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.

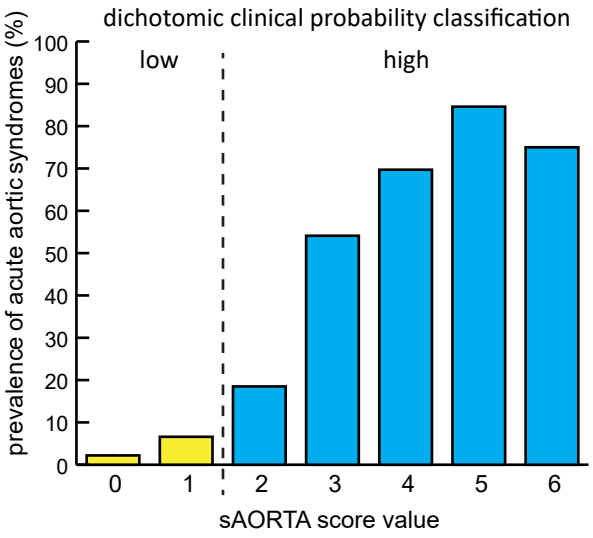

Figure S2. ROC curves of AORTAs and ADD score in the **(A)** derivation cohort, **(B)** high-prevalence validation cohort, and **(C)** low-prevalence validation cohort. AUC-ROC values, represented as insets, were compared using DeLong's test for paired AUCs.

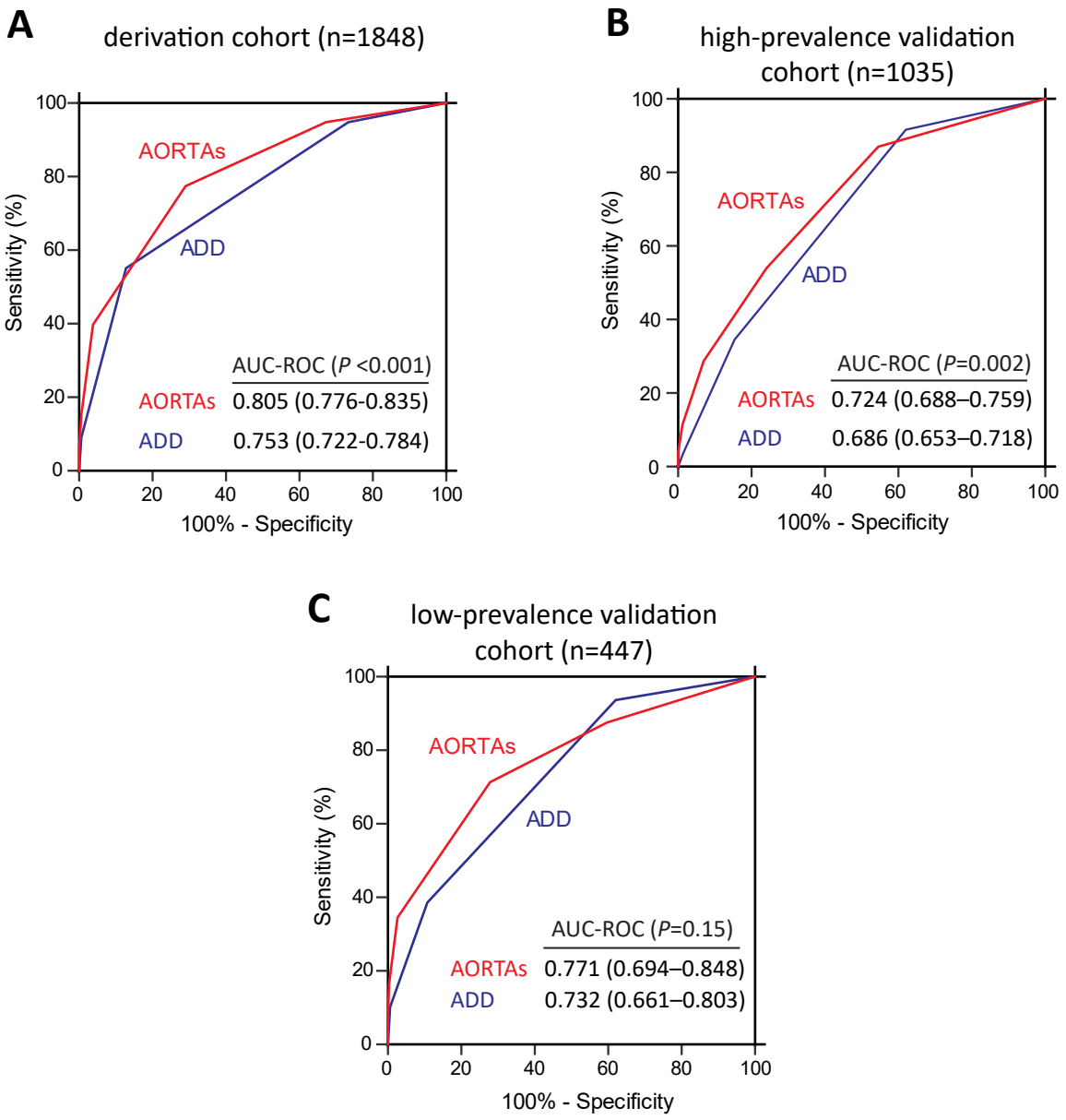

Figure S3. Diagnostic work-up and case adjudication in the prospective low-prevalence validation cohort.