

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1715430> since 2019-11-13T17:49:52Z

*Published version:*

DOI:10.1093/eurheartj/ehz207

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

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

Peiman Nazerian, M.D.<sup>1\*</sup>, Christian Mueller, M.D.<sup>2</sup>, Simone Vanni, M.D. Ph.D.<sup>1</sup>, Alexandre de Matos Soeiro, M.D.<sup>3</sup>, Bernd A. Leidel, M.D.<sup>4</sup>, Gabriele Cerini, M.D.<sup>1</sup>, Enrico Lupia, M.D. Ph.D.<sup>5</sup>, Andrea Palazzo B.I.<sup>1</sup>, Stefano Grifoni, M.D.<sup>1</sup>, Fulvio Morello, M.D. Ph.D.<sup>5</sup>

<sup>1</sup>Department of Emergency Medicine, Careggi University Hospital, Firenze, Italy.

<sup>2</sup>Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital of Basel, Basel, Switzerland

<sup>3</sup>Emergency Care Unit, Heart Institute, University of Sao Paulo, Brazil

<sup>4</sup>Department of Emergency Medicine, Campus Benjamin Franklin, Charite – Universitätsmedizin Berlin, Germany

<sup>5</sup>S.C.U. Medicina d’Urgenza, Molinette Hospital, A.O.U. Città della Salute e della Scienza, Torino, Italy.

\*On behalf of WINFOCUS and US SIMEU study group

**Corresponding author:** Peiman Nazerian, MD; Department of Emergency Medicine, Careggi University Hospital, largo Brambilla 3, 50134 Firenze, Italy; [pnazerian@hotmail.com](mailto:pnazerian@hotmail.com).

**Conflicts of interest:** the authors have no potential conflict of interest to disclose.

## ABSTRACT

1 **Aims.** The diagnosis of acute aortic syndromes (AAS) is challenging and requires integrated strategies.  
2  
3 Transthoracic focused cardiac ultrasound (FoCUS) is endorsed by guidelines as a first-line/triage tool  
4  
5 allowing rapid bedside assessment of the aorta. However, the performance of FoCUS in the European  
6  
7 Society of Cardiology-recommended workup of AAS awaits validation.  
8

9  
10  
11 **Methods and results.** This was a prespecified subanalysis of the ADvISED multicenter prospective study.  
12  
13 Patients with suspected AAS underwent FoCUS for detection of direct/indirect signs of AAS. Clinical  
14  
15 probability assessment was performed with the aortic dissection detection risk score (ADD-RS). Case  
16  
17 adjudication was based on advanced imaging, surgery, autopsy or 14-day follow-up.  
18  
19  
20  
21  
22

23 **Results.** AAS was diagnosed in 146 (17.4%) of 839 patients. Presence of direct FoCUS signs had a  
24  
25 sensitivity and specificity of 45.2% (95%CI, 37-53.6%) and 97.4% (95%CI 95.9-98.4%), while presence of  
26  
27 any FoCUS sign had a sensitivity and specificity of 89% (95%CI 82.8-93.6%) and 74.5% (95%CI 71-77.7%)  
28  
29 for AAS. The additive value of FoCUS was most evident within low clinical probability (ADD-RS $\leq$ 1).  
30  
31 Herein, direct FoCUS signs were identified in 40 (4.8%) patients ( $p<0.001$ ), including 29 with AAS. ADD-  
32  
33 RS $\leq$ 1 plus negative FoCUS for AAS rule-out had a sensitivity of 93.8% (95%CI 88.6-97.1%) and a failure  
34  
35 rate of 1.9% (95%CI 0.9-3.6%). Addition of negative D-dimer lead to a failure rate of 0% (95%CI 0-1.2%).  
36  
37  
38  
39  
40

41 **Conclusions.** FoCUS has additive value in the workup of AAS. Direct FoCUS signs can rapidly identify  
42  
43 patients requiring advanced imaging despite low clinical probability. In integrated bundles, negative FoCUS  
44  
45 is useful for rule-out of AAS.  
46  
47  
48  
49

50 **KEY WORDS:** aortic dissection, aortic syndrome, diagnosis, echocardiography, ultrasound.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## INTRODUCTION

1 Acute aortic syndromes (AAS) are deadly cardiovascular emergencies affecting 4-6 cases/100.000  
2  
3 individuals/year.<sup>1</sup> Their diagnosis is challenging because symptoms are unspecific and advanced imaging  
4  
5 with computed tomography angiography (CTA) or transesophageal echocardiography (TEE) is required for  
6  
7 conclusive diagnosis.<sup>1, 2</sup> However, these techniques cannot be performed in all patients with compatible  
8  
9 symptoms, owing to radiation and contrast exposure and to limits in resource availability and costs. This  
10  
11 defines a diagnostic conundrum apparent in Emergency Department (ED) practice: misdiagnosis of AAS  
12  
13 reaches 39%, but the rate of positive CTA performed for suspected AAS is <3%.<sup>3-6</sup>

14  
15  
16 To overcome this problem, algorithms allowing rapid, affordable and large-scale diagnostic  
17  
18 standardization have been promoted by guidelines.<sup>7, 8</sup> According to the European Society of Cardiology  
19  
20 (ESC) guidelines, the aortic dissection detection risk score (ADD-RS) should be used to define if the pre-test  
21  
22 probability of AAS is low ( $ADD-RS \leq 1$ ) or high ( $ADD-RS > 1$ ). For patients at high probability of AAS,  
23  
24 CTA/TEE is warranted. For patients at low probability, instead, decision on CTA/TEE necessitates  
25  
26 additional evaluations.  
27

28  
29 Echocardiography, a safe and inexpensive tool easily applicable at the patient's bedside in the form  
30  
31 of a focused cardiac ultrasound (FoCUS), has been widely adopted for evaluation of acute patients.<sup>9, 10</sup>  
32  
33 Ultrasound allows visualization of the thoracic aorta and can detect both direct and indirect signs of AAS,  
34  
35 with higher accuracy for proximal forms.<sup>11-15</sup> Accordingly, the ESC and the European Association of  
36  
37 Echocardiography have indicated transthoracic echocardiography as an appropriate triage/first-line imaging  
38  
39 technique for suspected AAS.<sup>8, 16</sup> In particular, the role of FoCUS appears key for ultimate decision on  
40  
41 CTA/TEE in patients at low probability of AAS, in whom also D-dimer is recommended. However, FoCUS  
42  
43 accuracy in this setting has not been prospectively assessed so far.  
44  
45  
46

47  
48 The current study was designed to address this gap in evidence and to provide on-field validation of  
49  
50 the ESC algorithm. Working hypotheses were the following: (1) FoCUS can help to rapidly identify patients  
51  
52 requiring CTA/TEE despite low clinical probability of AAS, and (2) in conjunction with low clinical  
53  
54 probability, negative FoCUS plus negative D-dimer define a safe rule-out strategy for AAS.  
55  
56  
57  
58  
59  
60  
61

## METHODS

### *Study design*

This was a predefined secondary analysis of the ADvISED prospective multicenter diagnostic accuracy study (ClinicalTrials.gov, No. NCT02086136), on data from 5 centers (all tertiary hospitals) in 4 countries.<sup>17</sup> 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  $\geq 1$  of the following symptoms dating  $\leq 14$  days: chest/abdominal/back pain, syncope, 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, 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  $\geq 1$  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  $\geq 1$  year of experience in FoCUS. FoCUS was performed 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: 2 MyLab 5, 2 MyLab30 Gold, 2 MyLab alpha (Esaote, Genova, Italy), 1 HD7 (Koninklijke Philips, Amsterdam, Netherlands), 3 Vivid S5 and 1 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  $\geq 1$  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 hematoma (circular

1 or crescentic thickening of the aortic wall >5 mm) and presence of a penetrating aortic ulcer (crater-like  
2 outpouching with jagged edges in the aortic wall). The following echocardiographic findings were also  
3 researched as potential indirect sonographic signs of AAS: thoracic aorta dilatation (diameter  $\geq 4$  cm),  
4  
5  
6 pericardial effusion or tamponade and aortic valve regurgitation at color-doppler (*figure 1* and *videos 1-4*).  
7  
8 After FoCUS completion, the sonographer completed a standardized form (*supplementary figure 1*).  
9

### 10 11 12 ***Clinical probability***

13  
14  
15 The tool used to assess the clinical probability of AAS was the ADD-RS, based on presence/absence  
16 of 12 risk-markers classified in 3 categories.<sup>18</sup> The ADD-RS of each patient was calculated as the number of  
17 categories where  $\geq 1$  risk-marker was present. *Per* ESC guidelines, patients with  $\geq 1$  risk-markers in 0 or 1  
18  
19  
20 risk category (ADD-RS $\leq 1$ ) were classified at low probability, while patients with  $\geq 1$  risk-markers in  $>1$   
21  
22  
23 risk category (ADD-RS $>1$ ) were classified at high probability.<sup>8</sup>  
24  
25  
26  
27  
28  
29  
30

### 31 ***D-dimer***

32  
33 Patients were subjected to venous sampling during the ED visit. Venous samples were immediately  
34 sent to the local laboratory for automated D-dimer assay. The test result was defined negative if  $<500$  ng/mL  
35  
36  
37 fibrinogen equivalent units.  
38  
39  
40  
41

### 42 ***Advanced imaging***

43  
44 The primary conclusive imaging method was chest and abdomen contrast-enhanced multi-detector  
45 CTA ( $\geq 64$  row-detectors). Other methods accepted for conclusive diagnosis of AAS were TEE and magnetic  
46  
47  
48 resonance angiography. Exams were performed and interpreted by specialized physicians not involved in the  
49  
50  
51 study.  
52  
53  
54

### 55 ***Follow-up***

56  
57 In all patients for whom conclusive diagnostic data was not obtained during the ED visit by  
58  
59  
60 advanced imaging (CTA/TEE/MRA) or surgery, entered a clinical follow-up for case adjudication.<sup>17</sup> Patients  
61  
62  
63  
64  
65

1 dismissed without conclusive diagnostic data were instructed to return to the ED in case of new, worsening  
2 or recurrent symptoms. After 14 days, patients or family members were interviewed by telephone using a  
3 structured questionnaire or underwent an outpatient visit. The following events were queried: diagnosis of  
4 any aortic disease, ED visit, admission to hospital, death.  
5  
6  
7  
8

