European Journal of Internal Medicine 128 (2024) 94–103

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Diagnosis of acute aortic syndromes with ultrasound and D-dimer: the PROFUNDUS study☆,☆☆

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ARTICLE INFO

Keywords:
Aorta
Dissection
Diagnosis
Probability
Score
Ultrasound
D-dimer

ABSTRACT

Background: In patients complaining common symptoms such as chest/abdominal/back pain or syncope, acute aortic syndromes (AAS) are rare underlying causes. AAS diagnosis requires urgent advanced aortic imaging (AAI), mostly computed tomography angiography. However, patient selection for AAI poses conflicting risks of misdiagnosis and overtesting.

Objectives: We assessed the safety and efficiency of a diagnostic protocol integrating clinical data with point-of-care ultrasound (POCUS) and D-dimer (single/age-adjusted cutoff), to select patients for AAI.

Methods: This prospective study involved 12 Emergency Departments from 5 countries. POCUS findings were integrated with a guideline-compliant clinical score, to define the integrated pre-test probability (iPTP) of AAS. If iPTP was high, urgent AAI was requested. If iPTP was low and D-dimer was negative, AAS was ruled out. Patients were followed for 30 days, to adjudicate outcomes.

Results: Within 1979 enrolled patients, 176 (9 %) had an AAS. POCUS led to net reclassification improvement of 20 % (24 %/-4 % for events/non-events, $P < 0.001$) over clinical score alone. Median time to AAS diagnosis was 60 min if POCUS was positive *vs* 118 if negative ($P = 0.042$). Within 941 patients satisfying rule-out criteria, the 30-day incidence of AAS was 0 % (95 % CI, 0–0.41 %); without POCUS, 2 AAS were potentially missed. Protocol

Abbreviation: AAS, Acute aortic syndrome; AD, Aortic dissection; ADD, Aortic dissection detection; ED, Emergency department; CTA, Computed tomography angiography; IMH, Intramural aortic hematoma; iPTP, POCUS-integrated pre-test probability; PAU, Penetrating aortic ulcer; PE, Pulmonary embolism; POCUS, Point-of-care ultrasound; PTP, Pre-test probability.

☆ **Funding**: grants MORF_RILO_21_02 and MORF_RILO_23_03 to Fulvio Morello from Università degli Studi di Torino; grant 2023 to Enrico Lupia from Fondazione Ricerca Molinette.☆☆ **Disclosures/conflicts of interest**: nothing to disclose

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[1] Members of the PROFUNDUS Study Investigators not in the author list are indicated in the acknowledgements section.

https://doi.org/10.1016/j.ejim.2024.05.029
Received 12 April 2024; Received in revised form 10 May 2024; Accepted 22 May 2024
Available online 12 June 2024

rule-out efficiency was 48 % (95 % CI, 46–50 %) and AAI was averted in 41 % of patients. Using age-adjusted D-dimer, rule-out efficiency was 54 % (difference 6 %, 95 % CI, 4–9 %, vs standard cutoff).
Conclusions: The integrated algorithm allowed rapid triage of high-probability patients, while providing safe and efficient rule-out of AAS. Age-adjusted D-dimer maximized efficiency.
CLINICAL TRIAL REGISTRATION: Clinicaltrials.gov, NCT04430400

1. Introduction

Acute aortic syndromes (AASs), including aortic dissection (AD), intramural aortic haematoma (IMH) and penetrating aortic ulcer (PAU), affect 5–7/100,000 individuals/year [1]. They are time-dependent emergencies burdened by up to 1–2 % mortality/hour, if left untreated. AASs cause unspecific symptoms such as chest/abdominal/back pain, syncope, neurological deficits and limb ischemia. Large numbers of patients are evaluated in Emergency Departments (EDs) for these common symptoms, but only few of them have an AAS, *e.g.* 1 of 980 with chest pain, and 1 of 327 with suspected stroke [2,3]. Facing this low signal to high noise challenge, the diagnosis of AAS is burdened by both frequent misdiagnoses (5–25 %) and low yield [4-6].

Conclusive diagnosis of AAS is based on advanced imaging, typically contrast-enhanced computed tomography angiography (CTA) of the thorax and abdomen. CTA has risks related to radiation, anaphylaxis and kidney injury, and is associated with resource/time restrictions, higher costs and longer ED stays [7]. Thus, patient selection for urgent CTA is cumbersome. Evidence-based criteria balancing safety and efficiency are needed, to improve clinical practice and to curb legal controversies [8].

The diagnostic approach to AAS primarily considers patient's stability and disease likelihood, or pre-test probability (PTP), inferred from clinical presentation and history, as in suspected pulmonary embolism [9]. The main PTP assessment tool for AAS is the aortic dissection detection (ADD) risk score [10]. PTP is clinically useful to partition the diagnostic pipeline, but *per se* is unsuitable for conclusive AAS rule-out; final decision on advanced testing must consider additional elements, including first-line imaging and blood tests [11,12].

Transthoracic echocardiography (TTE) can identify signs of AAS (*e.g.* aortic flap or dilatation), may aid in differential diagnosis, and rapidly detect complications, such as pericardial tamponade [13]. When performed at the bedside during clinical evaluation, ideally by the attending physician as a focus point-of-care ultrasound (POCUS), could improve triage of patients at high probability and increase diagnostic accuracy [14].

Circulating D-dimer levels increase in most patients with AAS [15]. Conversely, low levels of D-dimer argue against AAS, most strongly in patients at low PTP, potentially allowing rule-out without further tests [16]. Unfortunately, D-dimer lacks specificity, because levels increase in several conditions including aging. Preliminary studies have shown that age-adjusted interpretation of D-dimer, developed for pulmonary embolism, may increase test specificity without compromising sensitivity, also for suspected AAS [9,17].

So far, a diagnostic bundle applying PTP, ultrasonography and D-dimer, has been studied mostly in observational retrospective studies, with only one prospective study and no implementation data [14,18]. In this prospective study, we evaluated the outcomes of implementing a diagnostic protocol for AAS based on POCUS-integrated PTP (iPTP) and D-dimer. The study aimed to pragmatically assess protocol safety and efficiency, and to estimate the performance of an age-adjusted D-dimer test interpretation, with a working hypothesis of increased efficiency.

2. Material and methods

2.1. Study design and setting

This prospective management outcome study involved 12 EDs from 5 countries. Mean census was 60.000 visits/year, and 83 % were aortic hub centres. The study complied with the Declaration of Helsinki and was approved by the research ethics boards (for the Coordinating Center, Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino, nr. 42/2020/prot. 0029448). Patients provided informed consent. The study was spontaneous, investigator-driven and no-profit.

