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CLINICAL RESEARCH
Vascular medicine

Integration of transthoracic focused cardiac ultrasound in the diagnostic algorithm for suspected acute aortic syndromes

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Aims The diagnosis of acute aortic syndromes (AASs) is challenging and requires integrated strategies. Transthoracic focused cardiac ultrasound (FoCUS) is endorsed by guidelines as a first-line/triage tool allowing rapid bedside assessment of the aorta. However, the performance of FoCUS in the European Society of Cardiology-recommended workup of AASs awaits validation.

Methods and results This was a prespecified subanalysis of the ADvISED multicentre prospective study. Patients with suspected AAS underwent FoCUS for detection of direct/indirect signs of AAS. Clinical probability assessment was performed with the aortic dissection detection risk score (ADD-RS). Case adjudication was based on advanced imaging, surgery, autopsy, or 14-day follow-up. An AAS was diagnosed in 146 (17.4%) of 839 patients. Presence of direct FoCUS signs had a sensitivity and specificity of 45.2% [95% confidence interval (CI) 37–53.6%] and 97.4% (95% CI 95.9–98.4%), while presence of any FoCUS sign had a sensitivity and specificity of 89% (95% CI 82.8–93.6%) and 74.5% (95% CI 71–77.7%) for AAS. The additive value of FoCUS was most evident within low clinical probability (ADD-RS ≤1). Herein, direct FoCUS signs were identified in 40 (4.8%) patients ($P < 0.001$), including 29 with AAS. ADD-RS ≤1 plus negative FoCUS for AAS rule-out had a sensitivity of 93.8% (95% CI 88.6–97.1%) and a failure rate of 1.9% (95% CI 0.9–3.6%). Addition of negative D-dimer led to a failure rate of 0% (95% CI 0–1.2%).

Conclusion FoCUS has additive value in the workup of AASs. Direct FoCUS signs can rapidly identify patients requiring advanced imaging despite low clinical probability. In integrated bundles, negative FoCUS is useful for rule-out of AASs.

Keywords Aortic dissection • Aortic syndrome • Diagnosis • Echocardiography • Ultrasound

Introduction

Acute aortic syndromes (AASs) are deadly cardiovascular emergencies affecting 4–6 cases/100 000 individuals/year.[1] Their diagnosis is challenging because symptoms are unspecific and advanced imaging with computed tomography angiography (CTA) or transoesophageal echocardiography (TOE) is required for conclusive diagnosis.[1,2] However, these techniques cannot be performed in all patients with compatible symptoms, owing to radiation and contrast exposure, and to limits in resource availability and costs. This defines a

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diagnostic conundrum apparent in Emergency Department (ED) practice: misdiagnosis of AASs reaches 39% but the rate of positive CTA performed for suspected AASs is <3%.[3–6]

To overcome this problem, algorithms allowing rapid, affordable, and large-scale diagnostic standardization have been promoted by guidelines.[7,8] According to the European Society of Cardiology (ESC) guidelines, the aortic dissection detection risk score (ADD-RS) should be used to define if the pre-test probability of AAS is low (ADD-RS ≤1) or high (ADD-RS >1). For patients at high probability of AAS, CTA/TOE is warranted. For patients at low probability, instead, decision on CTA/TOE necessitates additional evaluations.

Echocardiography, a safe and inexpensive tool easily applicable at the patient's bedside in the form of a focused cardiac ultrasound (FoCUS), has been widely adopted for evaluation of acute patients.[9,10] Ultrasound allows visualization of the thoracic aorta and can detect both direct and indirect signs of AASs, with higher accuracy for proximal forms.[11–15] Accordingly, the ESC and the European Association of Echocardiography have indicated transthoracic echocardiography as an appropriate triage/first-line imaging technique for suspected AAS.[8,16] In particular, the role of FoCUS appears key for ultimate decision on CTA/TOE in patients at low probability of AAS, in whom also D-dimer is recommended. However, FoCUS accuracy in this setting has not been prospectively assessed so far.

The current study was designed to address this gap in evidence and to provide on-field validation of the ESC algorithm. Working hypotheses were the following: (i) FoCUS can help to rapidly identify patients requiring CTA/TOE despite low clinical probability of AAS and (ii) in conjunction with low clinical probability, negative FoCUS plus negative D-dimer defines a safe rule-out strategy for AASs.

Methods

Study design

This was a predefined secondary analysis of the ADvISED prospective multicentre diagnostic accuracy study (ClinicalTrials.gov, No. NCT02086136), on data from five centres (all tertiary hospitals) in four countries.[17] The study complied with the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent of participants was obtained.