### 9 ***Case definition and adjudication***

10  
11 The following etiological entities were considered in the definition of AAS based on the Svensson's  
12 classification: acute aortic dissection (AAD), intramural aortic hematoma (IMH), penetrating aortic ulcer  
13 (PAU) and spontaneous aortic rupture (SAR).<sup>19</sup> Local dissection and traumatic forms were excluded.  
14  
15 Anatomical involvement was defined with the Stanford classification. Case adjudication was performed by  
16 two expert physicians who independently reviewed the diagnostic data obtained during the ED visit and the  
17 follow-up period. For all patients admitted to hospital after the ED visit or with novel ED visits, medical  
18 records with full diagnostic data were carefully reviewed.  
19  
20  
21  
22  
23  
24  
25  
26

27 Case adjudication was dichotomic: AAS present or absent. A case of AAS was defined by evidence  
28 of AAS on CTA/TEE/MRA, surgery or autopsy. AAS was considered absent based on negative results of  
29 CTA/TEE/MRA, surgery or autopsy. If such data was not available, adjudication was clinical. AAS was  
30 considered absent: (1) in patients admitted to hospital after the ED visit if an alternative diagnosis (AltD)  
31 was available, and (2) in patients dismissed from the ED, if they had an uncomplicated clinical course or in  
32 presence of an AltD during the follow-up period in subsequent medical evaluations. For deaths occurring in  
33 patients in follow-up without conclusive imaging, surgery or autopsy data, adjudication was also clinical,  
34 based on all available *pre-mortem* data. In these cases, AAS was adjudicated as present if alternative death  
35 causes were confidently ruled out by both reviewers. In case of discordance, cases were adjudicated after  
36 discussion.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

### 52 ***Sample size***

53  
54 We aimed at including enough patients to provide accurate estimates, focusing on the exclusion of  
55 AAS with a minimum of missed of cases. Based on previous studies, we assumed that the point estimate of  
56 the failure rate of the composite diagnostic rule-out strategy (ADD-RS<sub>≤1</sub>/FoCUS-/D-dimer-) would be  
57  
58  
59  
60  
61

0.2%.<sup>15, 20</sup> 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 $\leq$ 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% confident interval (CI) using Wilson's method and continuous data were expressed as mean  $\pm$  standard deviation (SD). 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 cases (FN) were assessed. Sensitivity, specificity, negative/positive predictive values and likelihood ratios were computed. Receiver operating characteristic curves (ROC) were obtained. The area under the curve (AUC) was 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 chi-squared 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, Illinois).



## RESULTS

### *Study population*

864 patients with suspected AAS underwent FoCUS and 839 were further analyzed (*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 figure 2*.

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, 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 ischemia (2, 0.2%), and other diagnoses (114, 13.6%). *Table 1* reports the clinical characteristics of study patients.

### *Diagnostic accuracy of FoCUS*

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 were 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 patients (8.8%). Direct FoCUS signs of AAS were detected in 84 (10%) patients, including 45 type A AAD, 11 type B AAD, 5 IMH, 4 SAR and 1 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 AAD, 20 type B AAD, 15 IMH, 10 SAR and 3 PAU. The FP cases were 177 and the FN cases were 16. The diagnostic performance of FoCUS for AAS is presented in *figure 3 and supplementary table 1*. When FoCUS was performed by a cardiologist, the sensitivity associated with direct signs was higher compared to non-cardiologist ( $p < 0.001$ ; *supplementary table 2*).

### *Additive value of FoCUS*

1 In multivariable logistic regression analysis, FoCUS findings except aortic valve regurgitation were  
2 independent positive predictors of AAS, in addition to clinical variables and D-dimer (*supplementary table*  
3 3). ROC analysis further showed that integration of FoCUS with clinical probability assessment by ADD-RS  
4 significantly increased the diagnostic accuracy for AAS (*figure 4A*). A Fagan nomogram was used to  
5 visualize the additive value of FoCUS (*figure 4B*). In 671 (80%) patients with  $ADD-RS \leq 1$  (defining low  
6 clinical probability of AAS *per ESC*), 67 patients had AAS. Hence, the prior probability of AAS in this  
7 group was 10%. Detection of direct FoCUS signs led to a posterior probability (post *P*) of AAS of  $\approx 65\%$ ,  
8 while absence of direct FoCUS signs of AAS led to a post *P* of  $\approx 6\%$ . Detection of any FoCUS sign of AAS  
9 led to a post *P* of  $\approx 28\%$ , while absence of any FoCUS sign of AAS led to a post *P* of  $\approx 2\%$ .

10 Use of “direct FoCUS sign present” as a criterion for re-classification of patients at high integrated  
11 probability of AAS applied to 40 (4.8%) patients ( $p < 0.001$  vs ADD-RS alone, *supplementary table 4*),  
12 including 29 with AAS. Use of “absence of any FoCUS sign” as a criterion confirming patients at low  
13 integrated probability of AAS applied to 476 (56.7%) patients, including 9 with AAS. Using  $ADD-RS \leq 1$   
14 plus negative FoCUS for rule-out of AAS, the sensitivity was 93.8% (95%CI 88.6-97.1%) and the failure  
15 rate was 1.9% (95%CI 0.9-3.6%), corresponding to 1 missed case in 52 patients with AAS (*supplementary*  
16 *table 5*).

### 17 ***Integrated rule-out strategy***

18 A D-dimer test result was available in 812 (96.8%) study patients, including 652 with  $ADD-RS \leq 1$   
19 (*figure 5 and supplementary figure 3*). In this group, D-dimer was FN in 2 (0.3%) patients with AAS, who  
20 presented both direct and indirect FoCUS signs of AAS. Decision-tree analysis validated ADD-RS, FoCUS  
21 and D-dimer as significant diagnostic classification nodes for AAS and confirmed significance of sequential  
22 application of FoCUS and D-dimer for AAS rule-out in patients with  $ADD-RS \leq 1$  (*supplementary figure 4*).  
23 The performance of a diagnostic rule-out strategy integrating ADD-RS, FoCUS and D-dimer is detailed in  
24 *table 2*. The AUC-ROC and model optimism estimates for the integrated diagnostic strategies are presented  
25 in *supplementary table 6*.

## DISCUSSION

1 In the last decade, increase of CTA use in EDs has not substantially affected the misdiagnosis rate of  
2  
3 AAS, inferring that improvement of diagnostic algorithms in this field is a primary objective. The present is  
4  
5 by far the largest prospective study of FoCUS for AAS. Current results validate ESC recommendations for  
6  
7 FoCUS as a tool providing relevant bedside data in the diagnostic approach to suspected AAS and support its  
8  
9 adoption in clinical practice. The main utility of FoCUS is represented by identification of direct signs of  
10  
11 AAS in a relatively small but significant subset of patients at low clinical probability. In these stable patients,  
12  
13 representing  $\approx 80\%$  of individuals in whom AAS is considered in differential diagnosis, decision on  
14  
15 CTA/TEE is notoriously difficult and both misdiagnosis (leading to diagnostic delay, inappropriate  
16  
17 treatments and ED dismissal) and overt-testing are major concerns.<sup>3-6</sup>  
18  
19  
20

21 Within minutes, bedside FoCUS can identify red flags warranting urgent aortic imaging or transfer  
22  
23 to expert centers. The trade-off in terms of false positives appears largely favorable if direct FoCUS signs are  
24  
25 used for rapid re-classification of patients. Use of indirect FoCUS sign, instead, is associated with a  
26  
27 substantially higher false positive rate and appears more questionable for routine probability up-grading. A  
28  
29 similar role was originally intended for chest radiography. However, given the low diagnostic accuracy of  
30  
31 this technique, radiation exposure and long turn-around time, the role of chest radiography in the routine  
32  
33 approach to AAS needs further scrutiny.<sup>21</sup>  
34  
35  
36

37 Study results clearly recapitulate the known limits of transthoracic echocardiography for evaluation  
38  
39 of the thoracic aorta.<sup>11-15</sup> The highest diagnostic sensitivity was found for AAS forms involving the  
40  
41 ascending aorta and dropped for AAS forms involving exclusively the descending aorta. The notion that  
42  
43 FoCUS as a standalone test may not be used for conclusive rule-out of AAS should therefore be stressed.  
44  
45 This applies also to patients at low clinical probability, owing to a suboptimal sensitivity and failure rate.  
46  
47 Nonetheless, a key finding of the present study is that integration of FoCUS with D-dimer provided an  
48  
49 exceptionally safe and fairly efficient rule-out criterion for AAS. Previous studies have shown that D-dimer  
50  
51 is highly sensitive for AAS.<sup>22, 23</sup> Based on present results, the probability of AAS is extremely low in patients  
52  
53 at low clinical probability without direct FoCUS signs of AAS and a negative D-dimer. Practical  
54  
55 considerations indicate that CTA/TEE could be omitted without consequences even in patients with only  
56  
57 indirect FoCUS signs if D-dimer is negative, provided case-by-case evaluation of alternative diagnoses and  
58  
59  
60  
61  
62  
63  
64  
65

clinical stability.

1           With respect to technical issues, only a minority of patients presented an inadequate sonographic  
2  
3 window, indicating that FoCUS can provide diagnostic data in most cases. FoCUS data were mostly  
4  
5 obtained from the left parasternal echocardiographic view. The highest diagnostic performance was obtained  
6  
7 by specialized cardiologists for type A aortic dissection, as previously reported.<sup>13</sup> In our study, cardiologist  
8  
9 providers showed increased capacity to identify direct signs of AAS as compared to non-cardiologists, but  
10  
11 the overall diagnostic performance was similar when also indirect signs were considered. The utility of  
12  
13 FoCUS also for the evaluation of alternative diagnoses (*e.g.* pulmonary embolism, acute coronary syndromes  
14  
15 and decompensated heart failure) and for detection of AAS complications (*e.g.* cardiac tamponade and aortic  
16  
17 valve regurgitation), further support large-scale implementation of this tool in EDs.  
18  
19  
20  
21  
22

### 23 **Limitations**

24  
25           The present study constitutes a pre-specified sub-analysis of the ADvISED trial, whose aim was to  
26  
27 evaluate the diagnostic characteristics of D-dimer for rule-out of AAS.<sup>17</sup> Therefore, current analyses provide  
28  
29 primary incremental evidence only for FoCUS, while the results obtained for D-dimer-based strategies are  
30  
31 not fully independent from previous findings. Further studies on new cohorts are needed for their external  
32  
33 validation. Second, the study was performed at tertiary centers where FoCUS is routinely applied and results  
34  
35 may not apply to contexts with limited experience/availability. Third, for ethical reasons operators were  
36  
37 unblinded to all diagnostic variables, thus potentially introducing some degree of selection bias. Fourth,  
38  
39 advanced aortic imaging data was available only for half study patients. However, patients not subjected to  
40  
41 CTA/TEE in the ED were followed-up for case adjudication: the majority were hospitalized after the index  
42  
43 visit, underwent thorough clinical scrutiny and independent medical evaluation, while only 5.8% were  
44  
45 dismissed from the ED. Nonetheless, we cannot exclude with certainty that few cases of AAS with  
46  
47 mild/atypical symptoms might have been missed. Finally, the study was not powered to detect statistical  
48  
49 differences between different rule-out strategies.  
50  
51  
52  
53  
54  
55