2.2. Outcomes

The primary outcome was protocol safety, measured as the cumulative 30-day incidence of AAS in rule-out patients. The secondary outcomes were: (1) protocol efficiency, measured as the proportion of rule-out patients avoiding advanced imaging, (2) protocol feasibility, measured as the adherence of advanced imaging requests to protocol indications, and (3) difference in safety and efficiency using age-adjusted D-dimer interpretation.

2.3. Study patients

Outpatients were enrolled before decision on advanced imaging. Inclusion criteria were presence of at least one AAS-compatible symptom (thoracic/back/abdominal pain, syncope, organ perfusion deficit, *i.e.* focal neurologic deficit, limb ischemia) lasting for up to 14 days, and AAS considered a meaningful diagnostic concern. Exclusion criteria were: age lower than 18 years, evident alternative diagnosis, primary trauma, history of previous AAS, patient's inaccessibility for follow-up and patient's refusal to participate.

2.4. Clinical evaluation

The attending emergency physician obtained the medical history and performed physical examination. Demographic and clinical data were prospectively registered on a site-specific paper or electronic case report form, and the ADD score was calculated. This score (*Supplementary Table 1*) is based on 12 items and ranges from 0 to 3, depending on the number or risk-categories with at least one item present [10-12]. An ECG was recorded and venous blood was sampled for routine tests.

2.5. Point-of-care ultrasound

The attending emergency physician or another physician (*e.g.* cardiology consultant) expert in POCUS performed a focused exam during the index visit. POCUS images were not recorded and were not centrally evaluated, as this method was used as a bedside clinically-integrated tool. The POCUS protocol, compliant with guidelines, was provided to all participating centers [13] All centers declared their expertise in POCUS, with internal auditing for data quality. The thoracic aorta and the heart were scanned from the left parasternal long-axis and suprasternal notch views, with the patient in the supine or left lateral decubitus position (Fig. 1).

At her/his discretion, the physician could use additional cardiac views (other parasternal, subcostal, apical) and views for neck arteries, abdominal aorta and limb arteries. POCUS was used to identify direct signs of AAS, which included: presence of an intimal flap separating two aortic lumens, presence of a circular or crescentic thickening (>5 mm) of the aortic wall, and presence of a crater-like outpouching with jagged edges in the aortic wall. The physician also searched for indirect signs of AAS, which included: thoracic aortic dilatation (diameter ≥40 mm,

measured fom leading edge to leading edge at the largest portion of thoracic aorta), pericardial effusion, and aortic valve regurgitation at least moderate at colour Doppler. Representative POCUS videos are provided as *Supplementary Online Material.*

2.6. Integrated pre-test probability assessment

Patients were defined at low iPTP if direct POCUS signs were absent and the ADD score was 0–1 (*Supplementary Table 2*). Patients were defined at high iPTP if any direct POCUS sign was present or if the ADD score was 2–3. The physician could define patients at high iPTP also if only indirect POCUS signs were present and the ADD score was 0–1, but the patient was unstable or if an alternative diagnosis was unlikely.

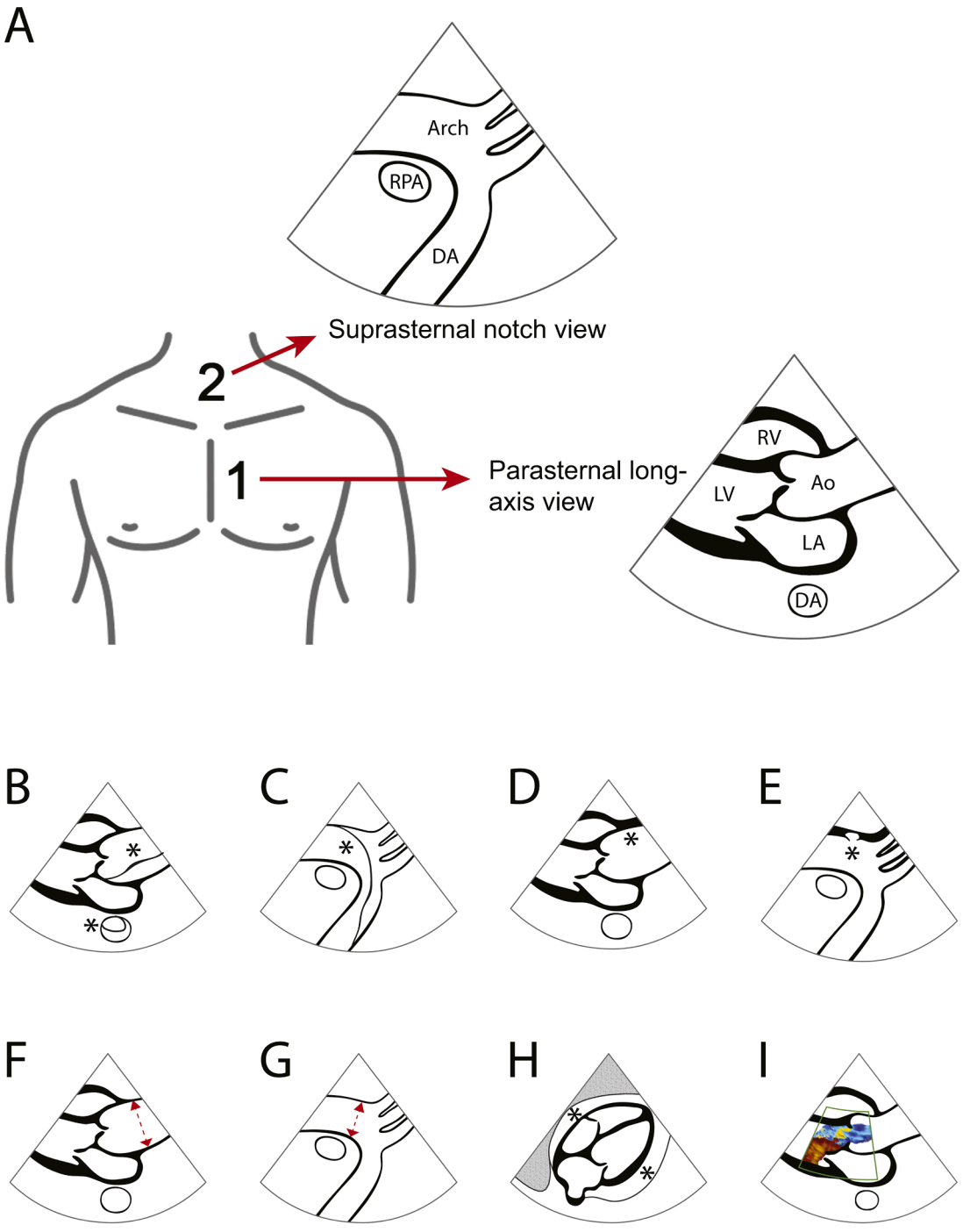

Fig. 1. Point-of-care ultrasound (POCUS) views and signs used in the study protocol. (**A**) Protocol views used to detect signs of acute aortic syndromes (AAS). Sketch representations of direct (**B-E**) and indirect (**F-I**) POCUS signs of AAS, as defined in the study protocol. Ao: ascending thoracic aorta; DA: descending thoracic aorta; LA: left atrium; LV: left ventricle; RPA: right pulmonary artery; RV: right ventricle. The asterisk indicates: in B, intimal flap (ascending and descending aorta); in C, intimal flap (aortic arch and descending aorta); in D, aortic wall thickening (ascending aorta); in E, aortic wall outpouching (aortic arch); in F-G, aortic dilatation (≥40 mm, leading edge to leading edge); in H, pericardial effusion; in I, aortic valve regurgitation at colour Doppler. Representative POCUS clips are provided as online supplements.