Enrolment

From September 2014 to December 2016, consecutive outpatients aged >18 years presenting to the ED were eligible if they experienced ≥1 of the following symptoms dating ≤14 days: chest/abdominal/back pain, syncope, and signs/symptoms of perfusion deficit. The latter were defined as symptoms compatible with malperfusion to any of the following organs: central/peripheral nervous system, myocardium, abdominal organs, and limbs. Patients were included only if AAS was considered in differential diagnosis by the attending physician, and if FoCUS was performed in the ED before advanced diagnostic imaging or surgery. Exclusion criteria were primary trauma and unwillingness/inadequacy to participate. Patients were managed by ≥1 emergency physician. Clinical decisions were determined by the attending physicians irrespective of study participation.

Transthoracic focused cardiac ultrasound

FoCUS was performed by a cardiologist or by a non-cardiologist physician (internal or emergency medicine physician) with ≥1 year of experience in FoCUS, immediately after enrolment and before advanced aortic imaging tests or surgery. The following multiprobe machines with a 2–5 MHz phased array probe were used: two MyLab 5, two MyLab30 Gold, two MyLab alpha (Esaote, Genova, Italy), one HD7 (Koninklijke Philips, Amsterdam, Netherlands), three Vivid S5, and one Vivid S6 (GE Healthcare, Wauwatosa, WI, USA). Evaluation of the aorta was performed with the patient in the supine or left lateral decubitus positions, using ≥1 of the following views: left/right parasternal, apical, suprasternal, subcostal, abdominal, and view for carotid arteries. The following were considered as direct sonographic signs of AAS: presence of an intimal flap separating two aortic lumens, presence of an intramural aortic haematoma (IMH; circular or crescentic thickening of the aortic wall >5 mm), and presence of a penetrating aortic ulcer (PAU; crater-like outpouching with jagged edges in the aortic wall). The following echocardiographic findings were also researched as potential indirect sonographic signs of AAS: thoracic aorta dilatation (diameter ≥4 cm), pericardial effusion or tamponade, and aortic valve regurgitation at colour Doppler (*Figure 1* and Supplementary material online, *Videos S1–S4*). After FoCUS completion, the sonographer completed a standardized form (Supplementary material online, *Figure S1*).

Clinical probability

The tool used to assess the clinical probability of AAS was the ADD-RS, based on presence/absence of 12 risk markers classified in three categories.[18] The ADD-RS of each patient was calculated as the number of categories where ≥1 risk marker was present. *Per* ESC guidelines, patients with ≥1 risk markers in 0 or 1 risk category (ADD-RS ≤1) were classified at low probability, while patients with ≥1 risk markers in >1 categories (ADD-RS >1) were classified at high probability.[8]

D-dimer

Patients were subjected to venous sampling during the ED visit. Venous samples were immediately sent to the local laboratory for automated D-dimer assay. The test result was defined negative if <500 ng/mL fibrinogen equivalent units.

Advanced imaging

The primary conclusive imaging method was chest and abdomen contrast-enhanced multi-detector CTA (≥64 row detectors). Other methods accepted for conclusive diagnosis of AASs were TOE and magnetic resonance angiography (MRA). Exams were performed and interpreted by specialized physicians not involved in the study.

Follow-up

All patients for whom conclusive diagnostic data was not obtained during the ED visit by advanced imaging (CTA/TOE/MRA) or surgery, entered a clinical follow-up for case adjudication.[17] Patients dismissed without conclusive diagnostic data were instructed to return to the ED in case of new, worsening, or recurrent symptoms. After 14 days, patients or family members were interviewed by telephone using a structured questionnaire or underwent an outpatient visit. The following events were queried: diagnosis of any aortic disease, ED visit, admission to hospital, and death.