### 56 **Conclusions**

57  
58           Detection of direct FoCUS signs of AAS should prompt to advanced aortic imaging irrespective of  
59  
60  
61  
62  
63  
64  
65

1 clinical probability classification. In patients at low probability, integration of FoCUS with D-dimer provides  
2 a safe and efficient method to decide on urgent CTA/TEE. A diagnostic flow-chart integrating study results  
3 with additional clinical considerations is proposed in *figure 6*. Further studies are warranted for external  
4 validation, especially to define the best rule-out protocol.  
5  
6  
7  
8

## 9 **ACKNOWLEDGMENTS**

10 We are grateful to Dr. Emanuele Pivetta (Molinette Hospital, Torino, Italy) for his contribution to  
11 statistical revision. This work was supported by the University of Firenze (Firenze, Italy) [grant number  
12 16DPPN].  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

## 23 **REFERENCES**

- 24 1. Bossone E, LaBounty TM, Eagle KA. Acute aortic syndromes: diagnosis and management, an  
25 update. *Eur Heart J* 2018; 39: 739-749d.  
26  
27
- 28 2. Nienaber CA, von Kodolitsch Y, Nicolas V, Siglow V, Piepho A, Brockhoff C, Koschyk DH,  
29 Spielmann RP. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. *N Engl J Med*  
30 1993; 328: 1-9.  
31  
32
- 33 3. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis  
34 of acute aortic dissection. *Am J Cardiol* 2007; 99: 852-6.  
35  
36
- 37 4. Pourafkari L, Tajlil A, Ghaffari S, Parvizi R, Chavoshi M, Kolahehdouzan K, Khaki N, Parizad R,  
38 Hobika GG, Nader ND. The frequency of initial misdiagnosis of acute aortic dissection in the emergency  
39 department and its impact on outcome. *Intern Emerg Med* 2016: 1-11.  
40  
41
- 42 5. Lovy AJ, Bellin E, Levsky JM, Esses D, Haramati LB. Preliminary development of a clinical  
43 decision rule for acute aortic syndromes. *Am J Emerg Med* 2013; 31: 1546-50.  
44  
45
- 46 6. Ohle R, Anjum O, Bleeker H, Wells G, Perry JJ. Variation in emergency department use of  
47 computed tomography for investigation of acute aortic dissection. *Emerg Radiol* 2018.  
48  
49
- 50 7. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Jr., Eagle KA, Hermann LK,  
51 Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA,  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Svensson LG, Williams DM, American College of Cardiology Foundation/American Heart Association Task Force on Practice G, American Association for Thoracic S, American College of R, American Stroke A, Society of Cardiovascular A, Society for Cardiovascular A, Interventions, Society of Interventional R, Society of Thoracic S, Society for Vascular M. 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: e266-369.

8. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwoger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ, Guidelines ESCCfP. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014; 35: 2873-926.

9. Labovitz AJ, Noble VE, Bierig M, Goldstein SA, Jones R, Kort S, Porter TR, Spencer KT, Tayal VS, Wei K. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr* 2010; 23: 1225-30.

10. Via G, Hussain A, Wells M, Reardon R, ElBarbary M, Noble VE, Tsung JW, Neskovic AN, Price S, Oren-Grinberg A, Liteplo A, Cordioli R, Naqvi N, Rola P, Poelaert J, Gulic TG, Sloth E, Labovitz A, Kimura B, Breikreutz R, Masani N, Bowra J, Talmor D, Guarracino F, Goudie A, Xiaoting W, Chawla R, Galderisi M, Blaivas M, Petrovic T, Storti E, Neri L, Melniker L, International Liaison Committee on Focused Cardiac U, International Conference on Focused Cardiac U. International evidence-based recommendations for focused cardiac ultrasound. *J Am Soc Echocardiogr* 2014; 27: 683 e1-683 e33.

11. Shiga T, Wajima Z, Apfel CC, Inoue T, Ohe Y. Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. *Archives of Internal Medicine* 2006; 166: 1350-1356.
12. Evangelista A, Avegliano G, Aguilar R, Cuellar H, Igual A, Gonzalez-Alujas T, Rodriguez-Palomares J, Mahia P, Garcia-Dorado D. Impact of contrast-enhanced echocardiography on the diagnostic algorithm of acute aortic dissection. *Eur Heart J* 2010; 31: 472-9.
13. Cecconi M, Chirillo F, Costantini C, Iacobone G, Lopez E, Zanolli R, Gili A, Moretti S, Manfrin M, Munch C, Torracca L, Perna GP. The role of transthoracic echocardiography in the diagnosis and management of acute type A aortic syndrome. *Am Heart J* 2012; 163: 112-8.
14. Evangelista A, Carro A, Moral S, Teixido-Tura G, Rodriguez-Palomares JF, Cuellar H, Garcia-Dorado D. Imaging modalities for the early diagnosis of acute aortic syndrome. *Nat Rev Cardiol* 2013; 10: 477-486.
15. Nazerian P, Vanni S, Castelli M, Morello F, Tozzetti C, Zagli G, Giannazzo G, Vergara R, Grifoni S. Diagnostic performance of emergency transthoracic focus cardiac ultrasound in suspected acute type A aortic dissection. *Intern Emerg Med* 2014; 9: 665-70.
16. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, Sicari R, Nihoyannopoulos P, Zamorano J, European Association of E, Document R, Pepi M, Breithardt OA, Plonska-Gosciniak E. Echocardiography in aortic diseases: EAE recommendations for clinical practice. *Eur J Echocardiogr* 2010; 11: 645-58.
17. Nazerian P, Mueller C, Soeiro AM, Leidel BA, Salvadeo SAT, Giachino F, Vanni S, Grimm K, Oliveira MT, Jr., Pivetta E, Lupia E, Grifoni S, Morello F, Investigators AD. Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes: The ADvISED Prospective Multicenter Study. *Circulation* 2018; 137: 250-258.
18. Rogers AM, Hermann LK, Booher AM, Nienaber CA, Williams DM, Kazerooni EA, Froehlich JB, O'Gara PT, Montgomery DG, Cooper JV, Harris KM, Hutchison S, Evangelista A, Isselbacher EM, Eagle KA. 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: 2213-8.

19. Svensson LG, Labib SB, Eisenhauer AC, Butterly JR. Intimal tear without hematoma: an important variant of aortic dissection that can elude current imaging techniques. *Circulation* 1999; 99: 1331-6.
20. Nazerian P, Morello F, Vanni S, Bono A, Castelli M, Forno D, Gigli C, Soardo F, Carbone F, Lupia E, Grifoni S. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. *Int J Cardiol* 2014; 175: 78-82.
21. Evangelista A, Isselbacher EM, Bossone E, Gleason TG, Eusanio MD, Sechtem U, Ehrlich MP, Trimarchi S, Braverman AC, Myrmet T, Harris KM, Hutchinson S, O'Gara P, Suzuki T, Nienaber CA, Eagle KA, Investigators I. Insights From the International Registry of Acute Aortic Dissection: A 20-Year Experience of Collaborative Clinical Research. *Circulation* 2018; 137: 1846-1860.
22. Sodeck G, Domanovits H, Schillinger M, Ehrlich MP, Endler G, Herkner H, Laggner A. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. *Eur Heart J* 2007; 28: 3067-75.
23. Suzuki T, Distanto A, Zizza A, Trimarchi S, Villani M, Salerno Uriarte JA, De Luca Tupputi Schinosa L, Renzulli A, Sabino F, Nowak R, Birkhahn R, Hollander JE, Counselman F, Vijayendran R, Bossone E, Eagle K. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. *Circulation* 2009; 119: 2702-7.

## FIGURE LEGENDS

**Figure 1.** Representative focused cardiac ultrasound (FoCUS) findings (still images) of acute aortic syndromes. **(A)** Intimal flap (suprasternal view). **(B)** Ascending aorta dilation (>4 cm, left parasternal view, leading edge measurement). **(C)** Pericardial effusion (apical view). **(D)** Aortic valve regurgitation (left parasternal view, color-doppler). Still images were obtained from *videos 1-4* (available online).

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



1 **Figure 3.** Sensitivity and specificity of focused cardiac ultrasound (FoCUS) for diagnosis of acute aortic  
2 syndrome (AAS). **(A)** Sensitivity and specificity of FoCUS results for diagnosis of AAS. **(B)** Sensitivity and  
3 specificity of FoCUS results for diagnosis of type A acute aortic dissection (A-AAD) or other types of AAS.  
4  
5  
6  
7  
8

9 **Figure 4.** Additive diagnostic value of focused cardiac ultrasound (FoCUS) to clinical probability  
10 assessment. **(A)** ROC curves for diagnosis of acute aortic syndrome (AAS) of the aortic dissection detection  
11 risk score (ADD-RS, black line), ADD-RS plus FoCUS direct signs (blue line) and ADD-RS plus FoCUS  
12 any sign (red line). **(B)** Fagan nomogram showing the additive effect of FoCUS to clinical probability  
13 assessment. The clinical probability of AAS is displayed on the left as “Prior *P*”. The middle line represents  
14 the result of FoCUS. direct+: presence of direct signs of AAS; any+: presence of any sign (direct or indirect);  
15 direct-: absence of direct signs; any-: absence of any sign. When a straight line is drawn through the prior *P*  
16 and FoCUS result, the post-test *P* of AAS is found on the right line (“Post *P*”). The representative dotted  
17 lines represent the effect of FoCUS findings for patients at low clinical probability of AAS.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31

32 **Figure 5.** Results of focused cardiac ultrasound (FoCUS) and D-dimer test in patients classified at low  
33 clinical probability. AAS= acute aortic syndrome; ADD= aortic dissection detection; n.a.= not available. D-  
34 dimer test + if  $\geq 500$  ng/mL. % refer to 839 study patients. \*Data presented in *suppl. figure 3*.  
35  
36  
37  
38  
39  
40

41 **Figure 6.** Proposed diagnostic algorithm based on experimental results and clinical judgment. AAS= acute  
42 aortic syndrome; ADD-RS= aortic dissection detection risk score; CTA= computed tomography  
43 angiography; FoCUS= transthoracic focused cardiac ultrasound.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**Table 1.** Demographic and clinical characteristics of study patients.