2.7. D-dimer

Blood was sampled before advanced imaging and urgently processed in the local laboratory with a quantitative D-dimer assay. The test was considered positive if the result was ≥500 ng/mL fibrinogen equivalent unit (FEU), and negative if <500 ng/mL. In secondary analysis, the D-dimer test result was interpreted using an age-ajusted cutoff ($D_{age\text{-}adj}$). $D_{age\text{-}adj}$ was calculated as patient's age in years multiplied by 10, with a minimum value of 500 ng/mL [19].

2.8. Advanced aortic imaging

The study protocol (Fig. 2) indicated to perform urgent advanced aortic imaging in patients at high iPTP irrespective of D-dimer levels, and in patients at low iPTP with D-dimer ≥500 ng/mL. Rule-out of AAS without performing advanced aortic imaging was indicated in patients at low iPTP with D-dimer <500 ng/mL.

The preferred advanced aortic imaging method was ECG-synchronized contrast-enhanced CTA of the chest and abdomen, extended to the cranium in presesence of neurologic symptoms. Trans-esophageal echocardiography and magnetic resonance angiography were additional reference standard methods. Advanced aortic imaging exams were performed and interpreted by expert physicians not involved in the study.

2.9. Follow-up and adjudication

Upon discharge, participants were instructed to return to the ED if their symptoms did not improve or if new symptoms developed. All patients were followed for 30 days, through hospital data check and telephone contact. Queries included hospital admission, ED revisit and death. Data were acquired and used to adjudicate: (1) dichotomically, if a confirmed diagnosis of AAS was made, within 30 days; (2) for patients with AAS, the AAS subtype; (3) for patients without AAS, the preminent

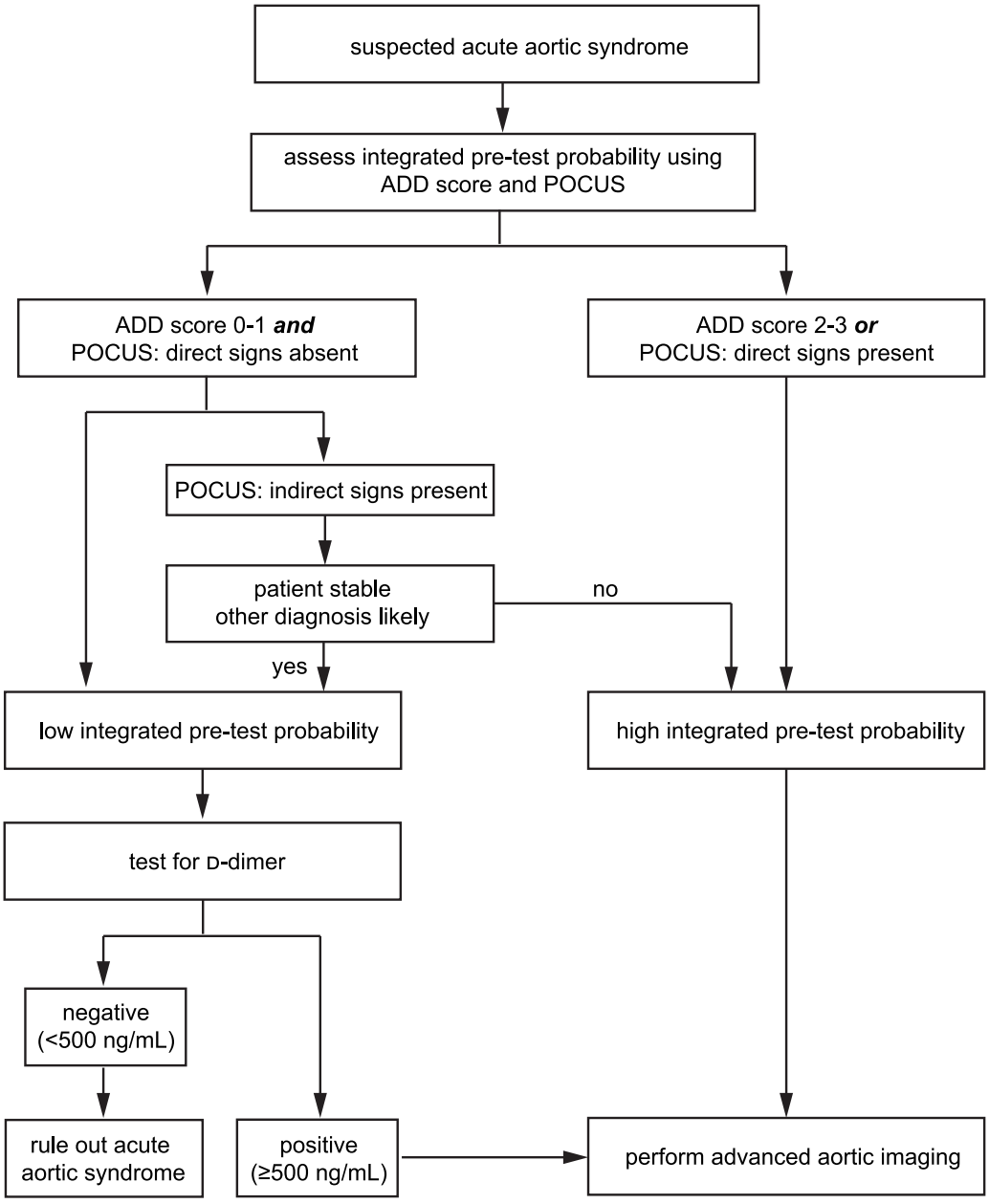

Fig. 2. Study protocol guiding diagnostic decision on advanced aortic imaging and rule-out of acute aortic syndromes. ADD: aortic dissection detection; POCUS: point-of-care ultrasound.

alternative diagnosis. The adjudication protocol is detailed in the *Supplemetary Appendix*.

