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

Published version:

DOI:10.1093/eurheartj/ehz207

(Article begins on next page)

Manuscript

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

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

[1]Department of Emergency Medicine, Careggi University Hospital, Firenze, Italy.

[2]Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital of Basel, Basel, Switzerland

[3]Emergency Care Unit, Heart Institute, University of Sao Paulo, Brazil

[4]Department of Emergency Medicine, Campus Benjamin Franklin, Charite – Universitatsmedizin Berlin, Germany

[5]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.

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

ABSTRACT

Aims. The diagnosis of acute aortic syndromes (AAS) 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 AAS awaits validation.

Methods and results. This was a prespecified subanalysis of the ADvISED multicenter 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.

Results. AAS was diagnosed in 146 (17.4%) of 839 patients. Presence of direct FoCUS signs had a sensitivity and specificity of 45.2% (95%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 lead to a failure rate of 0% (95%CI 0-1.2%).

Conclusions. FoCUS has additive value in the workup of AAS. 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 AAS.

KEY WORDS: aortic dissection, aortic syndrome, diagnosis, echocardiography, ultrasound.

INTRODUCTION

Acute aortic syndromes (AAS) 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 transesophageal echocardiography (TEE) 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 diagnostic conundrum apparent in Emergency Department (ED) practice: misdiagnosis of AAS reaches 39%, but the rate of positive CTA performed for suspected AAS 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/TEE is warranted. For patients at low probability, instead, decision on CTA/TEE 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 AAS, 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/TEE 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: (1) FoCUS can help to rapidly identify patients requiring CTA/TEE despite low clinical probability of AAS, and (2) in conjunction with low clinical probability, negative FoCUS plus negative D-dimer define a safe rule-out strategy for AAS.

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.[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, 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 ≥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. 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 ≥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 or crescentic thickening of the aortic wall >5 mm) and presence of a penetrating aortic ulcer (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 color-doppler (*figure 1* and *videos 1-4*). After FoCUS completion, the sonographer completed a standardized form (*supplementary figure 1*).

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 3 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 AAS were TEE and magnetic resonance angiography. Exams were performed and interpreted by specialized physicians not involved in the study.

Follow-up

In all patients for whom conclusive diagnostic data was not obtained during the ED visit by advanced imaging (CTA/TEE/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, death.

Case definition and adjudication

The following etiological entities were considered in the definition of AAS based on the Svensson's classification: acute aortic dissection (AAD), intramural aortic hematoma (IMH), penetrating aortic ulcer (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/TEE/MRA, surgery or autopsy. AAS was considered absent based on negative results of CTA/TEE/MRA, surgery or autopsy. If such data was not available, adjudication was clinical. AAS was considered absent: (1) in patients admitted to hospital after the ED visit if an alternative diagnosis (AltD) was available, and (2) 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, 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 AAS 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% confident interval (CI) using Wilson's method and continuous data were expressed as mean ± 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 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 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

In multivariable logistic regression analysis, FoCUS findings except aortic valve regurgitation were independent positive predictors of AAS, in addition to clinical variables and D-dimer (*supplementary table 3*). ROC analysis further showed that integration of FoCUS with clinical probability assessment by ADD-RS significantly increased the diagnostic accuracy for AAS (*figure 4A*). A Fagan nomogram was used to visualize the additive value of FoCUS (*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 re-classification of patients at high integrated probability of AAS applied to 40 (4.8%) patients (p<0.001 *vs* ADD-RS alone, *supplementary table 4*), 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 9 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 1 missed case in 52 patients with AAS (*supplementary table 5*).

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 figure 3*). 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 figure 4*). 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 table 6*.

DISCUSSION

In the last decade, increase of CTA use in EDs has not substantially affected the misdiagnosis rate of AAS, 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 AAS. 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 AAS in a relatively small but significant subset of patients at low clinical probability. In these stable patients, representing ≈80% of individuals in whom AAS is considered in differential diagnosis, decision on CTA/TEE is notoriously difficult and both misdiagnosis (leading to diagnostic delay, inappropriate treatments and ED dismissal) and overt-testing are major concerns.[3-6]

Within minutes, bedside FoCUS can identify red flags warranting urgent aortic imaging or transfer to expert centers. The trade-off in terms of false positives appears largely favorable if direct FoCUS signs are used for rapid re-classification 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 AAS 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 AAS 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 AAS. Previous studies have shown that D-dimer is highly sensitive for AAS.[22, 23] Based on present results, the probability of 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/TEE 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. The highest diagnostic performance was obtained by specialized cardiologists for type A aortic dissection, as previously reported.[13] In our study, cardiologist providers showed increased capacity to identify direct signs of AAS 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 pre-specified sub-analysis of the ADvISED trial, whose aim was to evaluate the diagnostic characteristics of D-dimer for rule-out of AAS.[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 centers 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 was available only for half study patients. However, patients not subjected to CTA/TEE 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/TEE. A diagnostic flow-chart integrating study results with additional clinical considerations is proposed in *figure 6*. Further studies are warranted for external validation, especially to define the best rule-out protocol.