	<b>All patients (n=839)</b>	<b>AAS (n=146)</b>	<b>AltD (n=693)</b>	<b><i>P</i></b>
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
<b>Predisposing conditions</b>				
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
<b>Pain features</b>				
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
<b>Physical findings</b>				
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

AAS= acute aortic syndromes; AltD= alternative diagnoses. Age is reported as mean ± standard deviation.

Categorical variables are expressed as absolute number and percent value (in brackets). *P* significant if <0.05 (AAS vs AltD).

**Table 2.** Diagnostic performance of strategies integrating aortic dissection detection risk score (ADD-RS), focused cardiac ultrasound (FoCUS) and D-dimer, for rule-out of acute aortic syndromes.

	<b>ADD-RS<math>\leq</math>1 direct FoCUS signs absent D-dimer &lt;500 ng/mL</b>	<b>ADD-RS<math>\leq</math>1 FoCUS negative* D-dimer &lt;500 ng/mL</b>
n. 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%)

+LR= positive likelihood ratio; -LR= negative likelihood ratio; NPV= negative predictive value; PPV= positive predictive value; 95% CI= 95% confidence interval; \*all signs absent.

**A**



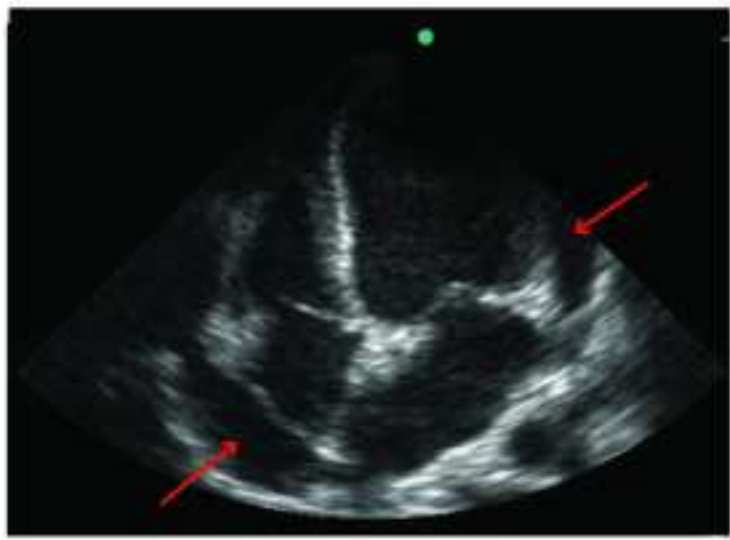
Intimal flap

**B**



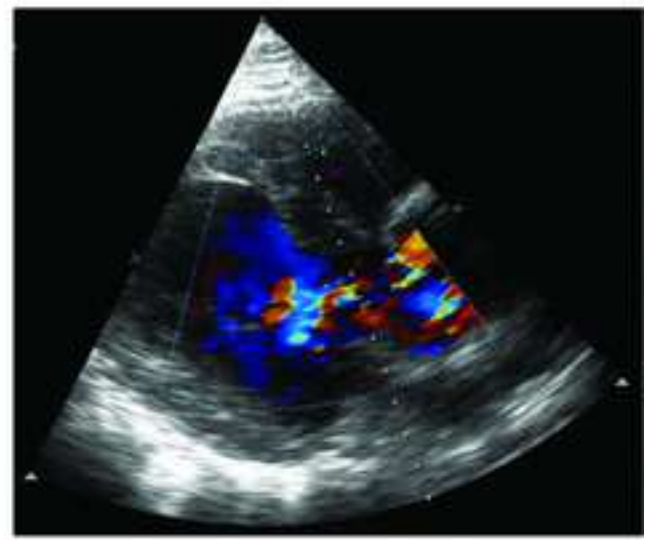
Thoracic aorta dilatation

**C**

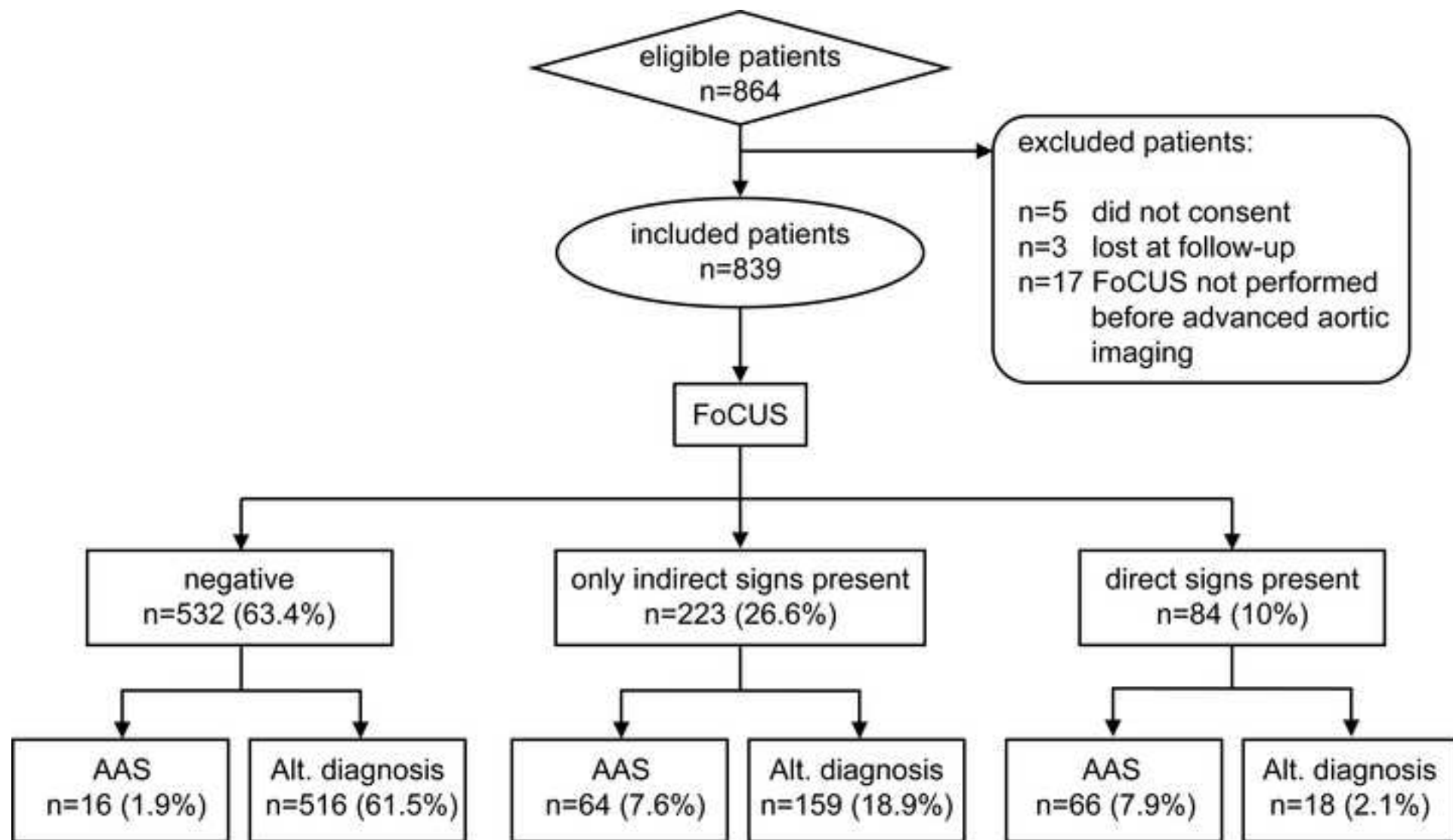


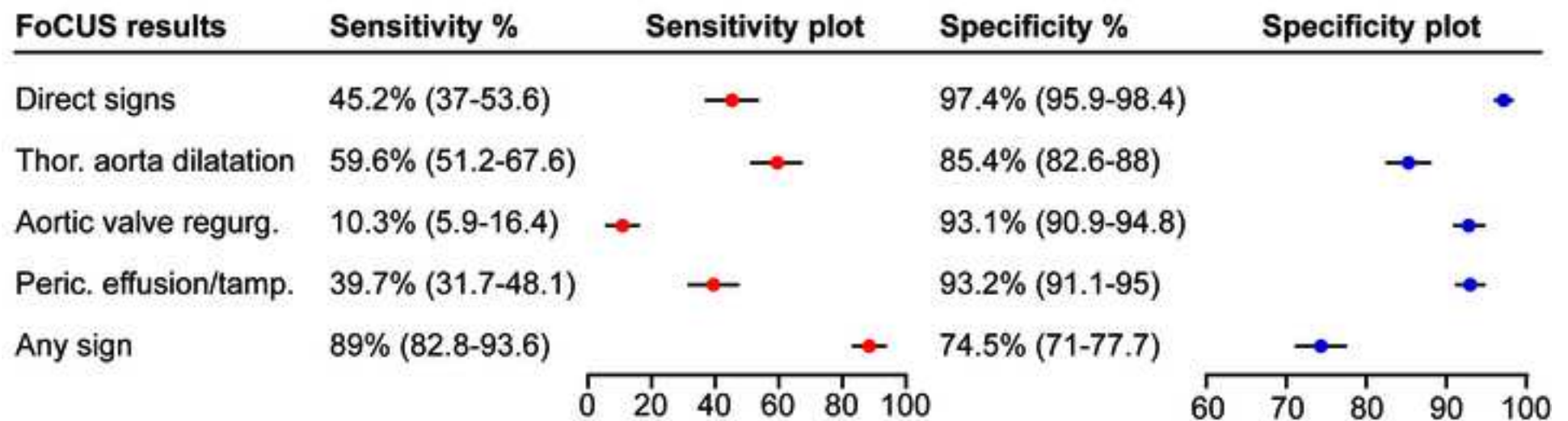
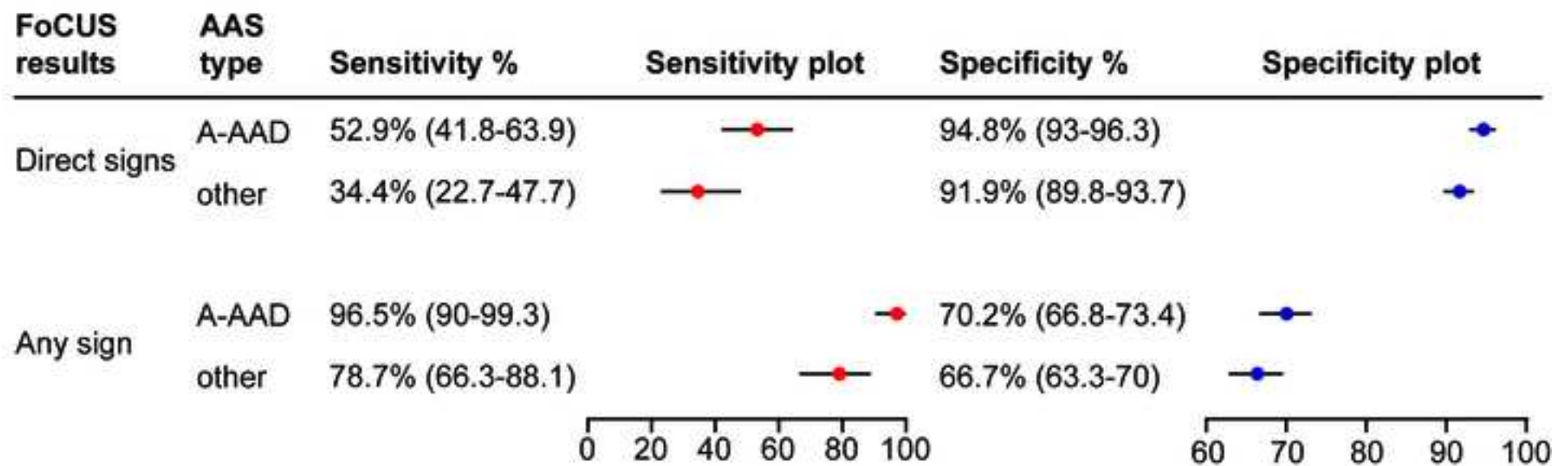
Pericardial effusion