2.10. Statistical analysis

Full statistical methods are detailed in the *Supplementary Appendix*. Dichotomous data were expressed as proportions with their 95 % confidence interval (CI), and continuous data were expressed as median and interquartile range (IQR). Comparisons were done with the χ^2 test and the Mann-Whitney *U test*, respectively. For outcome analysis, we used intention-to-diagnose, per-protocol and worst-case scenario analyses, as in similar diagnostic studies assessing rule-out of PE [20].

The diagnostic performance was assessed by computing sensitivity/specificity/likelihood ratios with their 95 % CI. The failure rate was calculated as the number of adjudicated AASs within patients satisfying rule-out criteria. Measures were compared using binomial exact test and Pearson's χ^2 test. Net reclassification improvement (NRI) was calculated as previously [21]. Decision curve analysis plots were built comparing the default strategies of "CTA to all" and "CTA to none" [22]. *P*-values were two-sided, and a *P*-value <0.05 was considered as statistically significant.

The study was sized to test the null hypothesis that the primary outcome exceeds 2 %, as in the only previous prospective study [18]. This was based on previous estimates that the testing threshold for AD is 4 % for TEE, 3 % for CTA and 2 % for MRA [23]. Assuming that the punctual failure rate is 0.5 %, with a type I error (alpha) of 0.05 and a type II error (beta) of 0.2, approximately 496 patients at low iPTP with D-dimer <500 ng/mL needed to be enrolled, to reject the null hypothesis. Assuming that such patients would be 30 %, approximately 1653 patients should be analysed. Assuming a 10 % rate of patients with incomplete data or lost at follow-up, at least 1837 patients should be enrolled.

3. Results

3.1. Patients

From January 2019 to December 2022, 3022 patients with suspected AAS were screened, and 1979 were enrolled (Fig. 3). Their demographic and clinical characteristics are summarized in Table 1 and *Supplementary Table 3*. The ADD score was ≤1 in 1690 (85 %) patients, and ≥2 in 289 (15 %). POCUS results are summarized in Table 2 and *Supplementary Table 4*. POCUS was performed by the attending emergency physician in 90 % of cases and by a cardiology consultant in 10 %.

398 (20 %) patients were classified at high iPTP of AAS. These included 109 (6 %) patients with ADD score ≤1, in whom high iPTP classification was due to POCUS findings: 53 patients with any direct sign, and 56 with any indirect sign coupled to clinical unstability or unlikelihood of an alternative diagnosis. 1581 (80 %) patients were classified at low iPTP and were tested for D-dimer, predominantly with the HemosIL (51 %) or STA-Liatest (45 %) assay, for decision on advanced aortic imaging. Median D-dimer turnaround time (from test order to result validation), available for 732 patients, was 01:17 hh:mm (IQR 01:02–01:37). 941 (48 %) patients had low PTP and D-dimer <500 ng/mL.

3.2. Follow-up data and case adjudication

1975 patients completed 30-day follow-up and 4 were lost. 636 (32 %) patients were admitted to hospital, 148 (8 %) had an ED revisit and 61 (3 %) died (17 during the index visit). An AAS was adjudicated in 176 (9 %) patients and an alternative diagnosis in 1799 (91 %). Their demographic, clinical and POCUS data are presented in Tables 1-2. Five patients provisionally diagnosed with AAS in the ED were adjudicated as not affected by AAS at follow-up (*Supplementary Table* 5).

76 % of AASs were ADs, and 69 % were Stanford type A (*Supplementary Table 6*). Most common alternative diagnoses were musculoskeletal pain (35 %), gastrointestinal disease (15 %) and acute coronary syndrome (12 %). 30-day mortality was 24 % for AASs and 1 % for alternative diagnoses.

3.3. Diagnostic protocol components

The ADD score had an AUC of 0.8 for AAS (*Supplementary Figure 1*). ADD score ≥2 had a sensitivity and specificity of 55.7 % (95 %CI 48.3–63 %) and 89.4 % (95 %CI 88–90.6 %), respectively. For POCUS, overall sensitivity and specificity were 44.3 %/98.4 % using any direct sign, and 87.5 %/81.3 % using any direct or indirect sign (Fig. 4). Using only direct signs, POCUS sensitivity for IMH/PAU was negligible; using any sign, POCUS had lower sensitivity for type B forms.

Within 108 patients classified at high PTP due to POCUS findings despite ADD score ≤1, 42 (39 %) had an AAS. POCUS-integrated PTP led to a NRI of 20 % ($P < 0.001$, NRI for events 24 %, $P < 0.001$, NRI for non-events −4 %, $P < 0.001$) over ADD-based classification (*Supplementary Table 7*). In AAS patients, time to advanced imaging was 60 (IQR 30–195) minutes if any POCUS sign was present and 118 (IQR 94–179) minutes if POCUS was negative ($P = 0.042$). Accordingly, advanced imaging was performed within 60 min in 53 % of patients if any POCUS sign was present, and in 10 % if POCUS was negative, respectively ($P < 0.001$).

D-dimer had an AUC of 0.91 (95 % CI 0.89–0.94; *Supplementary Figure 2*) for AAS. Using 500 ng/mL as cutoff, the sensitivity and specificity of D-dimer were 96.5 % (95 % CI 93.5–99.5) and 58.9 % (95 % CI 56.6–61.2), respectively. Using an age-adjusted cutoff, the sensitivity and specificity of D-dimer were 95.1 % (95 %CI 9.6–98.6) and 66.9 % (95 % CI 64.6–69.1), respectively ($P = 0.5$ for sensitivity, $P < 0.001$ for specificity, *vs* 500 ng/mL).

3.4. Rule-in

Within 398 patients at high PTP, 2 were lost to follow-up and 49 died, within 30 days. The corresponding incidence of AAS was 35 % (95 % CI, 31–40 %; 140 in 396) using intention-to-diagnose analysis, and 41 % (95 % CI, 35 to 46 %; 139 in 343) using per-protocol analysis. Median time to conclusive AAS imaging was 60 (IQR 30–180) minutes.

Within 640 patients at low iPTP with D-dimer ≥500 ng/mL, 1 was lost to follow-up and 12 died, within 30 days. The corresponding incidence of AAS was 6 % (95 % CI, 4 to 8 %; 36 in 639) using intention-to-diagnose analysis, and 8 % (95 % CI, 6 to 11 %; 36 in 442) using per-protocol analysis. Median time to conclusive AAS diagnosis was 122 (IQR 75–250) minutes.

3.5. Primary outcome

Within 941 patients at low PTP with D-dimer <500 ng/mL, 1 was lost to follow-up, none had AAS and none died, within 30 days. The corresponding incidence of AAS was 0 % (95 % CI, 0–0.41 %; 0 of 940) using intention-to-diagnose analysis, and 0 % (95 % CI, 0–0.47 %; 0 of 811) using per-protocol analysis. In a worst-case scenario analysis assuming that the patient lost to follow-up had an AAS, the incidence of AAS was 0.11 % (95 % CI, 0.01–0.60 %; 1 of 941 patients).