ACKNOWLEDGMENTS

We are grateful to Dr. Emanuele Pivetta (Molinette Hospital, Torino, Italy) for his contribution to statistical revision. This work was supported by the University of Firenze (Firenze, Italy) [grant number 16DPPN].

REFERENCES

1. Bossone E, LaBounty TM, Eagle KA. Acute aortic syndromes: diagnosis and management, an update. *Eur Heart J* 2018; 39: 739-749d.

2. Nienaber CA, von Kodolitsch Y, Nicolas V, Siglow V, Piepho A, Brockhoff C, Koschyk DH, Spielmann RP. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. *N Engl J Med* 1993; 328: 1-9.

3. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. *Am J Cardiol* 2007; 99: 852-6.

4. Pourafkari L, Tajlil A, Ghaffari S, Parvizi R, Chavoshi M, Kolahdouzan K, Khaki N, Parizad R, Hobika GG, Nader ND. The frequency of initial misdiagnosis of acute aortic dissection in the emergency department and its impact on outcome. *Intern Emerg Med* 2016: 1-11.

5. Lovy AJ, Bellin E, Levsky JM, Esses D, Haramati LB. Preliminary development of a clinical decision rule for acute aortic syndromes. *Am J Emerg Med* 2013; 31: 1546-50.

6. Ohle R, Anjum O, Bleeker H, Wells G, Perry JJ. Variation in emergency department use of computed tomography for investigation of acute aortic dissection. *Emerg Radiol* 2018.

7. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Jr., Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA,

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, Breitkreutz 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, Zanoli 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, Myrmel 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, Distante 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.

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

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

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

Figure 6. Proposed diagnostic algorithm based on experimental results and clinical judgment. AAS= acute aortic syndrome; ADD-RS= aortic dissection detection risk score; CTA= computed tomography angiography; FoCUS= transthoracic focused cardiac ultrasound.

Table

Table 1. Demographic and clinical characteristics of study patients.

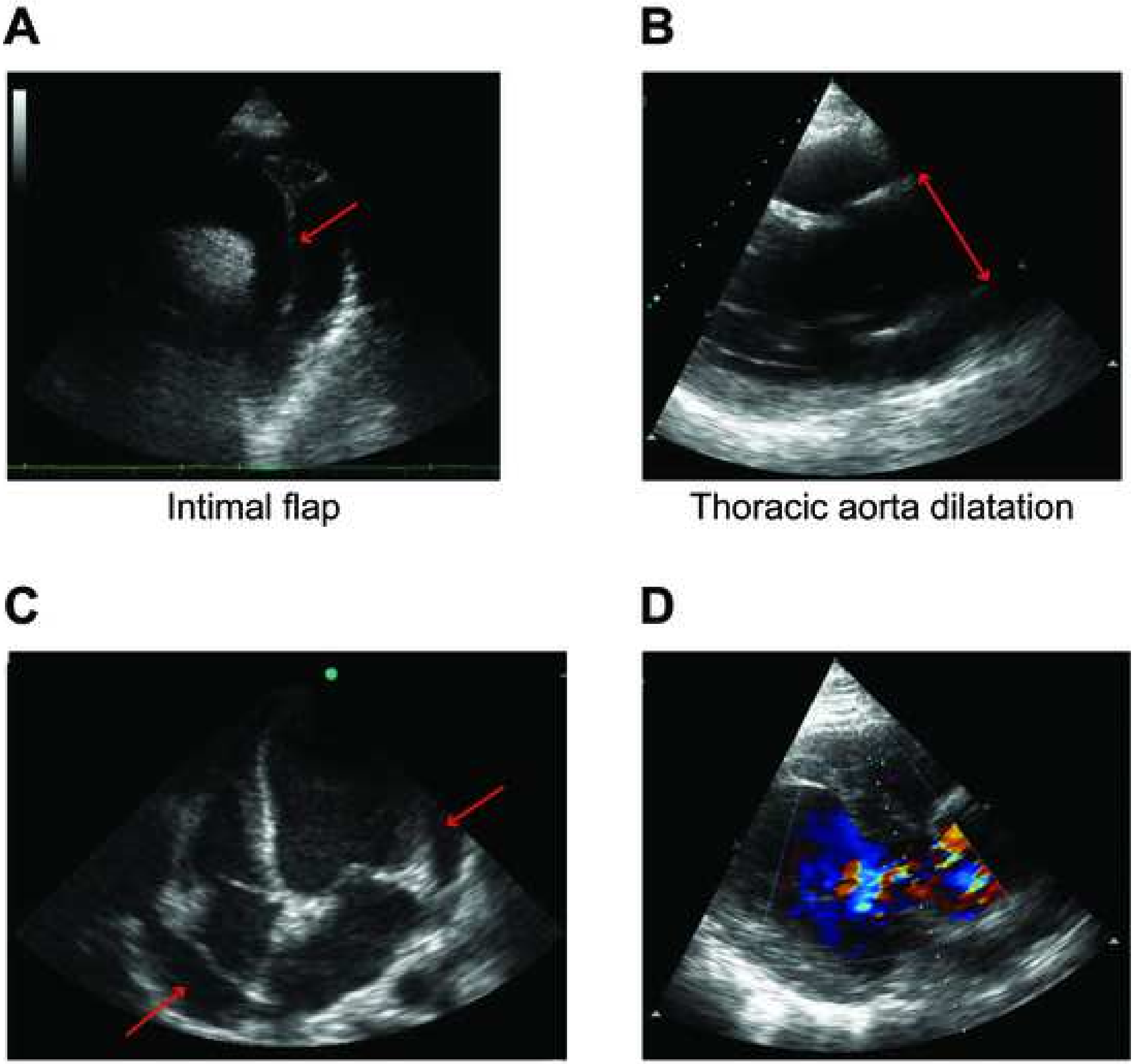
	All patients (n=839)	**AAS (n=146)**	**AltD (n=693)**	***P***
Female gender	299 (35.6%)	43 (29.5%)	256 (36.9%)	0.09
Age (years)	62±16.7	67.5±14.2	60.9 ± 17	<0.01
Predisposing conditions				
Marfan syndrome/connective tissue disease	7 (0.8%)	1 (0.7%)	6 (0.9%)	1
Family history of aortic disease	16 (1.9%)	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

