs 43 (10.9%) AltDs
Total		298 (67.3%) 14 (28.6%) AASs 284 (72.1%) AltDs	145 (32.7%) 35 (71.4%) AASs 110 (27.9%) AltDs	443 (100%) 49 AASs 394 AltDs

AASs: acute aortic syndromes; AltDs: alternative diagnoses; *P*: probability.

Table S8. Cross-tabulation of rule-in/out classification based on ADD≤1/DD_{500} and AORTAs≤1/$DD_{age\text{-}adj}$ rules in the retrospective high-prevalence validation cohort. The AORTAs≤1/$DD_{age\text{-}adj}$ rule reclassified 93 patients, including 4 with AASs (n=1 rule-out to rule-in, n=3 rule-in to rule-out; NRI -0.9%, *P*=0.32) and 89 with AltDs (n=45 rule-out to rule-in, n=44 rule-in to rule-out; NRI -0.1%, *P*=0.92).

		AORTAs ≤1/$DD_{age\text{-}adj}$		
		Rule-out	**Rule-in**	
ADD ≤1/DD_{500}	**Rule-out**	198 1 AAS 197 AltDs	46 1 AAS 45 AltDs	244 (23.6%) 2 (0.9%) AASs 242 (30.2%) AltDs
	Rule-in	47 3 AASs 44 AltDs	744 228 AASs 516 AltDs	791 (76.4%) 231 (99.1%) AASs 560 (69.8%) AltD
Total		245 (23.7%) 4 (1.7%) AASs 241 (30%) AltDs	790 (76.3%) 229 (98.3%) AASs 561 (70%) AltDs	1035 (100%) 233 AASs 802 AltDs

AASs: acute aortic syndromes; AltDs: alternative diagnoses.

Table S9. Cross-tabulation of rule-in/out classification based on ADD≤1/DD_{500} and AORTAs≤1/$DD_{age\text{-}adj}$ rules in the prospective low-prevalence validation cohort. The AORTAs≤1/$DD_{age\text{-}adj}$ rule reclassified 77 patients, including 1 with AAS (rule-out to rule-in; NRI 2%, *P*=0.32) and 76 with AltDs (n=46 rule-out to rule-in, n=30 rule-in to rule-out; NRI -4.1%, *P*=0.07).

		AORTAs ≤1/$DD_{age\text{-}adj}$		
		Rule-out	**Rule-in**	
ADD ≤1/DD_{500}	**Rule-out**	162 0 AAS 162 AltDs	47 1 AAS 46 AltDs	209 (47.2%) 1 (2%) AAS 208 (52.8%) AltDs
	Rule-in	30 0 AAS 30 AltDs	204 48 AASs 156 AltDs	234 (52.8%) 48 (98%) AASs 186 (47.2%) AltDs
Total		192 (43.3%) 0 AAS 192 (48.7%) AltDs	251 (56.7%) 49 (100%) AASs 202 (51.3%) AltDs	443 (100%) 49 AASs 394 AltDs

AASs: acute aortic syndromes; AltDs: alternative diagnoses.

Table S10. Diagnostic performance of the integrated AORTAs≤1/DD_{500} rule in the study cohorts**.**

	Study cohorts								
	Derivation cohort			**Validation cohorts**					
	(n=1848)			**High prevalence cohort (n=1035)**			**Low prevalence cohort (n=447)**		
Diagnostic performance	**AORTAs≤1/DD_{500}**	***P*-value vs ADD≤1/DD_{500}**	***P*-value vs AORTAs≤1/$DD_{age-adj}$**	**AORTAs≤1/DD_{500}**	***P*-value vs ADD≤1/DD_{500}**	***P*-value vs AORTAs≤1/$DD_{age-adj}$**	**AORTAs≤1/DD_{500}**	***P*-value vs ADD≤1/DD_{500}**	***P*-value vs AORTAs≤1/$DD_{age-adj}$**
Sensitivity	99.2% (98.0-100%)	1	1	99.1% (98.0-100%)	1	0.5	100% (92.7-100%)	1	1
Specificity	47.1% (44.7-49.6%)	<0.001	<0.001	25.6% (22.5-28.6%)	<0.001	<0.001	43.1% (38.3-48.1%)	<0.001	<0.001
LR+	1.87 (1.79-1.97)	<0.001	<0.001	1.33 (1.28-1.39)	<0.001	<0.001	1.76 (1.58-1.91)	<0.001	<0.001
LR-	0.02 (0.00-0.07)	0.77	0.5	0.03 (0.01-0.13)	0.81	0.29	0 (0-0.13)	<0.001[a]	<0.001[a]
AUC	0.731 (0.718-0.745)	<0.001	<0.001	0.624 (0.607-0.640)	<0.001	<0.001	0.716 (0.691-0.740)	0.005	<0.001

AUC: area under ROC curve; LR: likelihood ratio. [a]To allow LR comparison, a false negative unit was added in the corresponding cell

Figure S1. Prevalence of acute aortic syndromes associated with AORTAs score values in the derivation cohort.