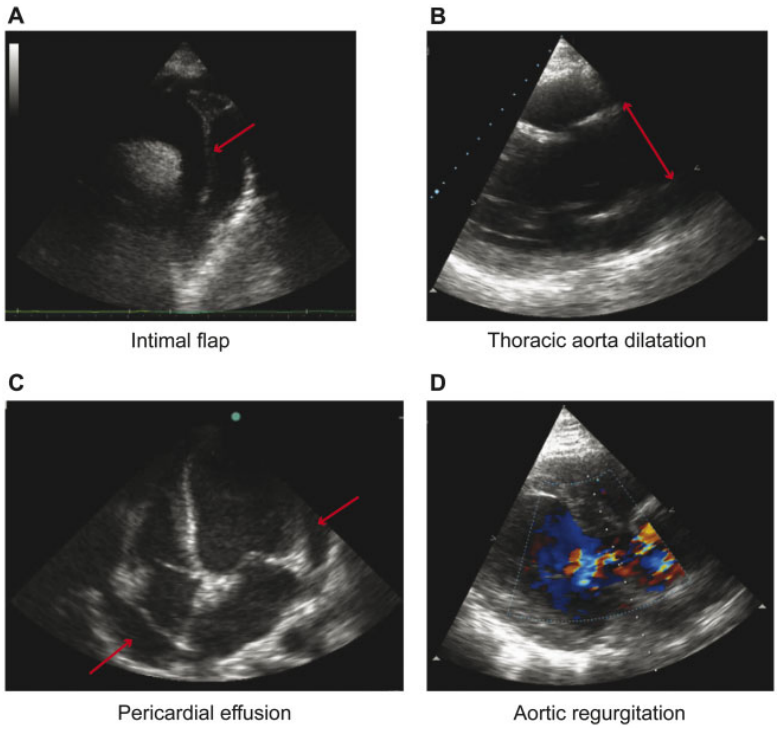


Figure 1 Representative focused cardiac ultrasound findings (still images) of acute aortic syndromes. (*A*) Intimal flap (suprasternal view), indicated by a red arrow. (*B*) Ascending aorta dilatation (>4 cm, left parasternal view, leading edge measurement as indicated by red arrow). (*C*) Pericardial effusion (apical view), indicated by two red arrows. (*D*) Aortic valve regurgitation (left parasternal view, colour Doppler). Still images were obtained from Supplementary material online, *Videos S1–S4*.

Case definition and adjudication

The following aetiological entities were considered in the definition of AASs based on the Svensson's classification: acute aortic dissection (AAD), IMH, PAU, and spontaneous aortic rupture (SAR).[19] Local dissection and traumatic forms were excluded. Anatomical involvement was defined with the Stanford classification. Case adjudication was performed by two expert physicians who independently reviewed the diagnostic data obtained during the ED visit and the follow-up period. For all patients admitted to hospital after the ED visit or with novel ED visits, medical records with full diagnostic data were carefully reviewed.

Case adjudication was dichotomic: AAS present or absent. A case of AAS was defined by evidence of AAS on CTA/TOE/MRA, surgery, or autopsy. An AAS was considered absent based on negative results of CTA/TOE/MRA, surgery, or autopsy. If such data were not available, adjudication was clinical. An AAS was considered absent: (i) in patients admitted to hospital after the ED visit if an alternative diagnosis (AltD) was available and (ii) in patients dismissed from the ED, if they had an uncomplicated clinical course or in presence of an AltD during the follow-up period in subsequent medical evaluations. For deaths occurring in patients in follow-up without conclusive imaging, surgery, or autopsy data, adjudication was also clinical, based on all available pre-mortem data. In these cases, an AAS was adjudicated as present if alternative death causes were confidently ruled out by both reviewers. In case of discordance, cases were adjudicated after discussion.

Sample size

We aimed at including enough patients to provide accurate estimates, focusing on the exclusion of AASs with a minimum of missed of cases. Based on previous studies, we assumed that the point estimate of the failure rate of the composite diagnostic rule-out strategy (ADD-RS ≤1/FoCUS-/D-dimer-) would be 0.2%.[15,20] The present study was powered to test the null hypothesis that the failure rate of the indicated diagnostic rule-out strategy exceeds 2%. Using a Type I error of 0.05 (one sided) and a Type II error of 0.2, we needed to include about 222 participants with ADD-RS ≤1/FoCUS-/D-dimer- to reject the null hypothesis. Hypothesizing that individuals satisfying rule-out criteria would be around 30% of total patients with suspected AAS, we estimated that at least 740 patients needed to be included.

Statistical analysis

Dichotomous data were expressed as proportions with 95% confidence interval (CI) using the Wilson's method and continuous data were expressed as mean ± standard deviation (SD). The Fisher's exact test was used for comparison of dichotomous data and the unpaired Student's *t*-test was used for continuous data.