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.

	ADD-RS≤1 **direct FoCUS signs absent** **D-dimer <500 ng/mL**	**ADD-RS≤1** **FoCUS negative*** **D-dimer <500 ng/mL**
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.

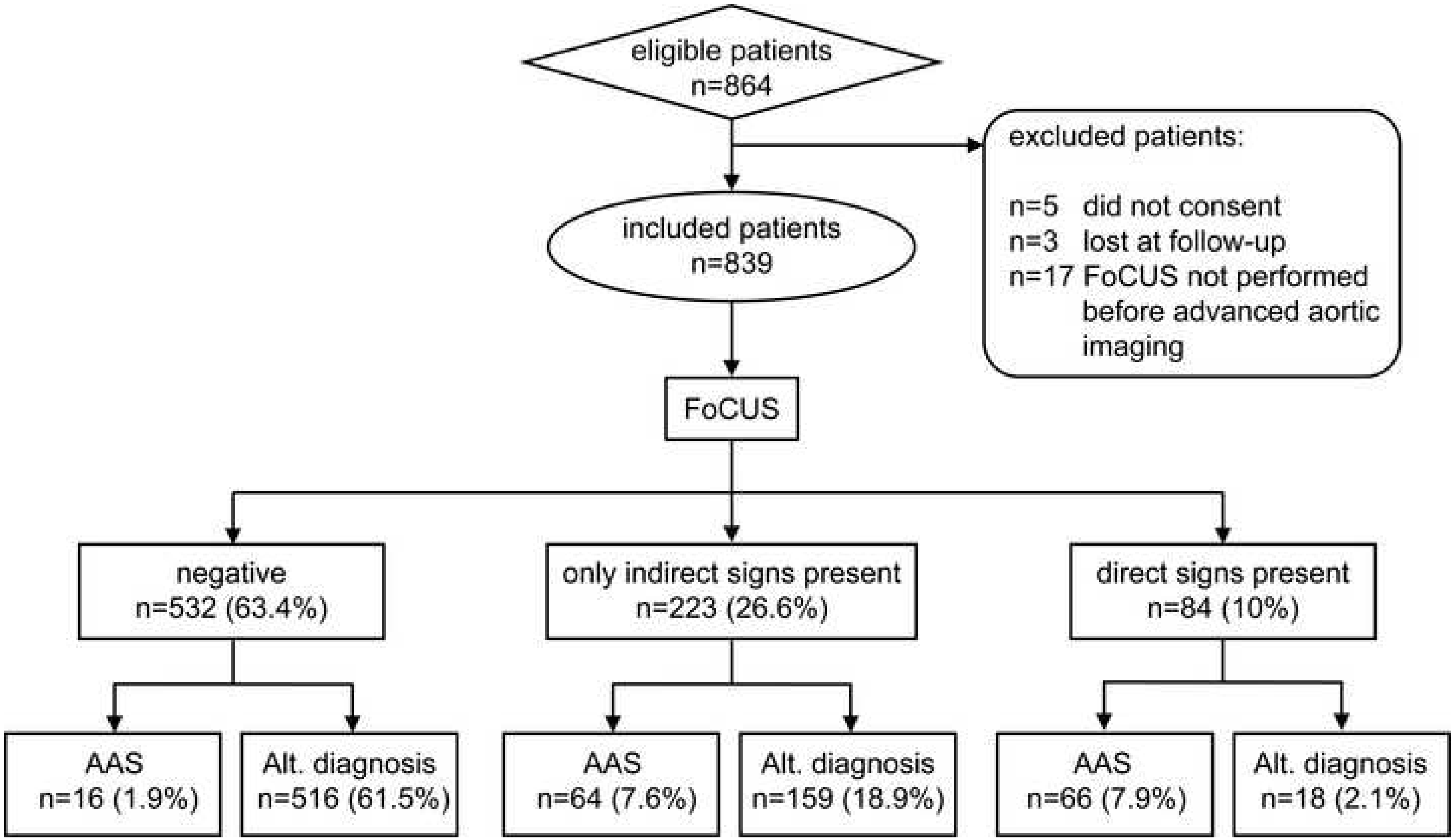


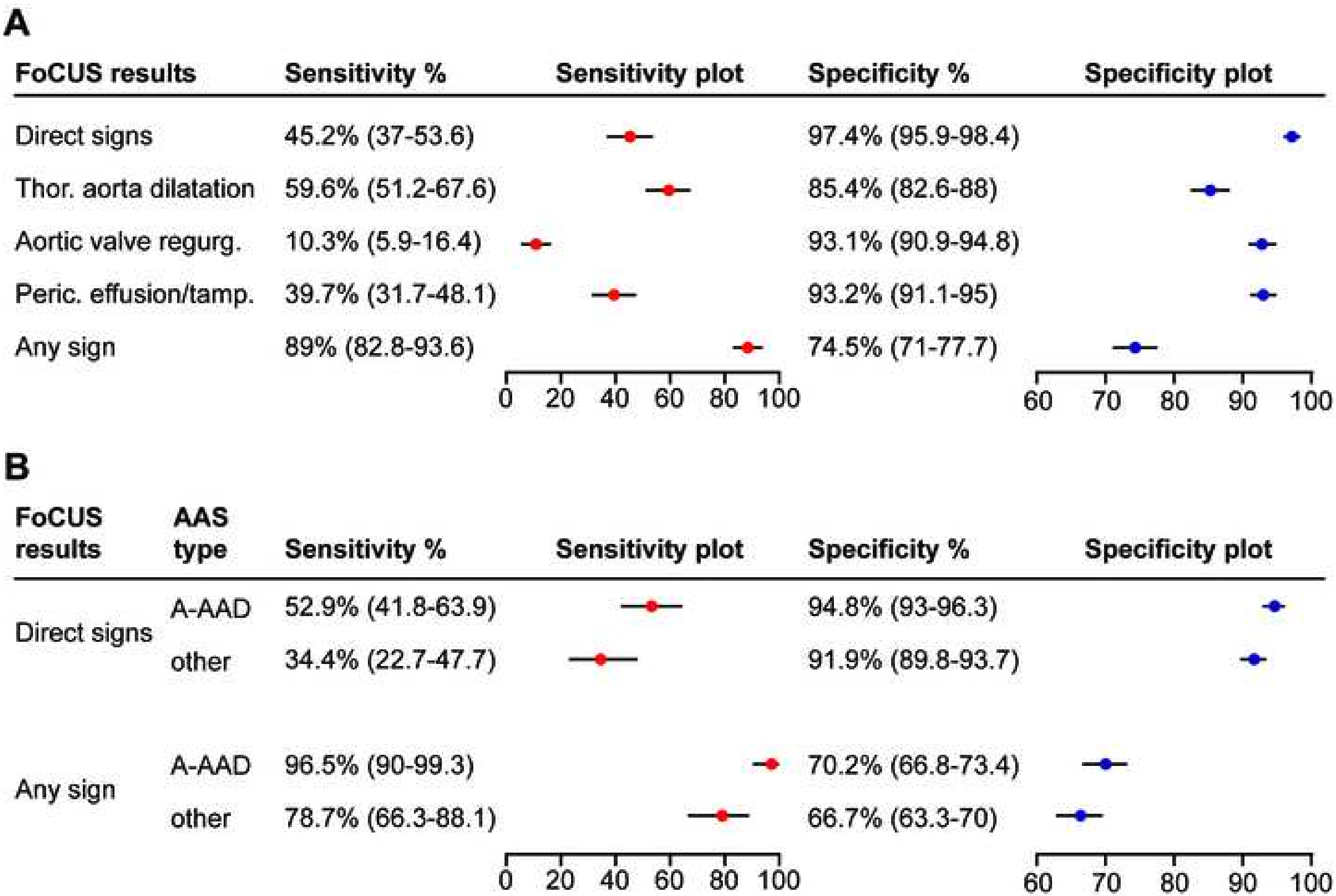
Intimal flap

Thoracic aorta dilatation

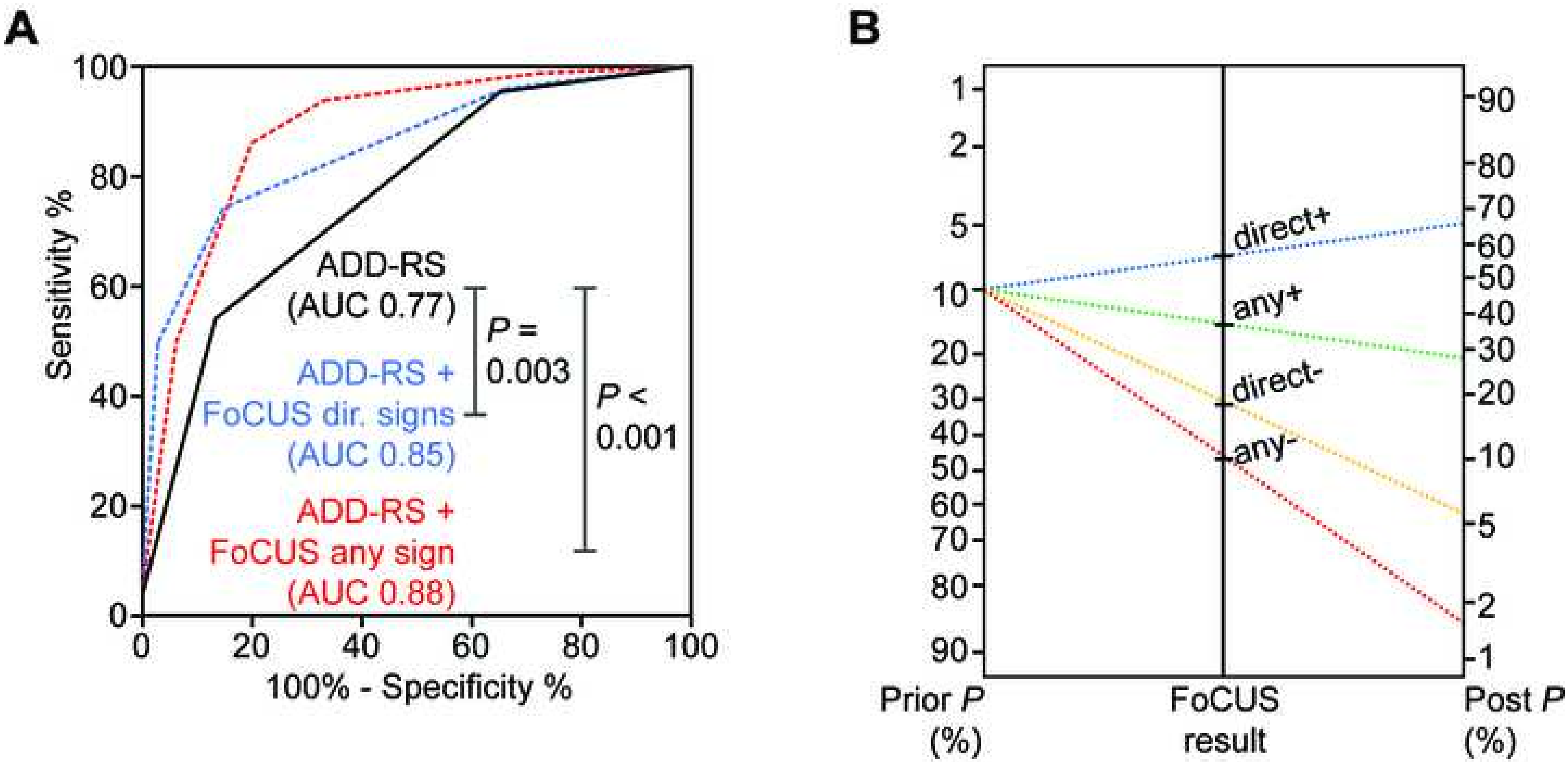
Pericardial effusion

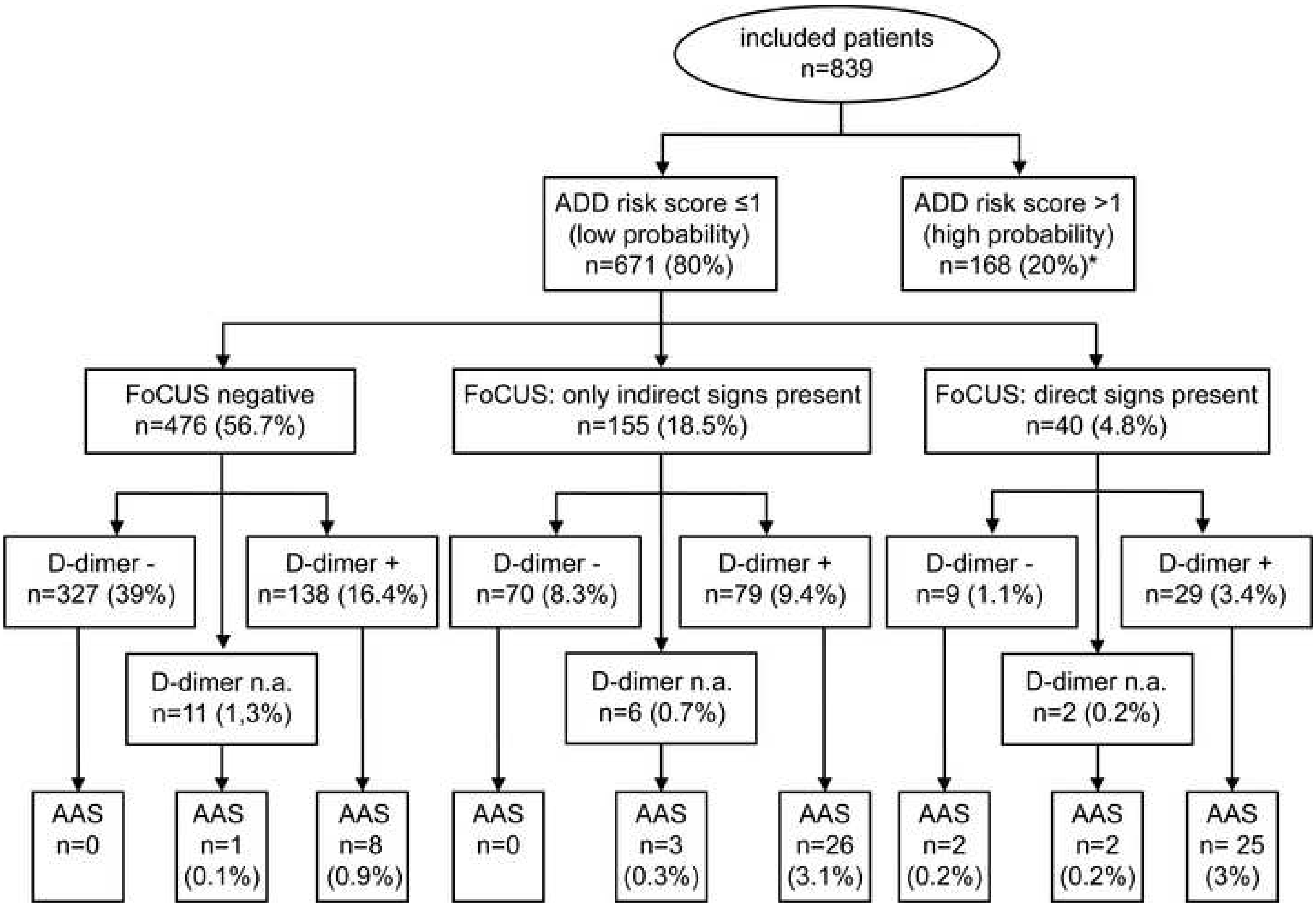
Aortic regurgitation

