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Original Article

Performance and costs of rule-out protocols for acute aortic syndromes: analysis of pooled prospective cohorts

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ABSTRACT

Background: Acute aortic syndromes (AAS) are deadly conditions causing unspecific symptoms, such as chest/abdominal/back pain, syncope and neurological deficit. They are diagnosed with computed tomography angiography (CTA), but the patient selection is challenging. To support physicians and standardize management, protocols combining a clinical score with D-dimer (DD) have been developed. However, direct comparison of their diagnostic performance and cost-effectiveness is lacking.

Methods: We used individual patient data from 3 prospective diagnostic studies of patients with suspected AAS, enrolled in 12 centers from 5 countries. Diagnostic accuracy, failure rate and costs were calculated for 5 protocols, applying 3 scores (aortic dissection detection [ADD], AORTAs and Canadian) and 2 DD thresholds (500 ng/mL [DD_{500}], age-adjusted [DD_{age}]). Costs were estimated using Italian and German reimbursements.

Results: Among 4907 patients, 506 (10.3 %) had an AAS. The sensitivity of the diagnostic protocols ranged from 97.6 % for Canadian/DD_{500} to 99.4 % for AORTAs/DD_{500} or DD_{age} ($P = 0.022$). The specificity was lowest for AORTAs/DD_{500} (46.8 %; $P < 0.001$ vs AORTAs/DD_{500}) and highest for ADD/DD_{age} (61.5 %; $P < 0.001$). The number of potential AAS misses was 4-fold higher with Canadian/DD_{500} vs AORTAs/DD_{500} or DD_{age}. The net clinical benefit was highest for ADD/DD_{age}. All protocols reduced CTA exams and costs over a CTA-to-all strategy. Numbers of predicted CTA exams and costs per 100 patients were lowest for ADD/DD_{age} (447 CTAs, 34,366 EUR) and highest (579 CTAs, 43,628 EUR) for AORTAs/DD_{500}.

Conclusions: Guideline-compliant clinical score/DD based protocols are highly sensitive. Differences in specificity and efficiency are present. Data may guide decision-making based on policies and resources.

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1. Introduction

Acute aortic syndromes (AASs) are life-threatening cardiovascular emergencies affecting 5–15 individuals per 100,000 person-years [1]. They are characterized by dissection, hematoma, ulceration or rupture, within the thoracic or thoraco-abdominal aorta. Timely diagnosis of AASs in the Emergency Department (ED) is mostly based on computed tomography angiography (CTA) of the chest and abdomen. However, appropriate selection of patients for urgent CTA is challenging, due to conflicting risks of misdiagnosis and overtesting [2,3]. The rate of AAS misdiagnosis is a major concern, reaching 1 in 3 patients in older studies, and averaging 1 in 8 patients in a more recent Canadian series [4,5]. On the other hand, the diagnostic yield of CTA for AAS ranged from to 1.3 % to 3.2 % in Australian and North American studies and audits, raising concerns about risk-benefit balancing [3,6,7].

Symptoms of AASs include any combination of chest/abdominal/back pain, syncope, neurological deficit and limb ischemia [8]. These common and unspecific symptoms account for around 10 % of ED visits, while AAS incidence has been estimated at 1 in 980 patients with atraumatic chest pain [9]. Risks of anaphylaxis, acute kidney injury and radiological exposure, as well as resource limitations and costs of CTA, further enforce the necessity of an appropriate patient selection for CTA. Both European and North American guidelines recommend basing decision on clinical pre-test probability (PP) assessment with a clinical score/rule, and on D-dimer (DD) testing [10–12]. Patients at high PP are directed to urgent CTA. In patients at low PP with a negative DD test, the likelihood of AAS is negligible, thus defining a diagnostic rule-out pathway [8,13]. A similar diagnostic approach is routinely applied for suspected pulmonary embolism [14].

Diagnostic protocols for AASs applying different clinical scores and alternative DD thresholds have been proposed, but comparison of their diagnostic performance and cost-effectiveness is still preliminary [15, 16]. Using pooled prospective outcome data from three diagnostic studies, we compared diagnostic performance, safety and costs of five guideline compliant protocols. Results could assist physicians and support health policy decisions.

2. Methods

2.1. Study population

We used individual patient data from three prospective diagnostic studies (ADvISED, AORTAs and PROFUNDUS studies) conducted in ED patients with suspected AAS [13,17,18]. All studies enrolled adult patients aged ≥18 years, with at least one acute symptom lasting ≤14 days amongst chest/abdominal/back pain, syncope and perfusion deficit, and a physician-defined suspicion of AAS. All studies were approved by the Ethics Committees of the participating centers, and patients provided their informed consent. The studies were conducted in conformity with the Declaration of Helsinki. In the present study, patients were excluded if DD measurement was required for PP assessment by any of the protocols, but was not requested by the treating physicians.