To evaluate diagnostic performance, the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) cases were assessed. Sensitivity, specificity, negative/positive predictive values, and likelihood ratios were computed. Receiver operating characteristic (ROC) curves were obtained. The area under the curve (AUC) was

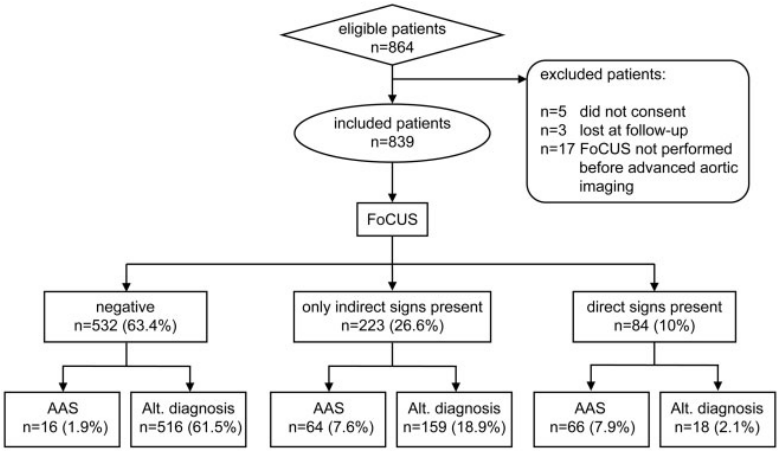


Figure 2 A flow diagram of the study. AAS, acute aortic syndrome; Alt., alternative; direct signs: intimal flap, intramural aortic haematoma, or penetrating aortic ulcer; FoCUS, transthoracic focused cardiac ultrasound; FoCUS negative: no direct or indirect signs of acute aortic syndrome; indirect signs: ascending aorta dilatation, pericardial effusion/tamponade, or aortic valve regurgitation. % refers to 839 study patients.

computed and compared *per* Hanley and McNeil. For rule-out strategies, the failure rate was = (number of adjudicated AAS diagnoses): (number of patients satisfying rule-out criteria), and efficiency was = (number of patients satisfying rule-out criteria): (number of enrolled patients). A Fagan nomogram was developed to visualize the effect of FoCUS findings on the probability of AAS.

To evaluate the statistical significance of a bundle integrating ADD-RS, FoCUS, and D-dimer, a tree-based classification model was used. The target variable was AAS, while ADD-RS, D-dimer, and FoCUS results were used as predictors. In compliance with guidelines, ADD-RS was forced to be the first split variable in the model. The growing method used was the χ^2 automatic interaction detection based on adjusted significance testing.

P-values were two-sided, and $P < 0.05$ was considered significant. The analysis was performed with the SPSS statistical package (version 25.0, SPSS Inc., Chicago, IL, USA).

Results

Study population

Eight hundred and sixty-four patients with suspected AAS underwent FoCUS, and 839 were further analysed (*Figure 2*). Presenting symptoms were anterior chest pain (568, 67.7%), posterior chest pain (264, 31.5%), lumbar pain (58, 6.9%), abdominal pain (149, 17.8%), syncope (59, 21%), and symptoms of perfusion deficit (83, 9.9%). Details on the diagnostic workup are presented in Supplementary material online, *Figure S2*.

An AAS was adjudicated in 146 (17.4%) patients: Type A AAD in 85 (10.1%) patients, Type B AAD in 27 (3.2%), IMH in 20 (2.4%), SAR in 11 (1.3%), and PAU in 3 (0.4%). In 693 (82.6%) patients, an AAS was adjudicated as absent, with the following AltD: muscle–skeletal chest pain (221 patients, 26.3%), gastrointestinal disease (101, 12%), acute coronary syndrome (91, 10.8%), syncope (52, 6.2%), pericarditis (46, 5.5%), pleuritis or pneumonia (21, 2.5%), uncomplicated aortic aneurysm (19, 2.3%), pulmonary embolism (17, 2%), stroke (15, 1.2%), limb ischaemia (2, 0.2%), and other diagnosis (114, 13.6%). *Table 1* reports the clinical characteristics of study patients.

Diagnostic accuracy of focused cardiac ultrasound

FoCUS was performed by a cardiologist in 170 (20.3%) patients and by a non-cardiologist physician in 669 (79.7%). The following FoCUS views where used: left parasternal 809 (96.9%), apical 756 (90.3%), subcostal 541 (64.7%), suprasternal 155 (18.5%), abdominal 123 (14.7%), right parasternal 25 (3%), and views for carotid arteries 56 (6.7%). A poor acoustic window was reported in 74 (8.8%) patients. Direct FoCUS signs of AAS were detected in 84 (10%) patients, including 45 Type A AADs, 11 Type B AADs, five IMHs, four SARs, and one PAU. The FP cases were 18 and the FN cases were 80. Any FoCUS sign of AAS was detected in 307 (36.6%) patients, including 82 Type A AADs, 20 Type B AADs, 15 IMHs, 10 SARs, and three PAUs. The FP cases were 177 and the FN cases were 16. The diagnostic performance of FoCUS for AASs is presented in *Figure 3* and Supplementary material online, *Table S1*. When FoCUS was performed by a cardiologist, the sensitivity associated with direct signs was higher compared with non-cardiologist ($P < 0.001$; Supplementary material online, *Table S2*).