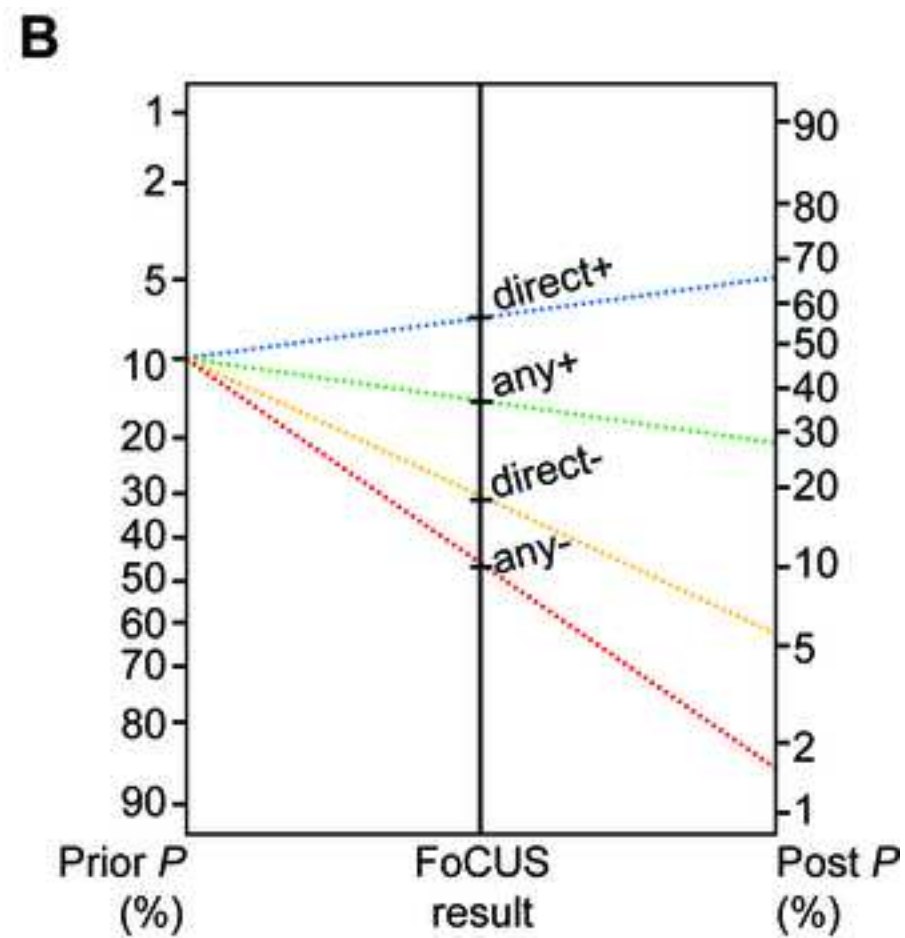
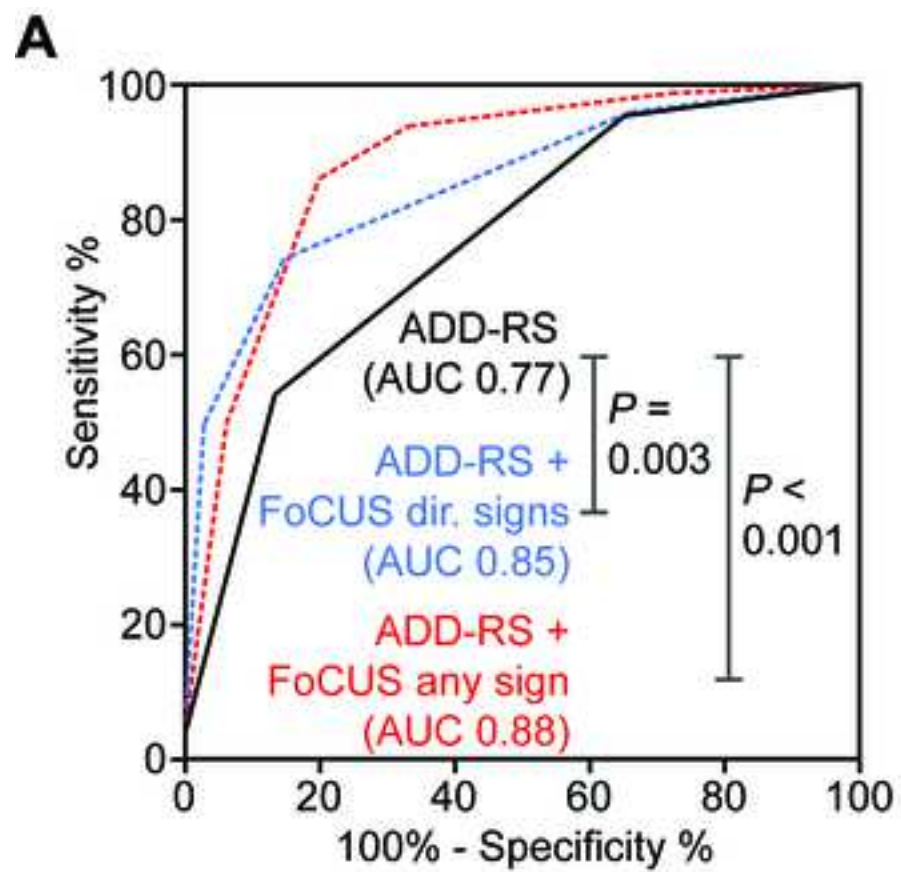
**D**