The final diagnosis of study patients was adjudicated by experts who independently assessed ED charts, blood test results excluding DD, imaging and follow-up data, including telephone or clinical follow-up performed 14 days (ADvISED study) or 30 days (AORTAs and PROFUNDUS study) after the index ED visit. The preferred aortic imaging method was ECG-synchronized contrast-enhanced CTA of the chest and abdomen. Transesophageal echocardiography and magnetic resonance angiography were additional reference standard methods. Advanced aortic imaging exams were performed and interpreted by expert physicians who were not involved in the studies.

2.2. Pre-test probability assessment and rule-out protocols

During the medical visit, the treating physician collected data used for PP assessment. For the present study, the PP of each patient was estimated using three guideline-endorsed tools: the aortic dissection detection (ADD) risk score, the AORTA simplified (AORTAs) score and the Canadian rule. The ADD score, endorsed by the European Society of Cardiology (ESC) and the American Heart Association (AHA)/American College of Cardiology (ACC), evaluates 12 items classified in 3 categories (***Suppl. Table 1***), and is calculated as the number of categories (value 0 to 3) satisfying at least one criterion [19,20]. The AORTAs score, endorsed by the AHA/ACC, is a simplified non-categorical score evaluating the presence of 6 items within the ADD score list (***Suppl. Table 2***) [11,13]. If the ADD or AORTAs score value is ≥2, the PP is considered high, and urgent CTA is suggested. If the ADD or AORTAs score value is ≤1, the PP is considered low, and DD testing is used for decision on CTA [11,12].

The Canadian rule evaluates 14 items, including 12 also present in the ADD score (***Suppl. Table 3***) [10]. It also includes a subjective evaluation by the treating physician scoring the suspicion of AAS *vs* an alternative diagnosis (value −1 to 2). Since this clinical gestalt variable was not systematically recorded, we defined it retrospectively. For patients who were rushed to CTA after the initial medical assessment (usually, in presence of ultrasonographic signs of AAS), the chosen score item was "AAS most likely diagnosis". For patients with an annotated alternative diagnosis after the initial evaluation, the chosen score item was "Suspicion for alternate diagnosis". For the other patients, the score item was defaulted to "Unsure". Migrating pain was defined as pain in ≥2 body parts/areas. If the score value is ≥2, the PP is considered high and urgent CTA is suggested. If the score value is 1, the PP is considered moderate and DD measurement is suggested. If the score value is 0, the PP is considered low and neither DD testing nor CTA is routinely suggested. The rule-out group is made up of those with Canadian score 0 or those with Canadian score 1 and DD < 500 ng/mL.

Two thresholds for DD were assessed in the present study, based on previous data: 500 ng/mL (DD_{500}) and age-adjusted ($DD_{age\text{-}adj}$), calculated as age in years, multiplied *10, with a minimum of 500 ng/mL. In compliance guideline indications, only the DD threshold of 500 ng/mL was assessed with the Canadian rule.

2.3. Economic evaluation

All monetary values were reported in euros (€). In Italy, the costs of DD and CTA are invoiced using the regional reimbursement system, which establishes standard fees for specific services. Basic costs in 2024 were 10.30 € for DD and 482 € for chest-abdomen CTA. To calculate the cost in Germany, we used the German scale of fees for physicians: 24.13 € for DD and 724 € for CTA [21].

2.4. Statistical analysis

Categorical variables were expressed as number, percent value and 95 % confidence interval (CI), and were compared with the Chi-squared test. Continuous variables were reported as median (first quartile - third quartile) and compared with the Mann-Whitney U test.

Diagnostic performance measures (sensitivity, specificity, positive and negative predictive values [PPV, NPV]) and their 95 % CI were calculated from 2 × 2 contingency tables and compared with the binomial test for paired samples (sensitivity and specificity) or the generalized score statistics (PPV, NPV). The analysis was conducted intention-to-diagnosis, *i.e.* assuming that CTA exams would be performed following protocol indications in all cases. The failure rate of each protocol, corresponding to (1 – NPV), was calculated as the number of AAS cases satisfying rule-out criteria divided by the total number of rule-out calls, *i.e.* FN: (FN + TN). All protocols were statistically compared to the Canadian protocol. Decision curve analysis was carried out comparing the default strategies of "CTA to all" and "CTA to none" [22].

No specific sample size calculation was carried out, as this was a secondary analysis of pooled studies. *P*-values were two-sided, and *P*-