Additive value of focused cardiac ultrasound

In multivariable logistic regression analysis, FoCUS findings except aortic valve regurgitation were independent positive predictors of AASs, in addition to clinical variables and D-dimer (Supplementary material online, *Table S3*). ROC analysis further showed that integration of FoCUS with clinical probability assessment by ADD-RS significantly increased the diagnostic accuracy for AASs (*Figure 4*A). A Fagan nomogram was used to visualize the additive value of FoCUS

Table 1 Demographic and clinical characteristics of study patients

	All patients ($n = 839$)	AAS ($n = 146$)	AltD ($n = 693$)	*P*-value
Female gender	299 (35.6)	43 (29.5)	256 (36.9)	0.09
Age (years)	62 ± 16.7	67.5 ± 14.2	60.9 ± 17	<0.01
Predisposing conditions				
Marfan syndrome/connective tissue disease	7 (0.8)	1 (0.7)	6 (0.9)	1
Family history of aortic disease	16 (1.9)	3 (2.1)	13 (1.9)	0.74
Known aortic valve disease	50 (6)	11 (7.5)	39 (5.6)	0.33
Recent aortic manipulation	14 (1.7)	2 (1.4)	12 (1.7)	1
Known thoracic aortic aneurysm	87 (10.4)	24 (16.4)	63 (9.1)	0.01
Pain features				
Abrupt onset of pain	319 (38)	100 (68.5)	219 (31.6)	<0.01
Severe pain intensity	361 (43)	102 (69.9)	259 (37.4)	<0.01
Ripping or tearing pain	80 (9.5)	30 (20.5)	50 (7.2)	<0.01
Physical findings				
Pulse deficit/systolic blood pressure differential	64 (7.6)	32 (21.9)	32 (4.6)	<0.01
Focal neurological deficit	49 (5.8)	20 (13.7)	29 (4.2)	<0.01
Murmur of aortic regurgitation	14 (1.7)	9 (6.2)	5 (0.7)	<0.01
Shock/hypotension	81 (9.7)	43 (29.5)	38 (5.5)	<0.01

Age is reported as mean ± standard deviation. Categorical variables are expressed as absolute number and percent value (in brackets). *P*-value significant if <0.05 (AAS vs. AltD).
AAS, acute aortic syndrome; AltD, alternative diagnosis.

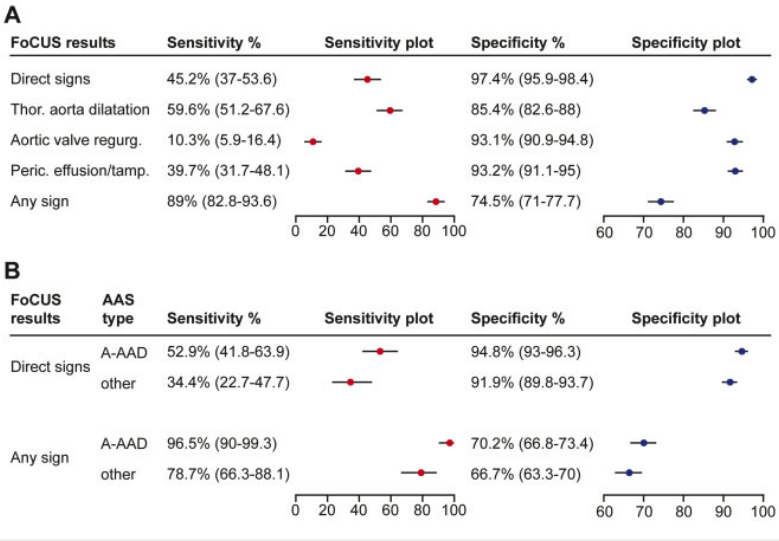


Figure 3 (*A*) Sensitivity and specificity of focused cardiac ultrasound results for diagnosis of acute aortic syndrome. (*B*) Sensitivity and specificity of focused cardiac ultrasound results for diagnosis of Type A acute aortic dissection or other types of acute aortic syndrome.

(*Figure 4B*). In 671 (80%) patients with ADD-RS ≤1 (defining low clinical probability of AAS *per* ESC), 67 patients had AAS. Hence, the prior probability of AAS in this group was 10%. Detection of direct FoCUS signs led to a posterior probability (post *P*) of AAS of ≈65%, while absence of direct FoCUS signs of AAS led to a post *P* of ≈6%. Detection of any FoCUS sign of AAS led to a post *P* of ≈28%, while absence of any FoCUS sign of AAS led to a post *P* of ≈2%.