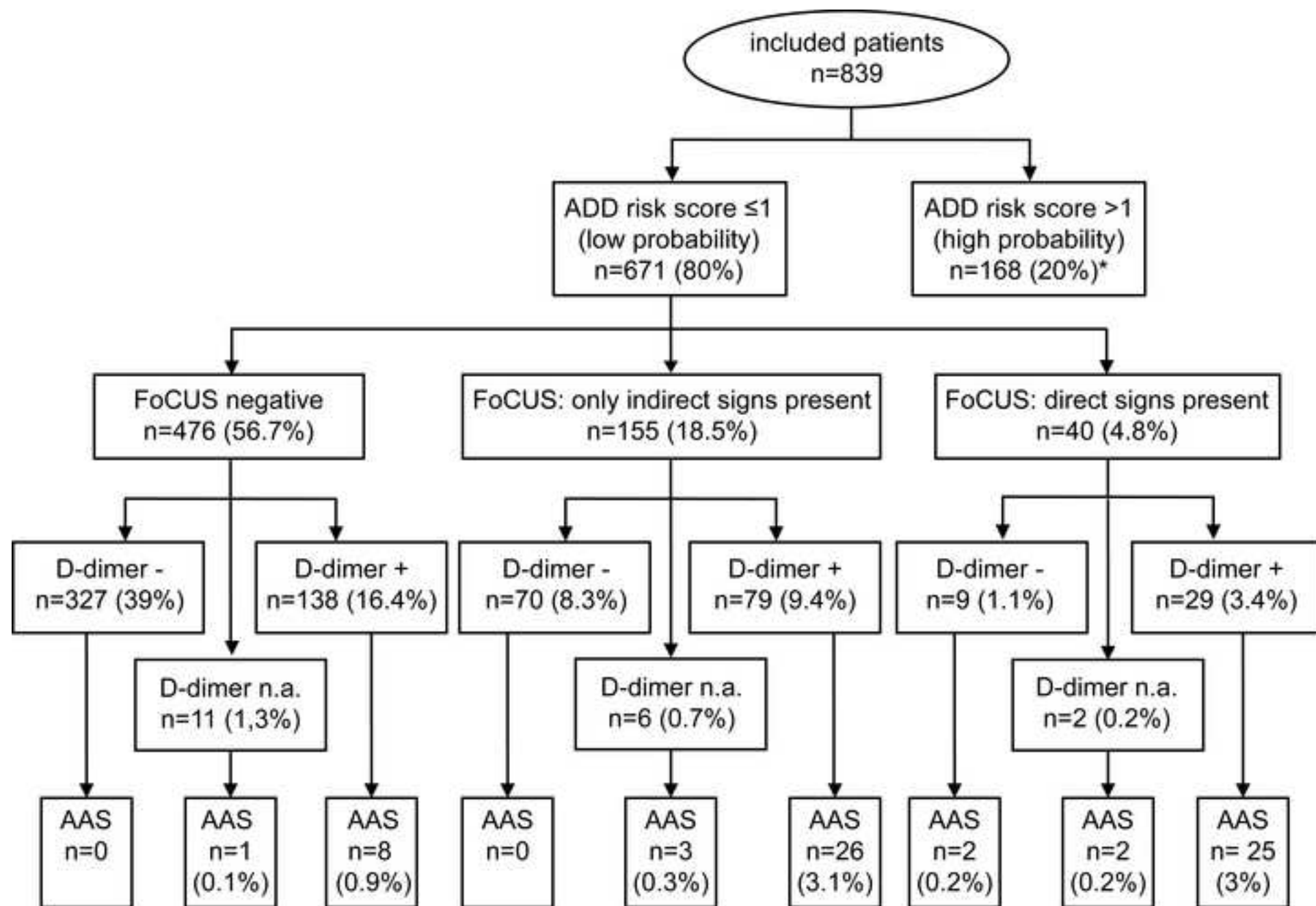
Aortic regurgitation



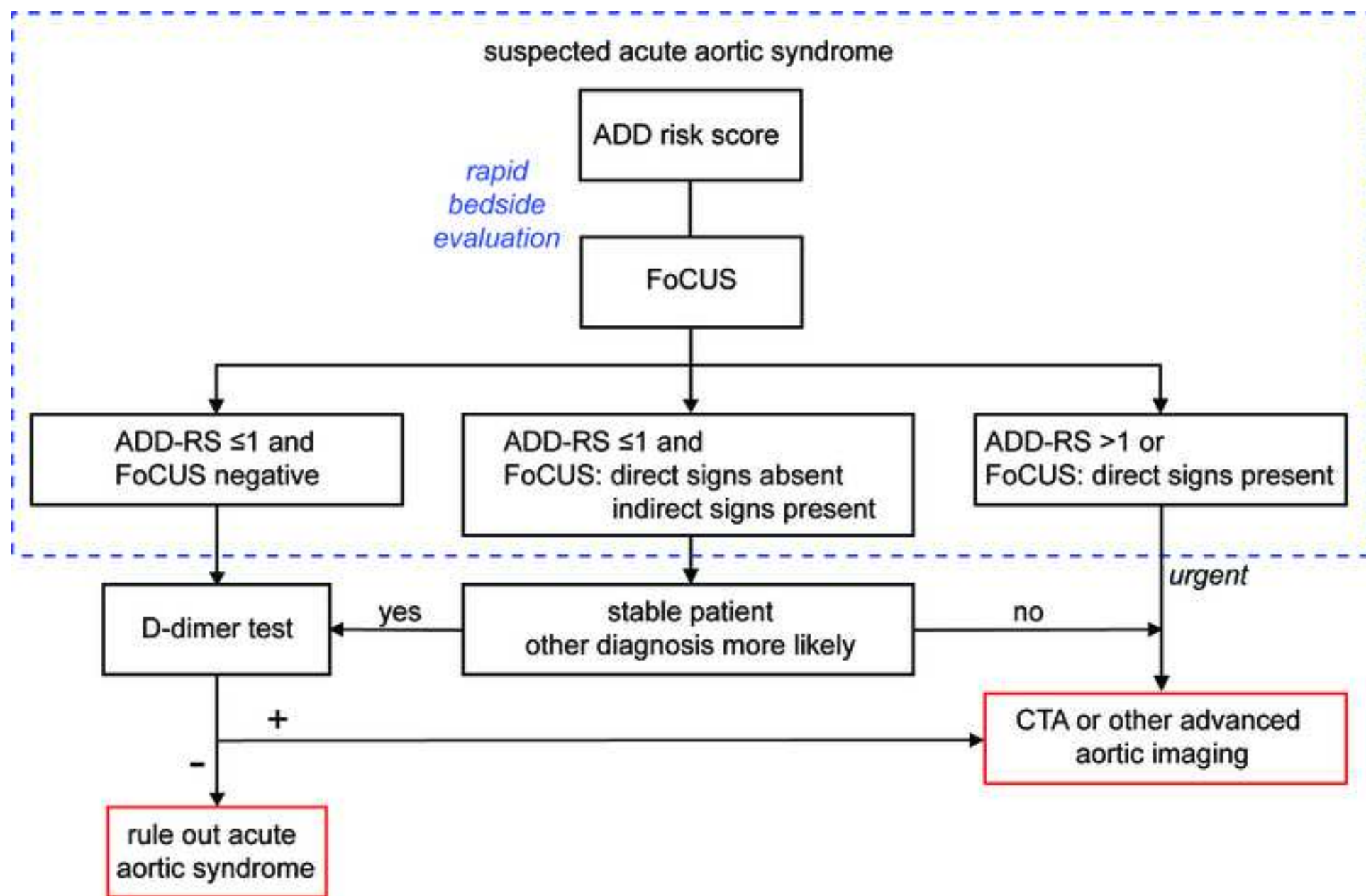
**A****B**











## SUPPLEMENTARY FIGURE AND VIDEO LEGENDS

**Supplementary figure 1.** Standardized form for data collection.

**Supplementary figure 2.** Flow chart summarizing diagnostic work-up in study patients classified at low clinical probability of acute aortic syndrome. ED= emergency department; CTA= computed tomography angiography; TEE= transesophageal echocardiography; AAS= acute aortic syndrome; Alt.= alternative. \*Without previous conclusive imaging.

**Supplementary figure 3.** Results of focused cardiac ultrasound (FoCUS) and D-dimer test in study patients classified at high clinical probability of acute aortic syndrome. ADD= aortic dissection detection; n.a.= not available; AAS= acute aortic syndrome. D-dimer test positive ( $\pm$ ) if  $\geq 500$  ng/mL. % refer to 839 study patients.

**Supplementary figure 4.** Decision-tree analysis. Final diagnosis of acute aortic syndrome was used as target variable, while aortic dissection detection risk score (ADD-RS), focused cardiac ultrasound (FoCUS) results and D-dimer test result were used as predictors, to generate statistically significant nodes (shown in red,  $p < 0.05$ ). The growing method used was chi-squared automatic interaction detection based on adjusted significance testing. At the level of each node, the number of patients with acute aortic syndrome (AAS) or alternative diagnosis (Alt D) (including % within node) and the total number of patients (with % of study cohort) are shown. **(A)** Decision-tree analysis using the following predictors: ADD-RS, any FoCUS sign and D-dimer test result. **(B)** Decision-tree analysis using the following predictors: ADD-RS, direct FoCUS signs and D-dimer test result.

**Video 1.** Representative video of focused cardiac ultrasound (FoCUS) visualizing intimal aortic flap of aortic dissection from suprasternal view.

**Video 2.** Representative video of focused cardiac ultrasound (FoCUS) visualizing ascending

aorta dilation from left parasternal view (~~leading edge measurement~~).

**Video 3.** Representative video of focused cardiac ultrasound (FoCUS) visualizing pericardial effusion from apical view.

**Video 4.** Representative video of focused cardiac ultrasound (FoCUS) visualizing aortic valve regurgitation (left parasternal view with color-doppler).

## Supplementary figure 1. Prospective Enrolment Form

### FOCUS<sup>1,2</sup>

Event date \_\_\_\_\_

Attending physician \_\_\_\_\_

<b>Patient data</b>
---------------------

Consecutive number \_\_\_\_\_

Gender  M  F

Name \_\_\_\_\_

Date of birth \_\_\_\_\_

Surname \_\_\_\_\_

**Ultrasonographer (surname)** \_\_\_\_\_

- Cardiologist
- Non cardiologist

- Good acoustic windows
- Bad acoustic windows

**Acoustic windows:**

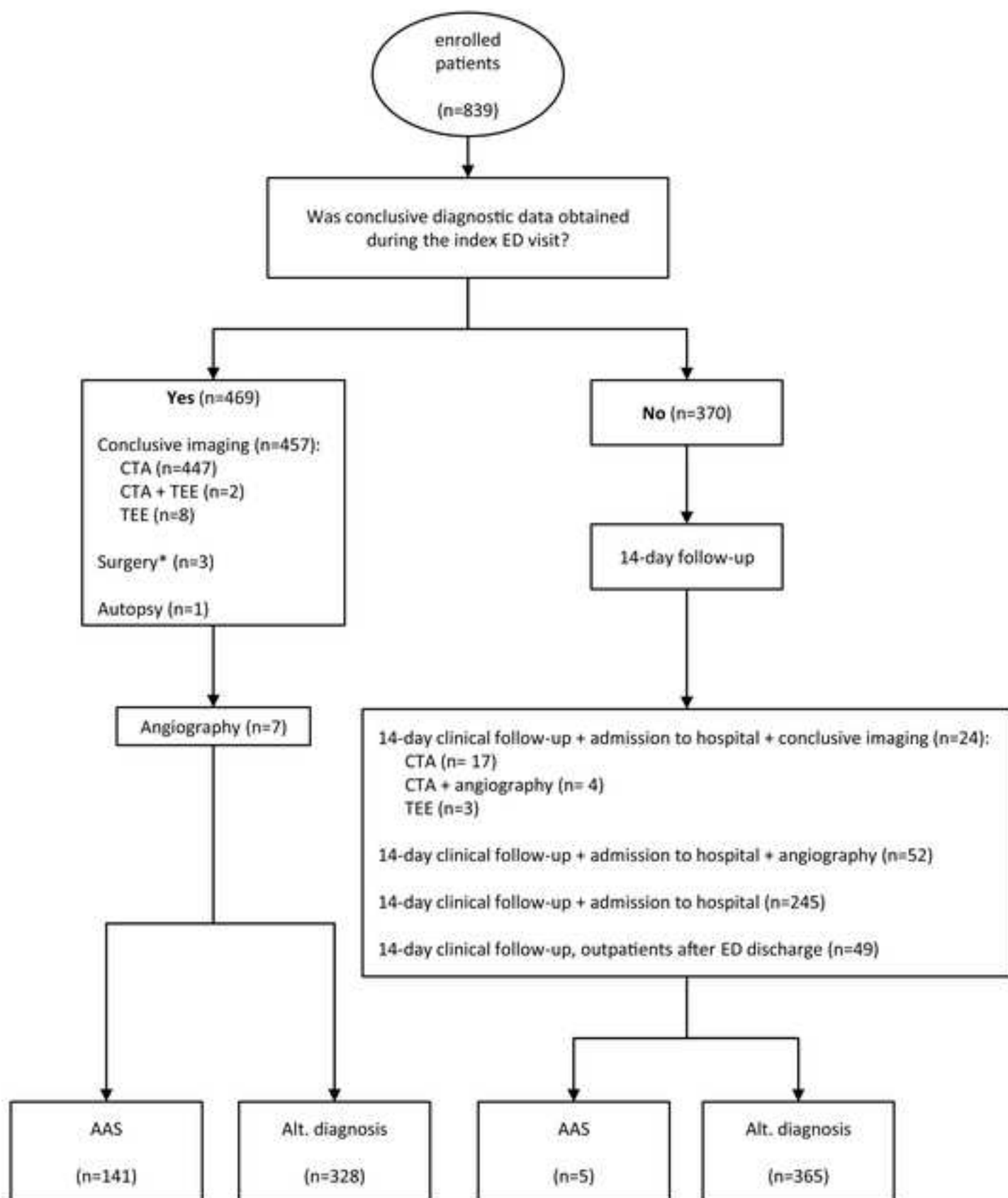
- Left parasternal
- Apical
- Subxiphoid
- Suprasternal
- Right parasternal
- Abdomen
- Extended to carotid arteries