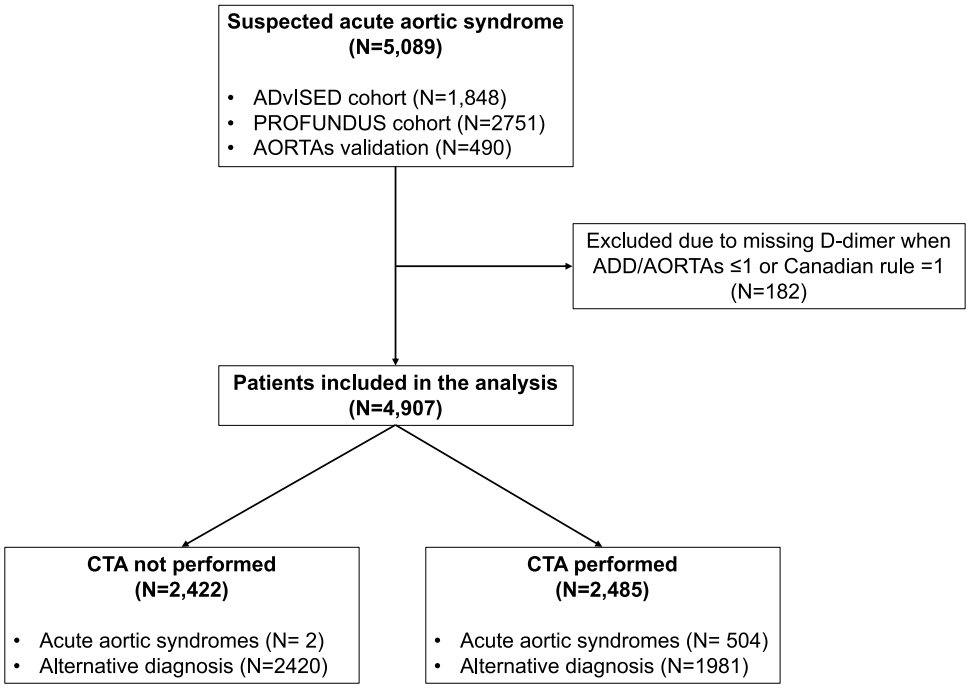

Fig. 1. Study flow diagram.

values <0.05 were considered as statistically significant. All analyses were carried out using R version 4.1.3 (R Foundation for Statistical Computing).

3. Results

3.1. Study population

After excluding 182 patients with missing DD, we analyzed 4907 prospectively enrolled patients with suspected AAS (*Fig. 1*). Advanced aortic imaging exams performed in the ED were CTA (2485), transesophageal echocardiography (51) and magnetic resonance angiography (4). All included patients completed clinical follow-up at 14 or 30 days *per* study protocol. 1879 (38.3 %) patients were hospitalized after the index ED visit.

The demographic and clinical characteristics of study patients are summarized in *Table 1*. The final diagnosis was an AAS in 506 (10.3 %) patients, and an alternative diagnosis in 4401 (89.7 %). The most common subtype of AAS was Stanford type-A aortic dissection (55.9 % of cases), followed by type-B aortic dissection (18.8 %), intramural hematoma (14.8 %), spontaneous aortic rupture (7.3 %) and penetrating atherosclerotic ulcer (3.2 %). AAS treatment included surgery in 272 (53.8 %) patients, thoracic endovascular aortic repair (TEVAR) in 31 (6.1 %), and surgery plus TEVAR in 4 (0.8 %). 30-day mortality in patients with AAS was 21.6 %, but for 241 individuals from the ADvISED cohort, the follow-up was truncated at 14 days *per* study protocol.

3.2. Risk-stratification

Patients at low PP were 4147 (84.5 %) according to the ADD score, 3419 (69.7 %) according to the AORTAs score, and 1217 (24.8 %) according to the Canadian rule. 1975 (40.2 %) were at moderate risk according to the Canadian rule. Overlap of the three PP classifications is represented in *Fig. 2*.

3.3. Diagnostic performance

Diagnostic performance measures of the 5 diagnostic protocols are shown in *Fig. 3*. The sensitivity and NPV were comparable. However, the AORTAs/DD_{500} and AORTAs/$DD_{age\text{-}adj}$ protocols had higher sensitivity and NPV than the Canadian/DD_{500} protocol ($P = 0.022$ and $P = 0.015$, respectively). The specificity and PPV, instead, differed significantly. The highest specificity and PPV (61.5 % and 22.7 %) were obtained by the ADD/$DD_{age\text{-}adj}$ protocol, and the lowest (46.8 % and 17.7 %) by the AORTAs/DD_{500} protocol. In a subgroup analysis, there were no differences in protocol performance between males and females, but specificity lowered with increasing age for all protocols (***Suppl. figure 1***).

Failure rate values were: 1 miss in 205 for the Canadian rule/DD_{500} protocol (0.5 % [0.2–0.8 %]), 1 in 340 for ADD/$DD_{age\text{-}adj}$ (0.3 % [0.1–0.5 %]), 1 in 404 rule-outs for ADD/DD_{500} (0.2 % [0–0.4 %]), 1 in 688 for AORTAs/DD_{500} (0.1 % [0–0.3 %]), 1 in 770 for AORTAs/$DD_{age\text{-}adj}$ (0.1 % [0–0.3 %]).

The decision curve analysis showed that the ADD/$DD_{age\text{-}adj}$ protocol had the greatest net benefit over the other protocols, up to 23 % threshold probability (*Fig. 4*).

3.4. Number of CTA and cost analysis

The numbers of DD tests and CTA exams mandated by the different protocols in study patients are shown in *Table 2*. Discrepancy from tests/exams actually ordered by treating physicians are shown in ***Suppl. Table 4***.