Use of 'direct FoCUS sign present' as a criterion for reclassification of patients at high integrated probability of AAS applied to 40 (4.8%)

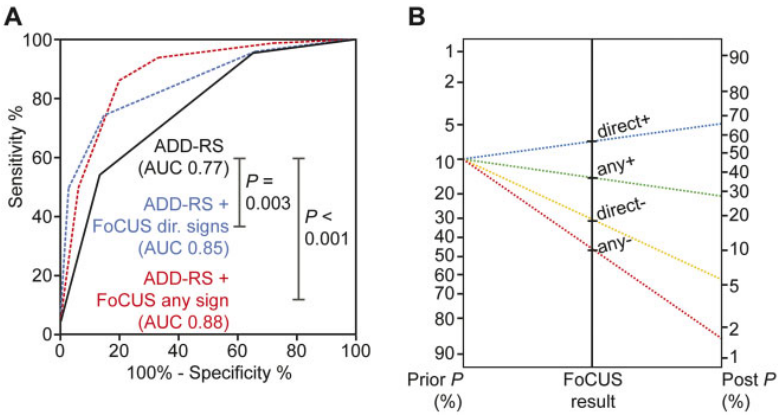


Figure 4 Additive diagnostic value of focused cardiac ultrasound to clinical probability assessment. (*A*) Receiver operating characteristic curves for diagnosis of acute aortic syndrome of the aortic dissection detection risk score (ADD-RS, black line), aortic dissection detection risk score plus focused cardiac ultrasound direct signs (ADD-RS + FoCUS dir. signs, blue line), and aortic dissection detection risk score plus focused cardiac ultrasound any sign (ADD-RS + FoCUS any sign red line). AUC, area under the curve. (*B*) Fagan nomogram showing the additive effect of focused cardiac ultrasound to clinical probability assessment. The clinical probability of acute aortic syndrome is displayed on the left as 'Prior *P*'. The middle line represents the result of focused cardiac ultrasound (FoCUS). When a straight line is drawn through the prior *P* and focused cardiac ultrasound result, the post-test *P* of acute aortic syndrome is found on the right line ('Post *P*'). The representative dotted lines represent the effect of focused cardiac ultrasound findings for patients at low clinical probability of acute aortic syndrome. any-, absence of any sign; any+, presence of any sign (direct or indirect); direct-, absence of direct signs; direct+, presence of direct signs of acute aortic syndrome.

patients ($P < 0.001$ vs. ADD-RS alone, Supplementary material online, *Table S4*), including 29 with AAS. Use of 'absence of any FoCUS sign' as a criterion confirming patients at low integrated probability of AAS applied to 476 (56.7%) patients, including nine with AAS. Using ADD-RS ≤1 plus negative FoCUS for rule-out of AAS, the sensitivity was 93.8% (95% CI 88.6–97.1%) and the failure rate was 1.9% (95% CI 0.9–3.6%), corresponding to one missed case in 52 patients with AAS (Supplementary material online, *Table S5*).

Integrated rule-out strategy

A D-dimer test result was available in 812 (96.8%) study patients, including 652 with ADD-RS ≤1 (*Figure 5* and Supplementary material online, *Figure S3*). In this group, D-dimer was FN in 2 (0.3%) patients with AAS, who presented both direct and indirect FoCUS signs of AAS. Decision-tree analysis validated ADD-RS, FoCUS, and D-dimer as significant diagnostic classification nodes for AAS and confirmed significance of sequential application of FoCUS and D-dimer for AAS rule-out in patients with ADD-RS ≤1 (Supplementary material online, *Figure S4*). The performance of a diagnostic rule-out strategy integrating ADD-RS, FoCUS, and D-dimer is detailed in *Table 2*. The AUC-ROC and model optimism estimates for the integrated diagnostic strategies are presented in Supplementary material online, *Table S6*.