3.6. Secondary outcome

The diagnostic protocol indicated to rule out AAS in 48 % (95 % CI, 45 to 50 %; 941 of 1979) of patients. Since 129 patients at low PTP and D-dimer <500 ng/mL underwent advanced imaging as a protocol violation (*Supplementary Table 8*), rule-out was applied per-protocol in 41 % (95 % CI, 39–43 %; 812 of 1979) of patients. The protocol efficiency was highest in younger patients and lowest in elder patients, in patients with aortic aneurysm, and in patients with any variable within high-risk conditions or exam features (Fig. 5). Overall adherence of

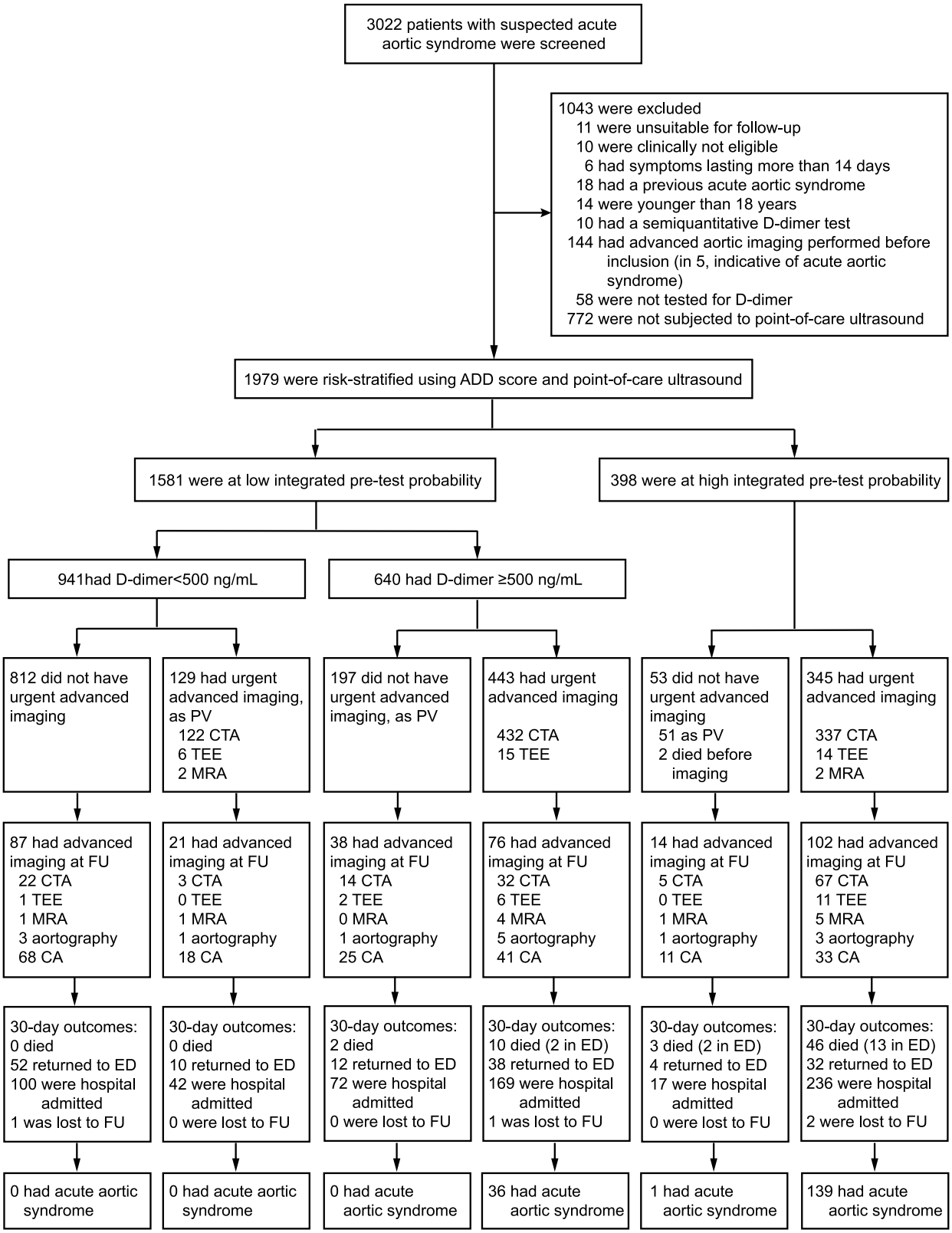

Fig. 3. Study flow diagram representing patient enrollment and exclusion, integrated pre-test probability assessment, D-dimer test results, performance of advanced aortic imaging, clinical outcomes and final case adjudication after 30-day follow-up. CA: coronary angiography; CTA: computed tomography angiography; ED: emergency department; FU: follow-up; MRA: magnetic resonance angiography; PV: protocol violation; TEE: transesophageal echocardiography.

Table 1
Demographic and clinical characteristics of study patients.

Characteristic	All (*n* = 1979)	Alternative diagnosis (*n* = 1799)	Acute aortic syndrome (*n* = 176)	*P*-value
Age, yr – median (IQR)	58 (47–71)	57 (46–70)	69 (57–78)	<0.001
Female sex – no. (%)	823 (41.6)	764 (42.5)	57 (32.4)	0.01
Hours from symptom onset – median (IQR)	7.5 (2.5–31)	8 (3–48)	3 (1–10)	<0.001
Clinical presentation				
Anterior chest pain – no. (%)	1584 (80)	1466 (81.5)	114 (64.8)	<0.001
Posterior chest pain – no. (%)	723 (36.5)	644 (35.8)	76 (43.2)	0.052
Abdominal pain – no. (%)	341 (17.2)	296 (16.5)	44 (25)	0.004
Lumbar pain – no. (%)	90 (4.5)	65 (3.6)	25 (14.2)	<0.001
Syncope – no. (%)	207 (10.5)	166 (9.2)	41 (23.3)	<0.001
Limb ischemia – no. (%)	26 (1.3)	15 (0.8)	10 (5.7)	<0.001
Neurological deficit – no. (%)	132 (6.7)	101 (5.6)	29 (16.5)	<0.001
Medical history				
Hypertension – no. (%)	903 (45.6)	773 (43)	127 (72.2)	<0.001
Diabetes – no. (%)	203 (10.3)	190 (10.6)	11 (6.3)	0.071
Smoking habit – no. (%)	508 (25.7)	458 (25.5)	49 (27.8)	0.49
Drug use – no. (%)	18 (0.9)	15 (0.8)	2 (1.1)	0.68
Coronary artery disease – no. (%)	266 (13.4)	247 (13.7)	18 (10.2)	0.19
Abdominal aortic aneurysm – no. (%)	58 (2.9)	38 (2.1)	20 (11.4)	<0.001
Recent fluoroquinolone use – no. (%)	4 (0.2)	4 (0.2)	0 (0)	0.53
Active cancer – no. (%)	78 (3.9)	70 (3.9)	8 (4.5)	0.67
ADD score variables				
Marfan syndrome or other connective tissue disease – no. (%)	16 (0.8)	14 (0.8)	2 (1.1)	0.61
Family history of acute aortic syndrome – no. (%)	33 (1.7)	27 (1.5)	5 (2.8)	0.18
Aortic valve disease or aortic valve graft	90 (4.5)	77 (4.3)	13 (7.4)	0.059
Recent aortic manipulation – no. (%)	12 (0.6)	12 (0.7)	0 (0)	0.28
Thoracic aortic aneurysm or tube graft – no. (%)	152 (7.7)	109 (6.1)	43 (24.4)	<0.001
Severe pain – no. (%)	678 (34.3)	558 (31)	116 (65.9)	<0.001
Sudden pain – no. (%)	803 (40.6)	676 (37.6)	124 (70.5)	<0.001
Ripping/tearing pain – no. (%)	281 (14.2)	214 (11.9)	67 (38.1)	<0.001
Pulse asymmetry or SBP differential – no. (%)	76 (3.8)	38 (2.1)	38 (21.6)	<0.001
Focal neurological deficit – no. (%)	70 (3.5)	43 (2.4)	26 (14.8)	<0.001
New/unknown diastolic aortic murmur – no. (%)	24 (1.2)	12 (0.7)	12 (6.8)	<0.001
Hypotension or shock state – no. (%)	78 (3.9)	32 (1.8)	46 (26.1)	<0.001