The number of CTA exams mandated by the different protocols and the associated costs per 100 patients, are represented in *Fig. 5*. All protocols were associated with a major reduction in the number of CTA exams and costs, compared to a "CTA-to-all" strategy. The protocol with the highest cost reduction was ADD/$DD_{age\text{-}adj}$. Compared to physician's requests in the study cohort, largely following the AORTAs/DD_{500} protocol, ADD/$DD_{age\text{-}adj}$ would lead to an estimated 12.7 % reduction in CTA scans and a cost reduction of 3267 € in Italy and 5028 € in Germany, per 100 patients. The AORTAs/DD_{500} protocol would lead to an estimated 13.3 % increase in CTA scans and a cost increase of 2985 € in Italy and 4234 € in Germany, per 100 patients.

Table 1
Demographic and clinical characteristics of study patients.

Characteristic	Overall $N = 4907$	Alternative diagnosis $N = 4401$	Acute aortic syndrome $N = 506$	*P*-value
Age (years)	60 (48 - 72)	59 (47 - 72)	69 (58 - 77)	<0.001
Sex (male)	2356 (48.1 %)	2119 (48.3 %)	237 (46.9 %)	0.57
Symptoms at presentation				
Anterior chest pain	3770 (76.8 %)	3439 (78.1 %)	331 (65.4 %)	<0.001
Dorsal pain	1567 (31.9 %)	1341 (30.5 %)	226 (44.7 %)	<0.001
Abdominal pain	830 (16.9 %)	697 (15.8 %)	133 (26.3 %)	<0.001
Lumbar pain	272 (5.5 %)	208 (4.7 %)	64 (12.6 %)	<0.001
Syncope	535 (10.9 %)	441 (10.0 %)	94 (18.6 %)	<0.001
Perfusion deficit	366 (7.5 %)	269 (6.1 %)	97 (19.2 %)	<0.001
Time from symptom onset (hours)	7.5 (3.0, 35.9)	8.0 (3.0, 48)	3.0 (1.5, 12.0)	<0.001
Comorbidities				
Hypertension	2418 (49.3 %)	2059 (46.8 %)	359 (71.4 %)	<0.001
Diabetes mellitus	579 (11.8 %)	542 (12.3 %)	37 (7.4 %)	0.001
Active smoking	1421 (29.0 %)	1272 (28.9 %)	149 (29.6 %)	0.74
Drug abuse	37 (0.8 %)	31 (0.8 %)	6 (1.2 %)	0.29
Coronary artery disease	733 (14.9 %)	686 (15.6 %)	47 (9.3 %)	<0.001
Abdominal aortic aneurysm	194 (4.0 %)	144 (3.3 %)	50 (9.9 %)	<0.001
Cancer	210 (4.3 %)	196 (4.5 %)	14 (2.8 %)	0.080
Predisposing conditions				
Collagenopathy	34 (0.7 %)	30 (0.7 %)	4 (0.8 %)	0.77
Familial thoracic aortic aneurism	102 (2.1 %)	84 (1.9 %)	18 (3.6 %)	0.014
Aortic valve disease	234 (4.8 %)	188 (4.3 %)	46 (9.1 %)	<0.001
Aortic manipulation	41 (0.8 %)	35 (0.8 %)	6 (1.2 %)	0.31
Thoracic aortic aneurysm	395 (8.0 %)	276 (6.3 %)	119 (23.5 %)	<0.001
High risk symptoms				
Severe pain	1915 (39.0 %)	1560 (35.4 %)	355 (70.2 %)	<0.001
Sudden pain	1911 (38.9 %)	1558 (35.4 %)	353 (69.8 %)	<0.001
Ripping pain	715 (14.6 %)	571 (13.0 %)	144 (28.5 %)	<0.001
High risk signs				
Pulse deficit	220 (4.5 %)	118 (2.7 %)	102 (20.2 %)	<0.001
Focal neurological deficit	199 (4.1 %)	134 (3.0 %)	65 (12.8 %)	<0.001
New aortic regurgitation murmur	61 (1.2 %)	29 (0.7 %)	32 (6.3 %)	<0.001
Shock	204 (4.2 %)	86 (2.0 %)	118 (23.3 %)	<0.001
Vital parameters				
Systolic blood pressure (mmHg)	140 (120 - 155)	140 (125 - 155)	130 (100 - 155)	<0.001
Diastolic blood pressure (mmHg)	80 (70 - 90)	80 (70 - 90)	80 (60 - 90)	<0.001
Heart rate (beats per minute)	77 (68 - 88)	77 (70 - 88)	75 (60 - 89)	0.002
Diagnostic procedures				
Chest X-ray	3014 (61.4 %)	2844 (64.6 %)	170 (33.6 %)	<0.001
Ultrasonography	3005 (61.2 %)	2650 (60.2 %)	355 (70.2 %)	<0.001
D-dimer (ng/mL)	499 (290 - 1072)	482 (286 - 791)	5390 (1807 - 17298)	<0.001

Legend. Categorical variables are presented as n (%). Continuous variables are presented as median (25th - 75th percentile).