Discussion

In the last decade, increase of CTA use in EDs has not substantially affected the misdiagnosis rate of AASs, inferring that improvement of diagnostic algorithms in this field is a primary objective. The present is by far the largest prospective study of FoCUS for AASs. Current results validate ESC recommendations for FoCUS as a tool providing relevant bedside data in the diagnostic approach to suspected AAS and support its adoption in clinical practice. The main utility of FoCUS is represented by identification of direct signs of AASs in a relatively small but significant subset of patients at low clinical probability. In these stable patients, representing ≈80% of individuals in whom AASs are considered in differential diagnosis, decision on CTA/TOE is notoriously difficult and both misdiagnosis (leading to diagnostic delay, inappropriate treatments, and ED dismissal) and over-testing are major concerns.[3–6]

Within minutes, bedside FoCUS can identify red flags warranting urgent aortic imaging or transfer to expert centres. The trade-off in terms of false positives appears largely favourable if direct FoCUS signs are used for rapid reclassification of patients. Use of indirect FoCUS sign, instead, is associated with a substantially higher false positive rate and appears more questionable for routine probability up-grading. A similar role was originally intended for chest radiography. However, given the low diagnostic accuracy of this technique, radiation exposure and long turn-around time, the role of chest radiography in the routine approach to AASs needs further scrutiny.[21]

Study results clearly recapitulate the known limits of transthoracic echocardiography for evaluation of the thoracic aorta.[11–15] The highest diagnostic sensitivity was found for AAS forms involving the ascending aorta and dropped for AAS forms involving exclusively the descending aorta. The notion that FoCUS as a standalone test may not be used for conclusive rule-out of AASs should therefore be stressed. This applies also to patients at low clinical probability, owing to a suboptimal sensitivity and failure rate. Nonetheless, a key finding of the present study is that integration of FoCUS with D-dimer provided an exceptionally safe and fairly efficient rule-out criterion for

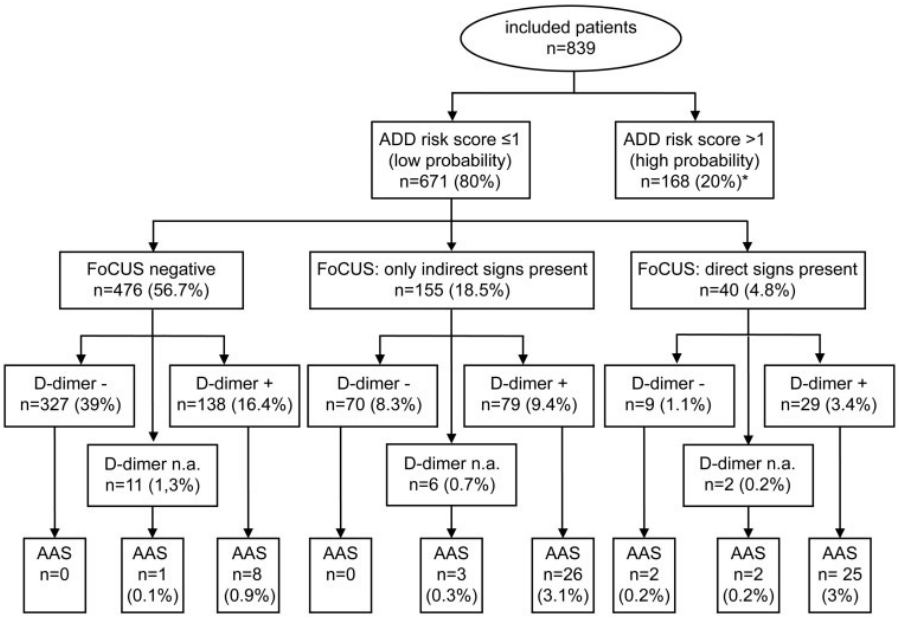


Figure 5 Results of focused cardiac ultrasound and D-dimer test in patients classified at low clinical probability. D-dimer test + if ≥500 ng/mL. % refers to 839 study patients. *Data are presented in Supplementary material online, *Figure S3*. AAS, acute aortic syndrome; ADD, aortic dissection detection; n.a., not available.

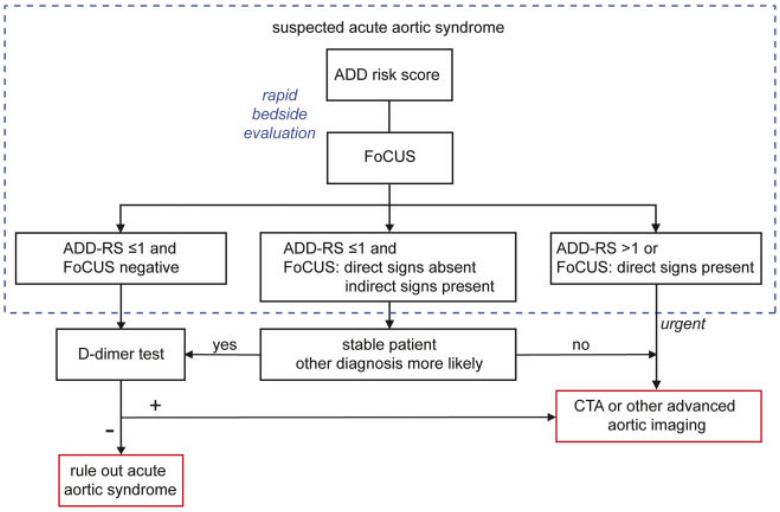
Table 2 Diagnostic performance of strategies integrating aortic dissection detection risk score, focused cardiac ultrasound, and D-dimer for rule-out of acute aortic syndromes