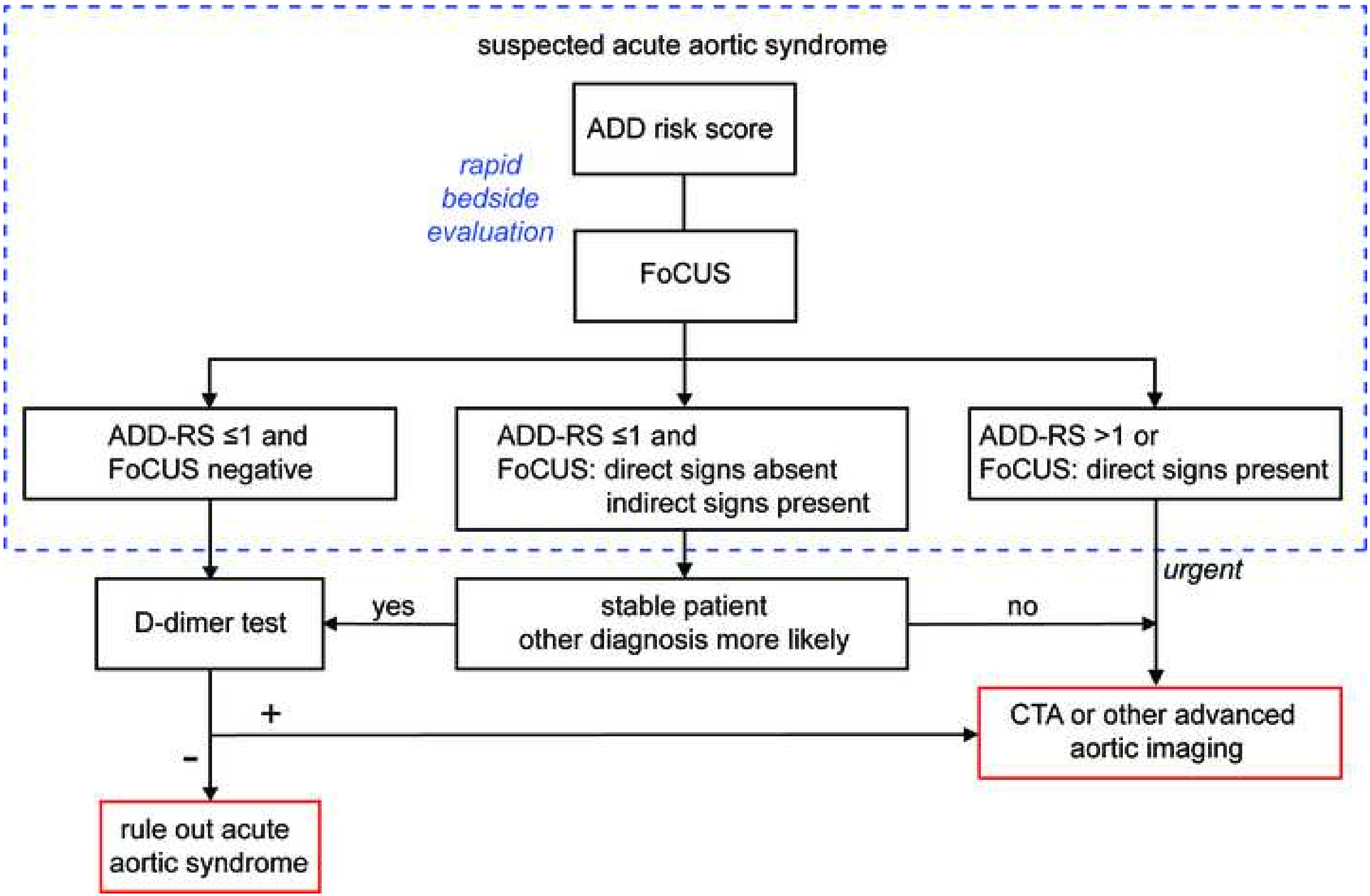

eligible patients
n=864
excluded patients:
n=5 did not consent
n=3 lost at follow-up
n=17 FoCUS not performed before advanced aortic imaging
included patients
n=839
FoCUS
negative
n=532 (63.4%)
only indirect signs present
n=223 (26.6%)
direct signs present
n=84 (10%)
AAS
n=16 (1.9%)
Alt. diagnosis
n=516 (61.5%)
AAS
n=64 (7.6%)
Alt. diagnosis
n=159 (18.9%)
AAS
n=66 (7.9%)
Alt. diagnosis
n=18 (2.1%)


A
FoCUS results
Sensitivity %
Sensitivity plot
Specificity %
Specificity plot