4. Discussion

Our study provides the largest comparative analysis of rule-out protocols for AAS, using prospective data from ED patients. The first key finding is that all ADD and AORTAs based protocols provided point estimates for diagnostic sensitivity exceeding 98 %. For AORTAs-based protocols, the point estimate was even higher than 99 %. Instead, the sensitivity point estimate for the Canadian protocol was lower than 98 %, *i.e.* statistically lower than the sensitivity of AORTAs-based protocols. For all protocols, the upper bounds of the 95 % CI of the failure rates were lower than 1 %. This was indicated as an acceptable miss rate for an AAS decision tool, in a Canadian survey involving emergency clinicians [23]. Nonetheless, the number of potential misses was 4-fold higher with the Canadian protocol compared to AORTAs based protocols, and 1.5 to 2-fold higher compared to ADD based protocols. These results infer that, in patients with clinically suspected AAS, rule-out with the Canadian protocol may not be as safe. All AASs potentially missed by the Canadian protocol had a score of 0, and more than 90 % of them had a DD exceeding 500 ng/mL.

All diagnostic protocols were associated with a major reduction in the number of CTA scans and consequent costs, compared to a "CTA to all strategy". This finding corroborates their application in clinical practice. The least expensive protocol was ADD/$DD_{age\text{-}adj}$ and the most expensive was AORTAs/DD_{500}. Differences between protocols were within the 15 % range, but could increase if protocols were applied to larger patient populations at lower PP [15]. These findings could be relevant for health systems with tighter economic restraints.

The study has limitations. First, individual patient data was obtained from methodologically homogenous, but different prospective studies. In the PROFUNDS cohort, for instance, the protocol recommended application of point-of-care ultrasonography in addition to clinical PP assessment. In the ADVISED study, follow-up for case adjudication was 14 and not 30 days. Second, none of the study cohorts used the Canadian guidelines as a reference. Clinical gestalt data used for the Canadian rule was not systematically recorded, and therefore, the external validity of our estimates for this protocol could be lower. Third, our cost-effectiveness analysis did not consider the costs of missed AAS diagnoses, due to the difficulty in averaging conditions with very different prognosis (*e.g.* type-A aortic dissection requiring urgent surgery *vs* medically treated type-B penetrating aortic ulcer); this analysis could possibly lead to different results, favoring the protocol with lowest failure rate (AORTAs/$DD_{age\text{-}adj}$). Lastly, the present analysis did not evaluate the potential impact of point-of-care ultrasonography or transthoracic echocardiography on diagnostic accuracy and cost-effectiveness, when used as a clinically integrated tool in conjunction with a risk score and DD testing [18,24]. Caution is also needed in the generalization of current results to special populations poorly represented in our cohort, such as individuals with connective tissue disease or with previous AAS [25].

In conclusion, the present study indicates that guideline-compliant

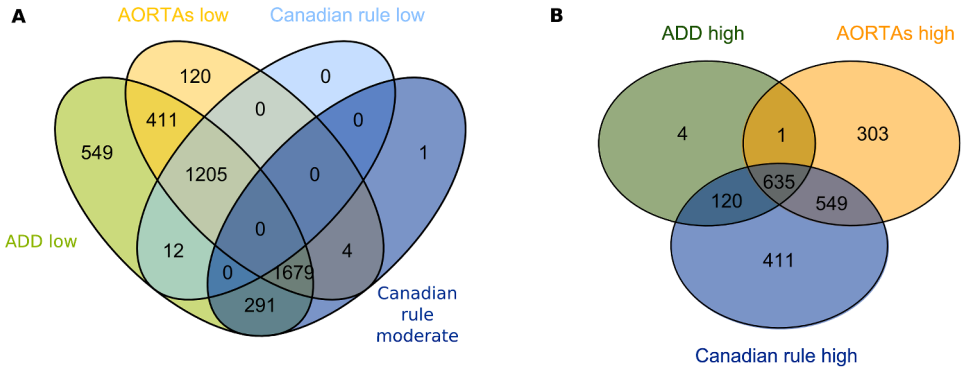

Fig. 2. Venn diagrams showing overlap of pre-test probability classification of study patients using the ADD score, AORTAs score and Canadian rule.

A

Method	TP	FP	FN	TN	Sensitivity	Sensitivity (95% CI)	P-value sensitivity	NPV	NPV (95% CI)	P-value NPV
ADD score and DD500	500	1982	6	2419		98.8% (97.9 - 99.8)	0.21		99.8% (99.6 - 100.0)	0.14
ADD score and DDage-adj	498	1693	8	2708		98.4% (97.3 - 99.5)	0.48		99.7% (99.5 - 99.9)	0.24
AORTAs and DD500	503	2340	3	2061		99.4% (98.7 - 100.0)	0.02		99.9% (99.7 - 100.0)	0.02
AORTAs and DDage-adj	503	2093	3	2308		99.4% (98.7 - 100.0)	0.02		99.9% (99.7 - 100.0)	0.02
Canadian rule	494	1958	12	2443		97.6% (96.3 - 99.0)	ref		99.5% (99.2 - 99.8)	ref