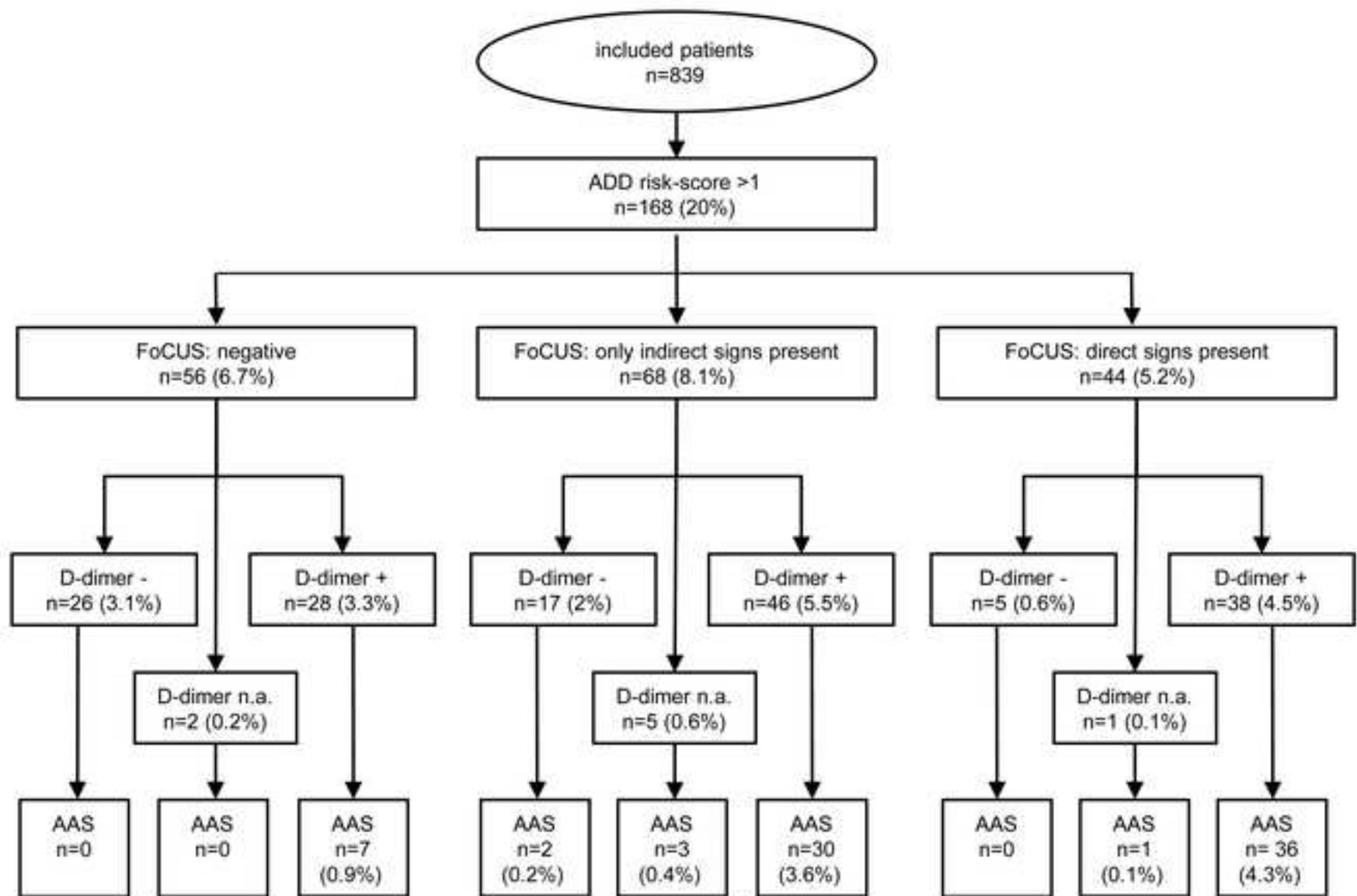
**Findings**

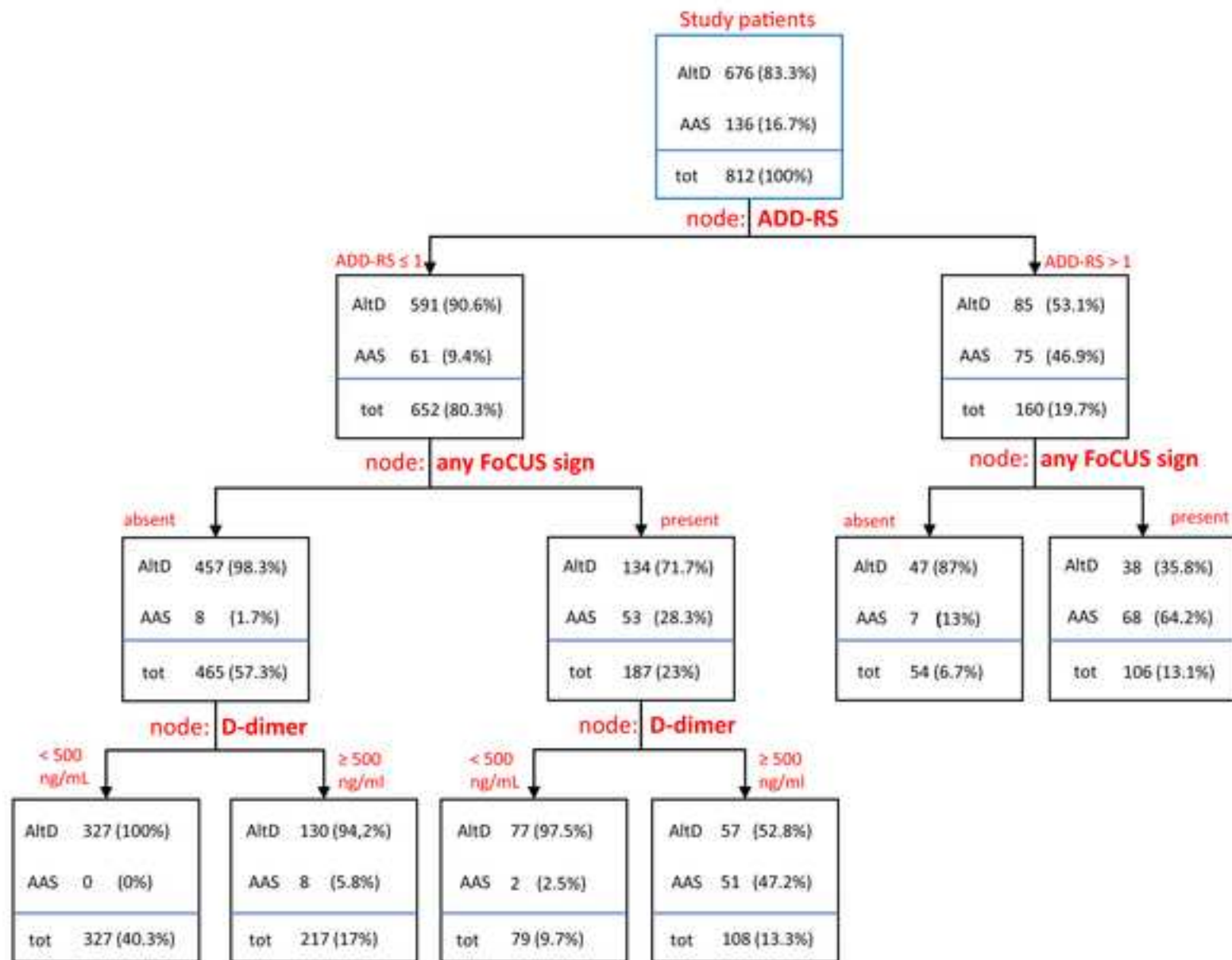
- Intimal flap / intramural hematoma/penetrating aortic ulcer
  
- Enlarged thoracic aortic root ( $\geq 40$ mm)
- Pericardial effusion/tamponade
- Aortic valve insufficiency

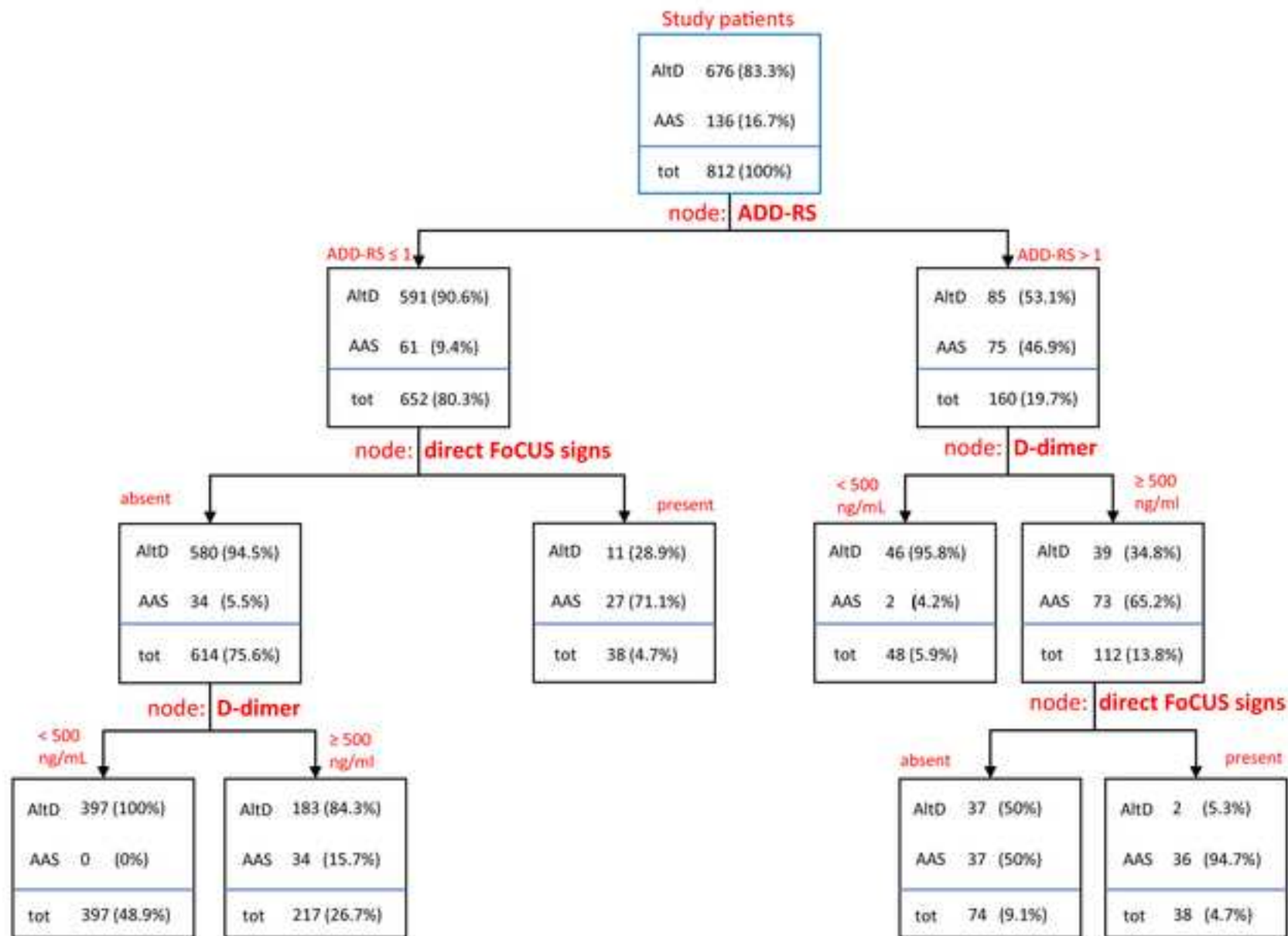
**Legend**

1. Report data only if FOCUS were performed before conclusive diagnosis (by CTA, TEE, MR, angiography, surgery)
2. FOCUS data must be filled by physician performing the exam











**Supplementary table 1.** Diagnostic variables of focused cardiac ultrasound (FoCUS) for diagnosis of acute aortic syndromes.