Direct signs
45.2% (37-53.6)
97.4% (95.9-98.4)
Thor. aorta dilatation
59.6% (51.2-67.6)
85.4% (82.6-88)
Aortic valve regurg.
10.3% (5.9-16.4)
93.1% (90.9-94.8)
Peric. effusion/tamp.
39.7% (31.7-48.1)
93.2% (91.1-95)
Any sign
89% (82.8-93.6)
74.5% (71-77.7)
0 20 40 60 80 100
60 70 80 90 100
B
FoCUS results
AAS type
Sensitivity %
Sensitivity plot
Specificity %
Specificity plot
Direct signs
A-AAD
52.9% (41.8-63.9)
94.8% (93-96.3)
other
34.4% (22.7-47.7)
91.9% (89.8-93.7)
Any sign
A-AAD
96.5% (90-99.3)
70.2% (66.8-73.4)
other
78.7% (66.3-88.1)
66.7% (63.3-70)
0 20 40 60 80 100
60 70 80 90 100

Figure


A
100
80
60
40
20
0
Sensitivity %
0
20
40
60
80
100
100% - Specificity %
ADD-RS
(AUC 0.77)
ADD-RS +
FoCUS dir. signs
(AUC 0.85)
ADD-RS +
FoCUS any sign
(AUC 0.88)
P =
0.003
P <
0.001
B
1
2
5
10
20
30
40
50
60
70
80
90
90
80
70
60
50
40
30
20
10
5
2
1
direct+
any+
direct-
any-
Prior P
(%)
FoCUS
result
Post P
(%)


included patients
n=839
ADD risk score ≤1
(low probability)
n=671 (80%)
ADD risk score >1
(high probability)
n=168 (20%)*
FoCUS negative
n=476 (56.7%)
FoCUS: only indirect signs present
n=155 (18.5%)
FoCUS: direct signs present
n=40 (4.8%)
D-dimer -
n=327 (39%)
D-dimer +
n=138 (16.4%)
D-dimer n.a.
n=11 (1,3%)
D-dimer -
n=70 (8.3%)
D-dimer +
n=79 (9.4%)
D-dimer n.a.
n=6 (0.7%)
D-dimer -
n=9 (1.1%)
D-dimer +
n=29 (3.4%)
D-dimer n.a.
n=2 (0.2%)
AAS
n=0
AAS
n=1
(0.1%)
AAS
n=8
(0.9%)
AAS
n=0
AAS
n=3
(0.3%)
AAS
n=26
(3.1%)
AAS
n=2
(0.2%)
AAS
n=2
(0.2%)
AAS
n= 25
(3%)