There were 4 patients lost to follow-up (see text). ADD: aortic dissection detection; IQR: interquartile range; SBP: systolic blood pressure.

Table 2
Findings of point-of-care ultrasound in study patients.

Characteristic	All (*n* = 1979)	Alternative diagnosis (*N* = 1799)	Acute aortic syndrome (*N* = 176)	*P*-value
Minutes from ED visit start to POCUS – median (IQR)	20 (10–90)	20 (10–95)	20 (6–45)	0.006
Ultrasound views				
Parasternal long axis and suprasternal – no. (%)	1317 (66.5)	1187 (66)	126 (71.6)	0.4
Parasternal long axis – no. (%)	1947 (98.4)	177 (9.8)	170 (96.6)	0.12
Suprasternal – no. (%)	1326 (67)	1194 (66.4)	128 (72.7)	0.4
Any additional view – no. (%)	1336 (67.5)	1191 (66.2)	142 (80.7)	<0.001
Type of additional view obtained				
Subcostal 4-chamber – no. (%)	1155 (58.4)	1031 (57.3)	122 (69.3)	0.002
Apical 4/5-chamber – no. (%)	1067 (53.9)	968 (53.8)	96 (54.5)	0.9
Abdominal aorta – no. (%)	282 (14.2)	240 (13.3)	42 (23.9)	<0.001
Neck arteries – no. (%)	25 (1.3)	18 (1)	7 (4)	0.005
Leg arteries – no. (%)	11 (0.6)	6 (0.3)	5 (2.8)	0.002
POCUS findings				
Intimal flap – no. (%)	96 (4.9)	22 (1.2)	73 (41.5)	<0.001
Intramural hematoma – no. (%)	14 (0.7)	7 (0.4)	7 (4)	<0.001
Ulcer-like projection – no. (%)	4 (0.2)	2 (0.1)	2 (1.1)	0.042
Aortic dilatation – no. (%)	344 (17.4)	216 (12)	127 (72.2)	<0.001
Maximum aortic diameter (mm)*	33 (30–40)	32 (30–38)	47 (40–52)	<0.001
Pericardial effusion – no. (%)	150 (7.6)	100 (5.6)	50 (28.4)	<0.001
Aortic regurgitation – no. (%)	106 (5.4)	63 (3.5)	43 (24.4)	<0.001
Any direct POCUS sign present – no. (%)	107 (5.4)	28 (1.6)	78 (44.3)	<0.001
Any POCUS sign present – no. (%)	492 (24.9)	337 (18.7)	154 (87.5)	<0.001

There were 4 patients lost to follow-up (see text). ED: Emergency Department; POCUS: point-of-care ultrasound. *expressed as median (25th-75th percentile).

advanced imaging requests to the protocol was 76 % (95 % CI, 73–78 %).

Table 3 represents the diagnostic performance of diagnostic protocols based on iPTP or ADD score alone, plus single cut-off or age-adjusted D-dimer. The study protocol (low iPTP/D-dimer <500 ng/mL) ruled out AAS with 100 % sensitivity, 52 % specificity and failure rate of 0 %, corresponding to a maximum of 1 miss in 244. A modified protocol using low iPTP/$D_{age\text{-}adj}$, ruled out AAS with 100 % sensitivity, 59 % specificity ($P < 0.001$ *vs* standard strategy) and failure rate of 0 %, corresponding to a maximum of 1 miss in 278. This $D_{age\text{-}adj}$ based protocol could rule out AAS in 1061 (54 %) patients *vs* 940 (48 %) with the standard protocol, corresponding to a difference of 6 % (95 % CI 5–7 %). Protocols using ADD score without POCUS had 2 false negative cases, corresponding to a maximum of 1 miss in 132 (ADD ≤1/D-dimer <500 ng/mL) or 1 miss in 147 (ADD ≤1/$D_{age\text{-}adj}$).

Decision curve analysis showed that the $D_{age\text{-}adj}$ protocol had a greater net benefit for threshold AAS probabilities of 5–19 % (Fig. 6).

4. Discussion

This is the first study prospectively evaluating application of POCUS-enhanced clinical assessment plus D-dimer, to rule-in/out AASs. The protocol stemmed from results of a previous observational study where PTP was based on ADD score alone and where POCUS data were only