95 96 97 98 99 100 95 96 97 98 99 100

B

Method	TP	FP	FN	TN	Specificity	Specificity (95% CI)	P-value specificity	PPV	PPV (95% CI)	P-value PPV
ADD score and DD500	500	1982	6	2419		55.0% (53.5 - 56.4)	0.43		20.1% (18.6 - 21.7)	0.99
ADD score and DDage-adj	498	1693	8	2708		61.5% (60.1 - 63.0)	<0.001		22.7% (21.0 - 24.5)	<0.001
AORTAs and DD500	503	2340	3	2061		46.8% (45.4 - 48.3)	<0.001		17.7% (16.3 - 19.1)	<0.001
AORTAs and DDage-adj	503	2093	3	2308		52.4% (51.0 - 53.9)	<0.001		19.4% (17.9 - 20.9)	0.004
Canadian rule	494	1958	12	2443		55.5% (54.0 - 57.0)	ref		20.1% (18.6 - 21.7)	ref

40 50 60 70 80 90 100 0 5 10 15 20

Fig. 3. Forest plot showing sensitivity and NPV (**panel A**), specificity and PPV (**panel B**) performance of the 5 diagnostic protocols. DD500: D-dimer <500 ng/mL; DDage-adj: D-dimer <age-adjusted cutoff; FN: false negative; FP: false positive; NPV: negative predictive value; PPV: positive predictive value; ref: reference; TN: true negative; TP: true positive.

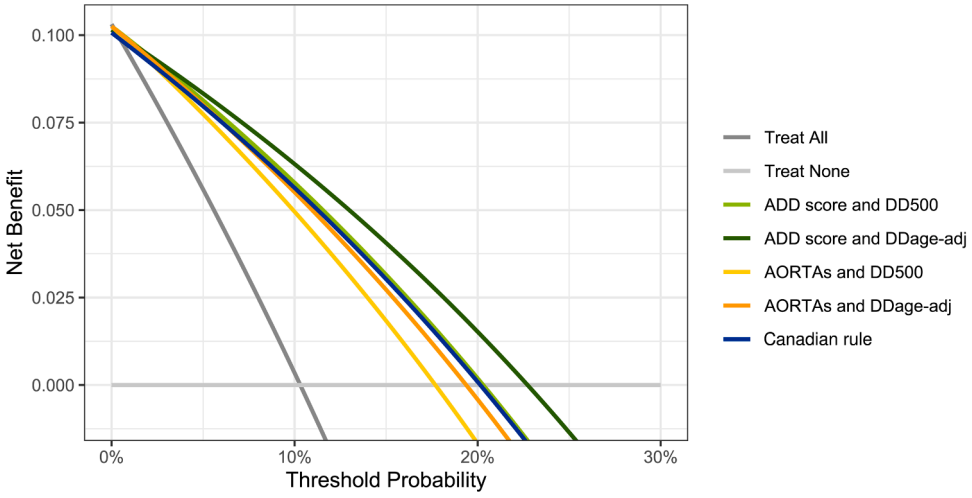

Fig. 4. Decision curve analysis. DD500: D-dimer <500 ng/mL; DDage-adj: D-dimer <age-adjusted cutoff.

Table 2
Number of exams and costs mandated by the different diagnostic protocols in $n = 4907$ study patients.

	ADD score		AORTAs score		Canadian score
D-dimer cutoff	500 ng/mL	age-adjusted	500 ng/mL	age-adjusted	500 ng/mL
D-dimer exams					
N	4147	4147	3419	3419	1975
Cost Italy (€)	42714	42714	35216	35216	20343
Cost Germany (€)	100067	100067	82500	82500	47657
CTA exams					
N	2482	2191	2843	2596	2452
Cost Italy (€)	1196324	1056062	1370326	1251272	1181864
Cost Germany (€)	1796968	1586284	2058332	1879504	1775248
Total costs (D-dimer + CTA exams)					
Cost Italy (€)	1239038	1098776	1405542	1286488	1202207
Cost Germany (€)	1897035	1686351	2140832	1962004	1822905

Legend. ADD: aortic dissection detection; AORTAs: AORTA simplified score; CTA: computed tomography angiography; €: euros.