	ADD-RS ≤1 and direct FoCUS signs absent and D-dimer <500 ng/mL	ADD-RS ≤1 and FoCUS negative[a] and D-dimer <500 ng/mL
Number of patients ruled out (AAS–AltD)	397 (0–397)	327 (0–327)
Sensitivity, % (95% CI)	100 (97.3–100%)	100 (97.3–100%)
Specificity, % (95% CI)	58.7 (55–62.4%)	48.4 (44.6–52.1%)
PPV, % (95% CI)	32.8 (28.4–37.4%)	28 (24.2–32.2%)
NPV, % (95% CI)	100 (99–100%)	100 (98.8–100%)
+LR (95% CI)	2.42 (2.2–2.64)	1.94 (1.79– 2.08)
-LR (95% CI)	0 (0–0.1)	0 (0–0.12)
Failure rate, % (95% CI)	0 (0–0.96%)	0 (0–1.16%)
Efficiency, % (95% CI)	48.9 (45.5–52.3%)	40.3 (37–43.7%)

95% CI, 95% confidence interval; AAS, acute aortic syndrome; AltD, alternative diagnosis; +LR, positive likelihood ratio; -LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
[a]Absence of all FoCUS signs of acute aortic syndromes.

AASs. Previous studies have shown that D-dimer is highly sensitive for AASs.[22,23] Based on present results, the probability of an AAS is extremely low in patients at low clinical probability without direct FoCUS signs of AAS and a negative D-dimer. Practical considerations indicate that CTA/TOE could be omitted without consequences even in patients with only indirect FoCUS signs if D-dimer is negative, provided case-by-case evaluation of alternative diagnoses and clinical stability.

With respect to technical issues, only a minority of patients presented an inadequate sonographic window, indicating that FoCUS can provide diagnostic data in most cases. FoCUS data were mostly obtained from the left parasternal echocardiographic view.



Take home figure Proposed diagnostic algorithm based on experimental results and clinical judgement. ADD-RS, aortic dissection detection risk score; CTA, computed tomography angiography; FoCUS, transthoracic focused cardiac ultrasound.

The highest diagnostic performance was obtained by specialized cardiologists for Type A AAD, as previously reported.[13] In our study, cardiologist providers showed increased capacity to identify direct signs of AASs as compared to non-cardiologists, but the overall diagnostic performance was similar when also indirect signs were considered. The utility of FoCUS also for the evaluation of alternative diagnoses (e.g. pulmonary embolism, acute coronary syndromes, and decompensated heart failure) and for detection of AAS complications (e.g. cardiac tamponade and aortic valve regurgitation), further support large-scale implementation of this tool in EDs.

Limitations

The present study constitutes a prespecified subanalysis of the ADvISED trial, whose aim was to evaluate the diagnostic characteristics of D-dimer for rule-out of AASs.[17] Therefore, current analyses provide primary incremental evidence only for FoCUS, while the results obtained for D-dimer-based strategies are not fully independent from previous findings. Further studies on new cohorts are needed for their external validation. Second, the study was performed at tertiary centres where FoCUS is routinely applied and results may not apply to contexts with limited experience/availability. Third, for ethical reasons operators were unblinded to all diagnostic variables, thus potentially introducing some degree of selection bias. Fourth, advanced aortic imaging data were available only for half study patients. However, patients not subjected to CTA/TOE in the ED were followed-up for case adjudication: the majority were hospitalized after the index visit, underwent thorough clinical scrutiny and independent medical evaluation, while only 5.8% were dismissed from the ED. Nonetheless, we cannot exclude with certainty that few cases of AAS with mild/atypical symptoms might have been missed. Finally, the study was not powered to detect statistical differences between different rule-out strategies.

Conclusions

Detection of direct FoCUS signs of AAS should prompt to advanced aortic imaging irrespective of clinical probability classification. In patients at low probability, integration of FoCUS with D-dimer provides a safe and efficient method to decide on urgent CTA/TOE. A diagnostic flowchart integrating study results with additional clinical considerations is proposed in *Take home figure*. Further studies are warranted for external validation, especially to define the best rule-out protocol.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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