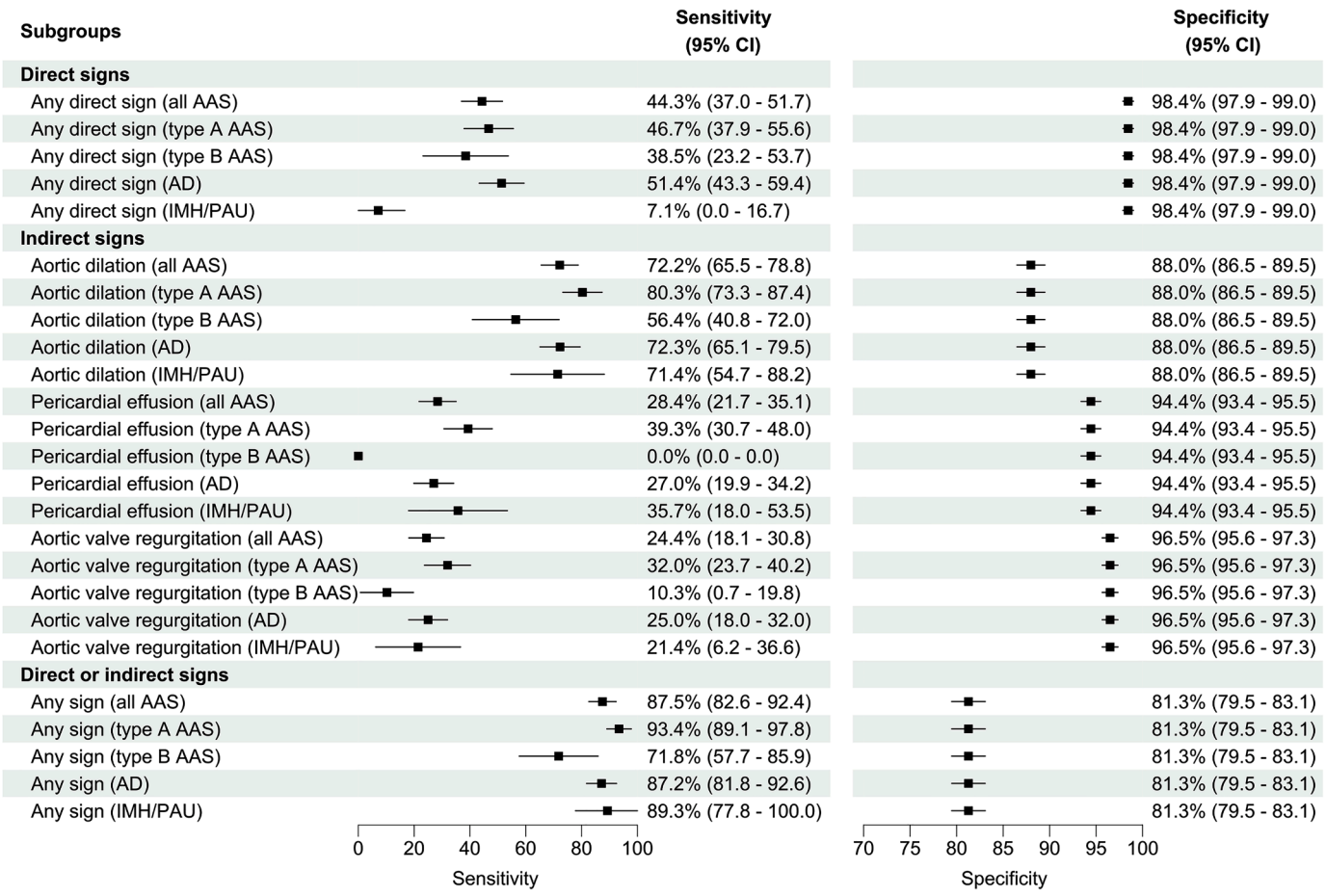

Fig. 4. Forrest plot representing the diagnostic sensitivity and specificity of point-of-care ultrasound for diagnosis of acute aortic syndromes. AAS: acute aortic syndrome(s); AD: aortic dissection; IMH: intramural aortic haematoma; PAU: penetrating aortic ulcer.

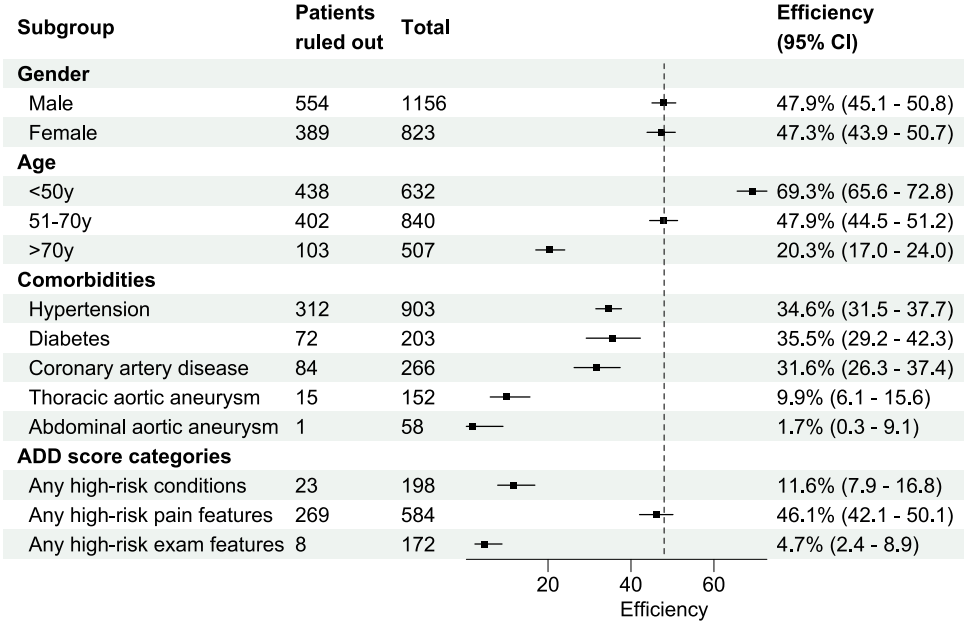

Fig. 5. Forrest plot representing the protocol rule-out efficiency in patient subgroups. Efficiency was calculated as the % of patients satisfying rule-out criteria (intention-to-treat analysis), in whom advanced aortic imaging can be avoided. The dotted line indicates protocol efficiency in the whole cohort. ADD: aortic dissection detection.

Table 3
Diagnostic performance of rule-out strategies.

Rule-out strategy	n.	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	LR+	LR-	Failure rate (%)
low POCUS-integrated PTP plus D-dimer <500 ng/mL	1975	176	859	940	0	100 (97.9–100)	52.3¶ (49.9–54.6)	2.09 (2–2.20)	0 (0–0.03)	0 (0–0.41)
low POCUS-integrated PTP plus D-dimer <age-adj. cutoff	1975	176	741	1058	0	100 (97.9–100)	58.8¶ (56.5–61.1)	2.43 (2.3–2.57)	0 (0–0.03)	0 (0–0.36)
ADD score ≤1 plus D-dimer <500 ng/mL	1912*	162	802	946	2	98.8 (97.1–100)	54.1§ (51.8–56.5)	2.15 (2.04–2.27)	0.02 (0–0.09)	0.21 (0.06–0.76)
ADD score ≤1 plus D-dimer <age-adj. cutoff	1912*	162	682	1066	2	98.8 (97.1–100)	61§ (58.7–63.3)	2.53 (2.38–2.69)	0.02 (0–0.08)	0.19 (0.05–0.68)

4 patients lost to follow-up were excluded (see text). ADD: aortic dissection detection; age-adj.: age-adjusted; PTP: pre-test probability; LR: likelihood ratio (+: positive; -: negative); FN: false negatives; FP: false positives; POCUS: point-of-care ultrasound; TN: true negatives; TP: true positives. *63 patients at high integrated PTP were excluded because D-dimer was not measured, following protocol indications. ¶,§$P < 0.001$.