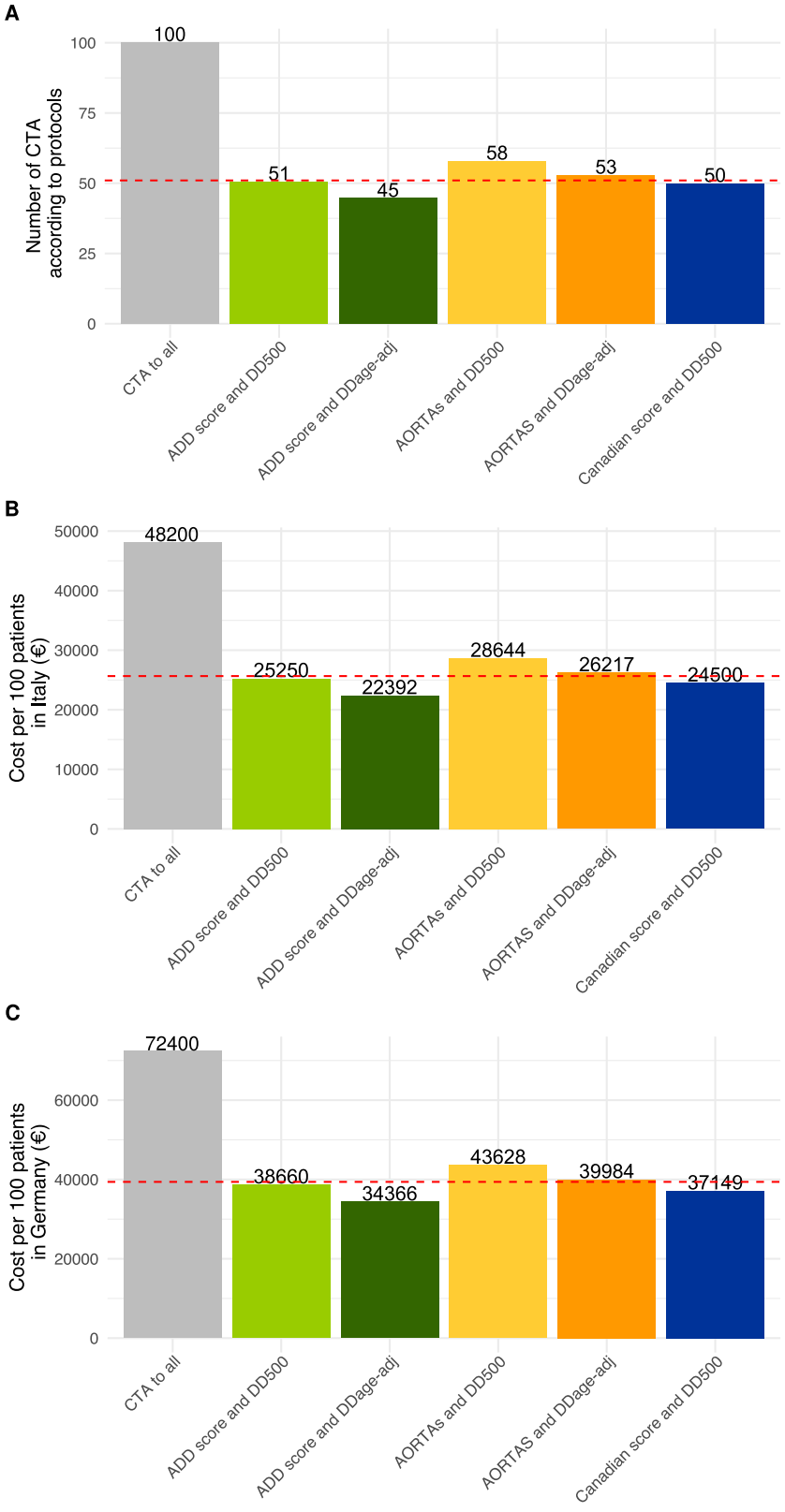

Fig. 5. Panel A: number of CTA exams mandated by different protocols, per 100 patients. The dashed red line indicates the number of CTAs actually requested by the attending physicians. **Panel B and C:** costs per 100 patients in Italy and Germany, according to different protocols. The dashed red lines indicates the costs according to the actual number of D-dimer and CTAs requested by the attending physicians.

diagnostic protocols for AASs are highly sensitive, but significantly differ in specificity, leading to measurable effects on CTA exams and costs. In clinical terms, the AORTAs/$DD_{age\text{-}adj}$ protocol provided the lowest risk of missing AAS with a marginal increase in resource use, and the ADD/$DD_{age\text{-}adj}$ protocol provided the highest net clinical benefit. Instead, the Canadian protocol, which suffers from lower sensitivity, higher failure rate and gestalt-dependency, without showing a significant economic benefit, awaits further study. Future studies in this field should also aim to overcome the limitations of conventional assessment tools through the application of artificial intelligence, as already attempted for other cardiovascular emergencies such as acute coronary syndromes and pulmonary embolism [26,27].

Conflicts of interest

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Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.03.039.