<b>FoCUS results</b>	<b>TP</b>	<b>FP</b>	<b>TN</b>	<b>FN</b>	<b>PPV, % (95%CI)</b>	<b>NPV, % (95%CI)</b>	<b>+LR (95%CI)</b>	<b>-LR (95%CI)</b>
Direct sonographic signs	66	18	675	80	78.6% (69.2-85.7%)	89.4% (87.9-90.7%)	17.4 (10.6-28.4)	0.56 (0.49-0.65)
Thoracic aorta dilatation	87	101	592	59	46.3% (40.8-51.9%)	90.9% (89.1-92.4%)	4.09 (3.27-5.12)	0.47 (0.39-0.58)
Aortic valve regurgitation	15	48	645	131	23.8% (15.2-35.2%)	83.1% (82.3-83.9%)	1.48 (0.85-2.58)	0.96 (0.91-1.02)
Pericardial effusion or tamp.	58	47	646	88	55.2% (46.7-63.4%)	88% (86.5-89.3%)	5.86 (4.17-8.24)	0.65 (0.57-0.74)
Any sonographic sign	130	177	516	16	42.3% (39-45.8%)	97% (95.3-98.1%)	3.49 (3.03-4.01)	0.15 (0.09-0.23)

FN= false negative; FP= false positive; +LR= positive likelihood ratio; -LR= negative likelihood ratio; NPV= negative predictive value; PPV= positive predictive value; TN= true negative; TP= true positive; tamp.= tamponade; 95%CI= 95% confidence interval.

**Supplementary table 2.** Comparison of the diagnostic accuracy of focused cardiac ultrasound (FoCUS) when performed by a cardiologist (n=170) or by a non-cardiologist physician (n=669).

FoCUS results	Sensitivity % (95%CI)			Specificity % (95%CI)		
	Cardiologist	Non-cardiologist	<i>P</i>	Cardiologist	Non-cardiologist	<i>P</i>
Direct sonographic signs	70% (45.7-88.1%)	41.3% (32.6-50.4%)	<0.001	98.7% (95.3-99.8%)	97.1% (95.3-98.3%)	0.24
Any sonographic sign	85% (62.1-96.8%)	89.7% (83-94.4%)	0.08	69.3% (61.3-76.6%)	75.9% (72-79%)	0.08

95%CI=95% confidence interval.

**Supplementary table 3.** Multivariable logistic regression analysis for prediction of acute aortic syndrome in study patients.

	<i>P</i>	Exp(B)	95% CI
Age (years)	0.498	0.991	0.965-1.017
Anterior chest pain	0.441	0.744	0.350-1.580
Posterior chest pain	0.174	1.670	0.797-3.497
Abdominal pain	0.844	1.086	0.478-2.467
Lumbar pain	0.165	0.420	0.123-1.429
Syncope	0.885	1.071	0.422-2.719
Hypertension	<i>0.01</i>	2.881	1.294-6.418
Diabetes	0.126	0.406	0.128-1.287
Smoke	0.150	1.793	0.810-3.970
Cancer	<i>0.029</i>	0.016	0.000-0.650
History of ischemic cardiac disease	<i>0.032</i>	0.287	0.092-0.897
Marfan syndrome/connective tissue disease	0.843	0.576	0.002-136.953
Family history of aortic disease	0.442	0.416	0.044-3.889
Previous acute aortic syndrome	0.371	1.942	0.454-8.306
Known aortic valve disease	0.811	1.177	0.309-4.489
Recent aortic manipulation	0.223	0.248	0.026-2.336
Known thoracic aortic aneurysm	0.765	1.165	0.428-3.168
known abdominal aortic aneurysm	0.576	1.419	0.416-4.834
Severe pain intensity	0.084	2.014	0.909-4.460
Abrupt onset of pain	<i>0.001</i>	4.159	1.782-9.705
Ripping or tearing pain	0.582	1.325	0.486-3.612
Pulse deficit/systolic blood pressure differential	0.069	2.630	0.927-7.464
Focal neurological deficit	0.36	1.846	0.497-6.854

Murmur of aortic regurgitation	0.511	1.935	0.270-13.859
Shock/hypotension	0.102	2.272	0.850-6.073
D-dimer test positive	<0.001	86.820	19.938-378.061
Direct sonographic sign of AAS at FoCUS	<0.001	38.262	13.261-111.394
Thoracic aortic enlargement at FoCUS	<0.001	6.556	3.077-1.283
Aortic valve regurgitation at FoCUS	0.107	0.316	0.078-1.283
Pericardial effusion or tamponade at FoCUS	<0.001	9.071	3.655-22.512

30 variables were introduced in the model, for prediction of the diagnosis of acute aortic syndrome (AAS). Amongst clinical variables, independent negative predictors were cancer and ischemic cardiac disease, while positive predictors were hypertension and abrupt onset of pain. Amongst diagnostic findings, D-dimer test positive and focused cardiac ultrasound (FoCUS) findings (except for aortic valve insufficiency) were independent positive predictors of AAS. Exp(B) indicates the odds ratio; 95% CI = 95% confidence interval.

**Supplementary table 4.** Diagnostic performance of focused cardiac ultrasound (FoCUS) in patients classified according to the aortic dissection detection risk score (ADD-RS).

	Low probability (ADD-RS ≤1)		High probability (ADD-RS >1)	
	Direct FoCUS signs present	Any FoCUS sign present	Direct FoCUS signs present	Any FoCUS sign present
TP	29	58	37	72
FP	11	137	7	40
TN	593	467	82	49
FN	38	9	42	7
Sensitivity % (95% CI)	43.3% (31.2- 56%)	86.6% (76- 93.7%)	46.8% (35.5-58.4)	91.1% (82.6-96.4)
Specificity % (95% CI)	98.2% (96.8-99.1%)	77.3% (73.8-80.6%)	92.1% (84.5-96.8)	55.1% (44.1-65.6)
PPV % (95% CI)	72.5% (58-83.4%)	29.7% (26.2-33.5%)	84.1% (74.1-94.1)	64.3% (58.8-69.8)
NPV % (95% CI)	94% (92.7-95.1%)	98.1% (96.6-99%)	66.1% (61.3-77.3)	87.5% (79.5-95.5)
+LR (95% CI)	23.8 (12.5-45.4)	3.82 (3.2-4.55)	5.95 (2.82-12.59)	2.03 (1.6-2.58)
-LR (95% CI)	0.58 (0.47-0.71)	0.17 (0.09-0.32)	0.58 (0.47-0.72)	0.16 (0.08-0.33)

FN= false negative; FP= false positive; +LR= positive likelihood ratio; -LR= negative likelihood ratio; NPV= negative predictive value; PPV= positive predictive value; tamp.= tamponade; TN= true negative; TP= true positive; 95% CI= 95% confidence interval.

**Supplementary table 5.** Diagnostic performance of a rule-out strategy integrating negative focused cardiac ultrasound (FoCUS) with aortic dissection detection risk score (ADD-RS)  $\leq 1$  (low probability of AAS *per* ESC 2014 guidelines).

<b>Diagnostic variable</b>	<b>% (95% CI)</b>
n. patients satisfying rule-out criteria	476
<i>AAS</i>	9
<i>AltD</i>	467
Sensitivity %	93.8% (88.6-97.1)
Specificity %	67.4% (63.8-70.9)
PPV %	37.7% (35-40.4)
NPV %	98.1% (96.6-99.3)
+LR	2.88 (2.57–3.23)
-LR	0.09 (0.05–0.2)
Failure rate %	1.9% (0.9-3.6)
Efficiency %	56.7% (53.3-60.1)

*AAS* = acute aortic syndrome; *AltD* = alternative diagnosis; +LR = positive likelihood ratio; -LR = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; ~~95% CI = 95% confidence interval.~~

**Supplementary table 6.** Optimism and corrected area under the curve for integrated diagnostic strategies.

	<b>Diagnostic strategy</b>	<b>Optimism</b>	<b>AUC-ROC</b>
<b>RULE-OUT STRATEGIES</b>	ADD-RS $\leq 1$	0.08%	71.25%
	ADD-RS $\leq 1$ AND direct FoCUS signs absent	0.07%	80.36%
	ADD-RS $\leq 1$ AND FoCUS negative	-0.01%	80.86%
	ADD-RS $\leq 1$ AND direct FoCUS signs absent AND D-dimer negative	-0.03%	79.38%
	ADD-RS $\leq 1$ AND FoCUS negative AND D-dimer negative	0.05%	74.16%
	ADD-RS $> 1$	0.06%	71.25%
<b>RULE-IN STRATEGIES</b>	ADD-RS $> 1$ OR direct FoCUS signs present	0.24%	80.28%
	ADD-RS $> 1$ OR any FoCUS sign present	0.17%	80.78%

AUC-ROC = area under the ROC curve or *c*-index, corrected for model optimism via bootstrap approach. Optimism indicates the difference between the naïve measure of Somer's D (calculated using the model fitted to and evaluated on the original data) and the value obtained by applying the model fitted to the bootstrap datasets to the original data. FoCUS = focused cardiac ultrasound.