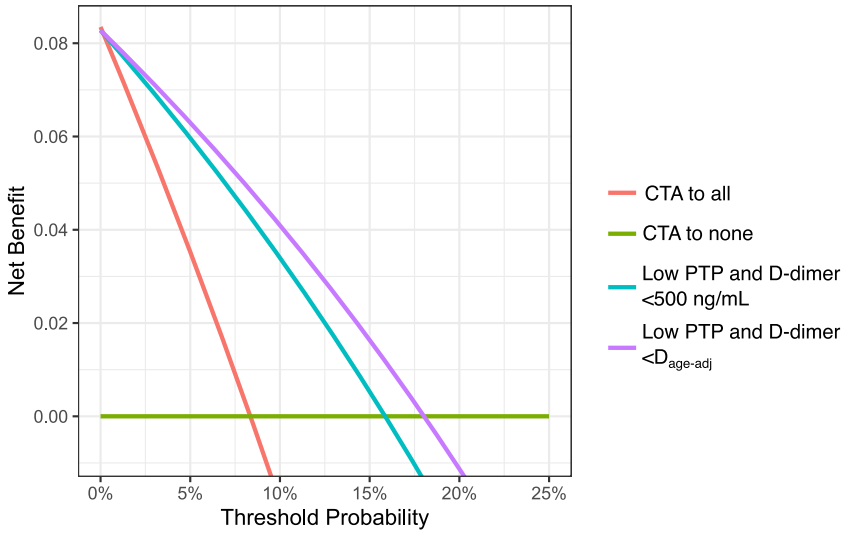

Fig. 6. Decision curve analysis plot depicting the net benefit of the different diagnostic protocols. CTA: computed tomography angiography; PTP: integrated pretest probability of acute aortic syndrome; $D_{age\text{-}adj}$: age-adjusted D-dimer cutoff.

retrospectively analyzed [14,18]. The protocol improved triage of patients towards advanced imaging and allowed safe and efficient AAS rule-out. Using the most conservative analysis, the higher end of the protocol failure rate was 0.41 %, *i.e.* 1 miss in 244 rule-outs. This result is in line with a Canadian national survey, where the majority of emergency clinicians considered acceptable, for an AAS decision tool, a miss rate <1 % [24]. The study failure rate is also coherent with a maximum testing threshold for AD of 0.6 %, for CTA order, found in a decision analysis encompassing D-dimer testing [25].

The diagnostic protocol could avert approximately 2 in 5 CTA orders, similar to algorithms applying pre-test probability with D-dimer for suspected PE [19]. The lowest efficiency was found in patients aged >70 years and in patients with known aortic aneurysm. Accordingly, age-adjusted D-dimer interpretation could increase protocol efficiency especially in elderly patients, without compromising safety, as previously hypothesized [16,17]. Compared to the standard cutoff, $D_{age\text{-}adj}$ could spare about 1 in 16 advanced imaging exams, with the largest gain in patients aged >70 years. The actual advantage of this effect on clinical/organizational endpoints is unknown. Nonetheless, use of $D_{age\text{-}adj}$ for both PE and AAS is practical and could promote guideline adherence.

Results show that an early AAS-targeted POCUS, started within 20 min, is feasible in busy EDs, with several potential benefits. First, in case of positive POCUS, time to conclusive diagnosis was shortened, while turn-around times of D-dimer could delay diagnosis. Second, only 6 % of patients were reclassified by POCUS, but a stunning 39 % of them had AAS. Third, POCUS improved rule-out safety over ADD score alone, since 2 AASs reclassified at high PTP by POCUS, had D-dimer <500 ng/mL (available after advanced imaging). Without POCUS, these cases could have been missed. Finally, POCUS recognition of AAS complications, such as tamponade or aortic regurgitation, has additional value in patient care.

A critique made to PTP/D-dimer based protocols is that, in clinical practice, they may paradoxically increase CTA use, without certain benefits [26]. Further studies focusing on the risk/benefit and cost-effectiveness profile of these protocols are warranted. Nonetheless, in everyday practice, the proposed algorithm is likely to show maximal utility in properly selected patients based on three-dimensional clinical judgment, especially amongst elderly patients.

4.1. Limitations

The study did not perform advanced imaging in all patients, as routinely done in diagnostic studies of pulmonary embolism and myocardial infarction. Few patients with rule-out criteria, affected by self-limiting forms of AAS (*e.g.* limited tears, small tybe B IMH/PAU), might have been missed. Therefore, the study may underestimate the risk of overlooking milder AAS forms. Since POCUS has lower accuracy for tears/IMH/PAU and type B forms, misdiagnosis risk could be higher in patients with these subtypes. To improve detection of type B forms, scanning of the abdominal aorta should be routinely added to the POCUS protocol. The study also did not evaluate the potentially negative impact of the protocol on detection of other diseases, both aortic and non-aortic. However, it must be stressed that the 30-day mortality was 0 % in patients with rule-out criteria, indicating general safety in the

short term.

Despite the number of involved physicians was large, results were mostly obtained in centers expert in POCUS and AAS. POCUS exams were not recorded nor centrally evaluated, thus limiting generalizability. However, we previosuly showed that interobserver agreement of POCUS for ascending aorta dilatation is excellent [27]. Another limit is that protocol adherence was suboptimal. Protocol violations included both an excess (6.5 %) and lack (13 %) of advanced imaging. Better adherence could reduce advanced imaging in patients with rule-out criteria and increase imaging in patients with rule-in criteria. Finally, different D-dimer assays have been previously shown to slightly differ in sensitivity and specificity, when applied for suspected venous thromboembolism [28]. In the current study, most patients were tested with the HemosIL or STA-Liatest assays. It is possible that small discrepancies in protocol accuracy may be caused by local laboratory assays and standards.

5. Conclusions

A diagnostic strategy using POCUS-integrated PTP plus D-dimer safely ruled out AAS. POCUS improved identification of patients requiring urgent CTA. The protocol averted advanced imaging in 41 % of patients. A modified protocol using age-adjusted D-dimer could increase this percentage to 54 %, further reducing the need for advanced aortic imaging, without compromising safety.

Acknowledgments

FM received grants from the Università degli Studi di Torino (MORF_RILO_21_02, MORF_RILO_23_03). EL received a grant from Fondazione Ricerca Molinette (2023). We thank all the ED staff members, arch. Silvia Raule (graphical editing, data management) and dr. Silvia Tarditi (data management), both from Turin, Italy.

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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.2024.05.029.

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