References

[1] Bossone E, Eagle KA. Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes. Nat Rev Cardiol 2021;18(5):331–48. https://doi.org/10.1038/s41569-020-00472-6.
[2] Klompas M. Does this patient have an acute thoracic aortic dissection? JAMA 2002;287(17):2262–72. https://doi.org/10.1001/jama.287.17.2262.
[3] Kelly AM, Lee XQ, Curran J. What can be done to improve diagnosis of aortic dissection? Emerg Med Australas 2023;35(1):176–80. https://doi.org/10.1111/1742-6723.14127.
[4] Lovatt S, Wong CW, Schwarz K, et al. Misdiagnosis of aortic dissection: a systematic review of the literature. Am J Emerg Med 2022;53:16–22. https://doi.org/10.1016/j.ajem.2021.11.047.
[5] Ohle R, Savage DW, Caswell J, McIsaac S, Yadav K, Conlon M. Mortality and risk factors associated with misdiagnosis of acute aortic syndrome in Ontario, Canada: a population-based study. Emerg Med J 2024;41(3):145–50. https://doi.org/10.1136/emermed-2023-213331.
[6] Ohle R, Anjum O, Bleeker H, McIsaac S. What is the specificity of the aortic dissection detection risk score in a low-prevalence population? Acad Emerg Med 2019;26(6):632–8. https://doi.org/10.1111/acem.13634.
[7] Lovy AJ, Bellin E, Levsky JM, Esses D, Haramati LB. Preliminary development of a clinical decision rule for acute aortic syndromes. Am J Emerg Med 2013;31(11):1546–50. https://doi.org/10.1016/j.ajem.2013.06.005.
[8] Morello F, Bima P, Castelli M, Nazerian P. Acute aortic syndromes: an internist's guide to the galaxy. Eur J Intern Med 2022;106:45–53. https://doi.org/10.1016/j.ejim.2022.10.003.
[9] Alter SM, Eskin B, Allegra JR. Diagnosis of aortic dissection in emergency department patients is rare. West J Emerg Med 2015;16(5):629–31. https://doi.org/10.5811/westjem.2015.6.25752.
[10] Ohle R, Yan JW, Yadav K, et al. Diagnosing acute aortic syndrome: a Canadian clinical practice guideline. Cmaj 2020;192(29):E832–e843. https://doi.org/10.1503/cmaj.200021.
[11] Isselbacher EM, Preventza O, Hamilton Black 3rd J, et al. 2022 ACC/AHA Guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2022;146(24):e334–482. https://doi.org/10.1161/CIR.0000000000001106.
[12] Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC guidelines for the management of peripheral arterial and aortic diseases. Eur Heart J 2024;45(36):3538–700. https://doi.org/10.1093/eurheartj/ehae179.
[13] Morello F, Bima P, Pivetta E, et al. Development and validation of a simplified probability assessment score integrated with age-adjusted D-dimer for diagnosis of acute aortic syndromes. J Am Heart Assoc 2021;10(3):e018425. https://doi.org/10.1161/JAHA.120.018425.
[14] Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35(43). https://doi.org/10.1093/eurheartj/ehu283. 3033-693069a-3069k.
[15] Thokala P, Goodacre S, Cooper G, et al. Decision analytical modelling of strategies for investigating suspected acute aortic syndrome. Emerg Med J 2024;41(12):728–35. https://doi.org/10.1136/emermed-2024-214222.
[16] McLatchie R, Reed MJ, Freeman N, et al. Diagnosis of acute aortic syndrome in the emergency department (DAShED) study: an observational cohort study of people attending the emergency department with symptoms consistent with acute aortic syndrome. Emerg Med J 2024;41(3):136–44. https://doi.org/10.1136/emermed-2023-213266.
[17] Nazerian P, Mueller C, Soeiro AM, et al. Diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes: the ADvISED prospective multicenter study. Circulation 2018;137(3):250–8. https://doi.org/10.1161/CIRCULATIONAHA.117.029457.
[18] Morello F, Bima P, Castelli M, et al. Diagnosis of acute aortic syndromes with ultrasound and D-dimer: the PROFUNDUS study. Eur J Intern Med 2024;128:94–103. https://doi.org/10.1016/j.ejim.2024.05.029.
[19] Rogers AM, Hermann LK, Booher AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. Circulation 2011;123(20):2213–8. https://doi.org/10.1161/CIRCULATIONAHA.110.988568.
[20] Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121(13):e266–369. https://doi.org/10.1161/CIR.0b013e3181d4739e.
[21] Abrechnungsstelle. GOÄ-Ziffern Übersicht. Updated 2025/03/13. https://abrechnungsstelle.com/goae/ziffern/.
[22] Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26(6):565–74. https://doi.org/10.1177/0272989X06295361.
[23] Ohle R, McIsaac S, Yan J, Yadav K, Eagles D, Perry JJ. National survey of emergency physicians on the risk stratification and acceptable miss rate of acute aortic syndrome. CJEM 2020;22(3):309–12. https://doi.org/10.1017/cem.2019.489.
[24] Mani N, Cherian N, Burkert J, Jarman RD. Bedside-focused transthoracic echocardiography in acute atraumatic thoracic aortic syndrome: a systematic review and meta-analysis of diagnostic accuracy. Eur J Emerg Med 2024;31(6):398–412. https://doi.org/10.1097/MEJ.0000000000001174.
[25] Morello F, Santoro M, Giachino F, et al. Pre-test probability assessment and D-dimer based evaluation in patients with previous acute aortic syndrome. Medicina 2023;59(3). https://doi.org/10.3390/medicina59030548.
[26] Villacorta H, Pickering JW, Horiuchi Y, et al. Machine learning with D-dimer in the risk stratification for pulmonary embolism: a derivation and internal validation study. Eur Heart J Acute Cardiovasc Care 2022;11(1):13–9. https://doi.org/10.1093/ehjacc/zuab089.
[27] Doudesis D, Lee KK, Boeddinghaus J, et al. Machine learning for diagnosis of myocardial infarction using cardiac troponin concentrations. Nat Med 2023;29(5):1201–10. https://doi.org/10.1038/s41591-023-02325-4.