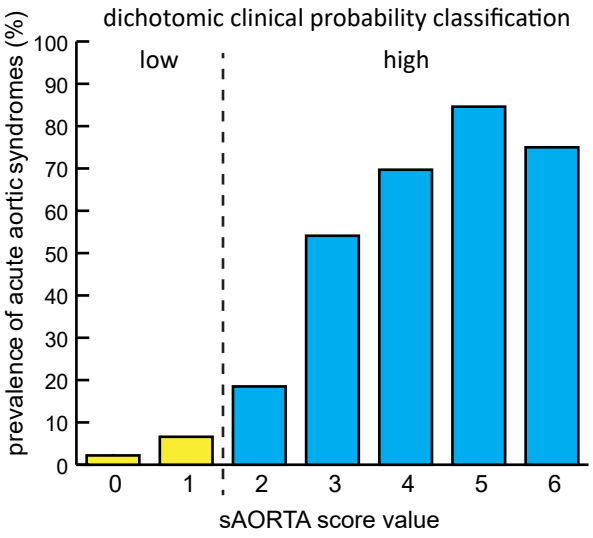

Figure S2. ROC curves of AORTAs and ADD score in the **(A)** derivation cohort, **(B)** high-prevalence validation cohort, and **(C)** low-prevalence validation cohort. AUC-ROC values, represented as insets, were compared using DeLong's test for paired AUCs.

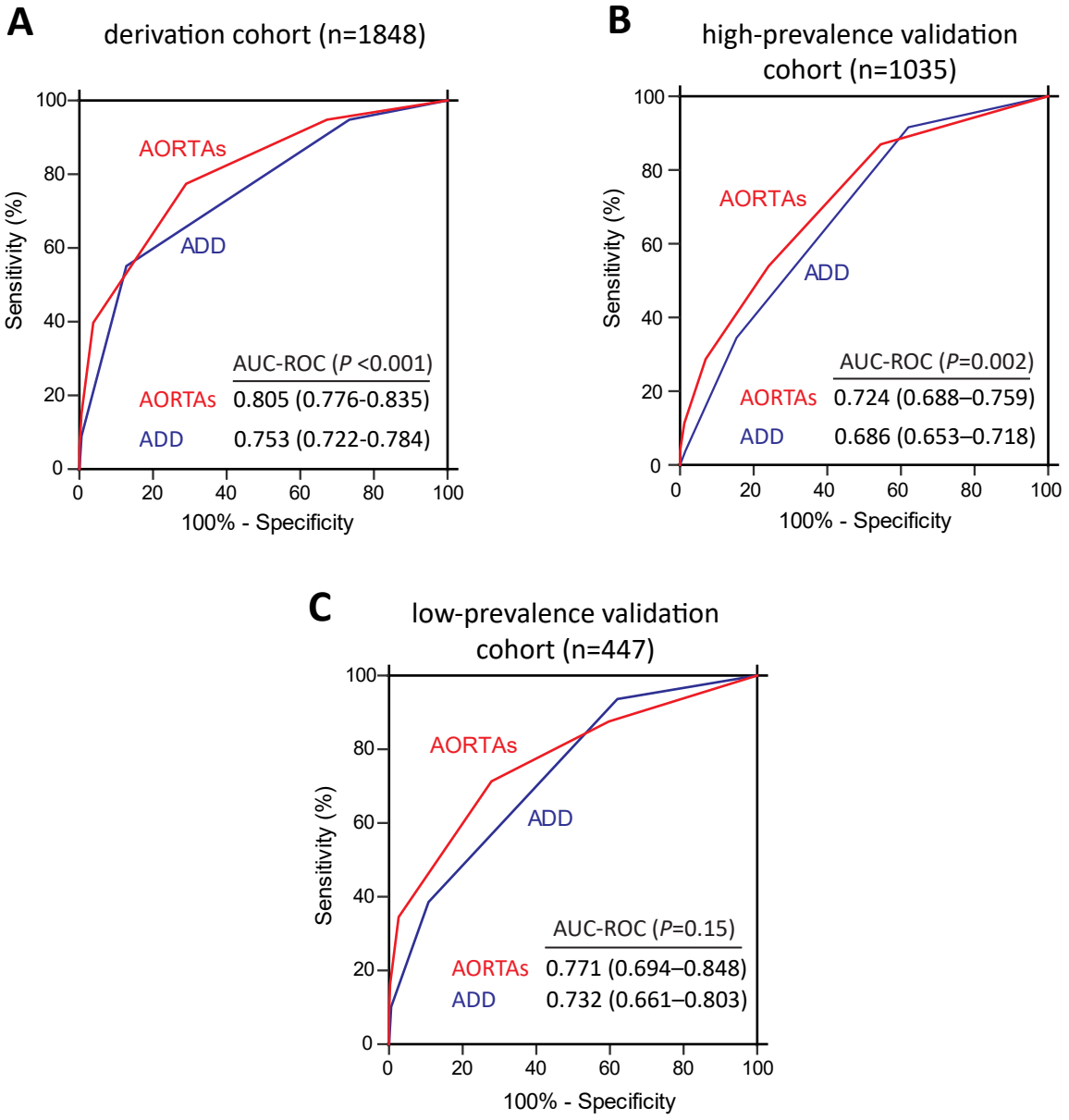

Figure S3. Diagnostic work-up and case adjudication in the prospective low-prevalence validation cohort.