suspected acute aortic syndrome
ADD risk score
rapid bedside evaluation
FoCUS
ADD-RS ≤1 and FoCUS negative
ADD-RS ≤1 and FoCUS: direct signs absent indirect signs present
ADD-RS >1 or FoCUS: direct signs present
urgent
D-dimer test
yes
stable patient other diagnosis more likely
no
+
-
CTA or other advanced aortic imaging
rule out acute aortic syndrome

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 (+) if ≥ 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[1,2]

Event date___________________ Attending physician ___________________

Patient data

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

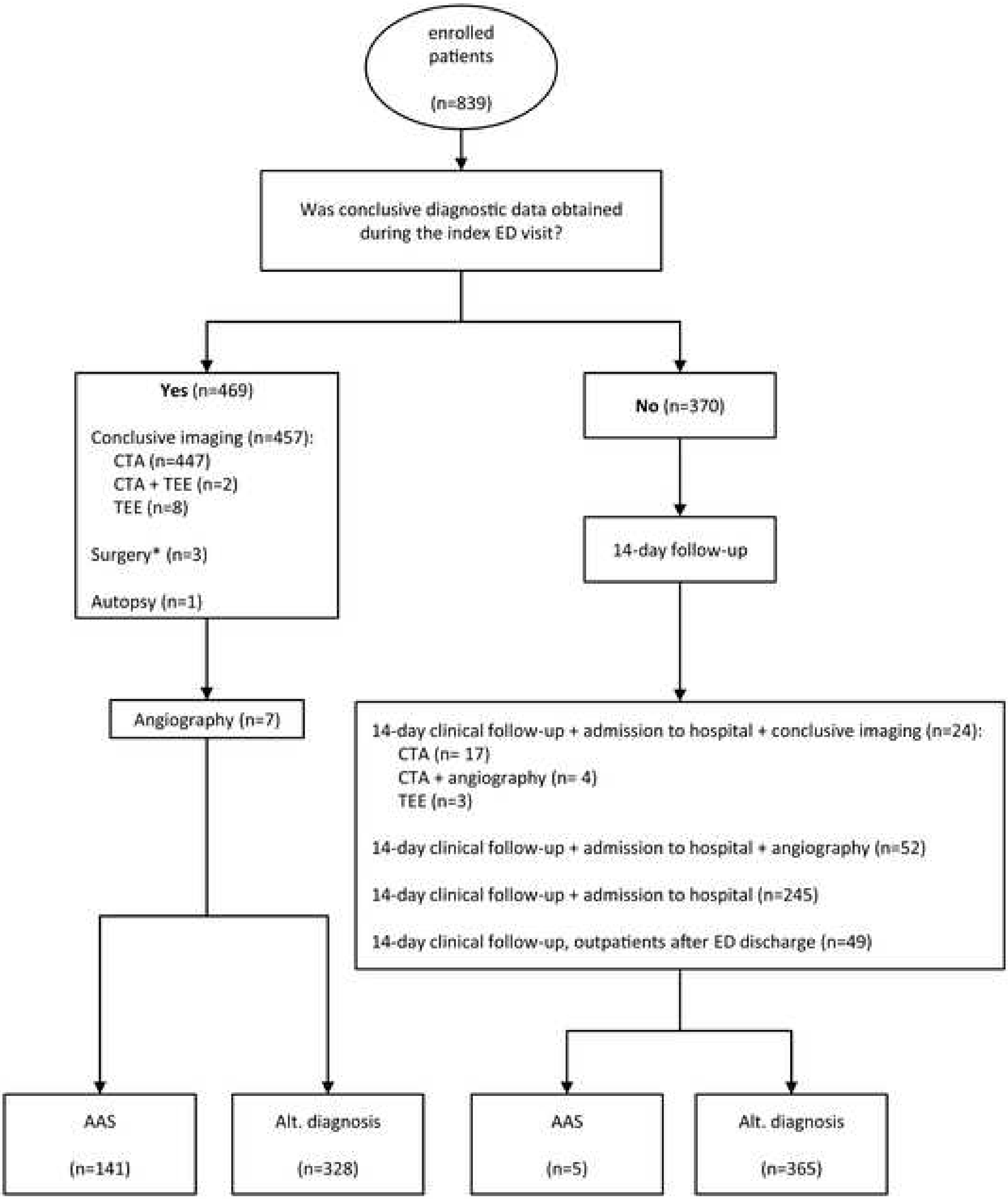
Findings
☐ Intimal flap / intramural hematoma/penetrating aortic ulcer

☐ Enlarged thoracic aortic root (≥40mm)
☐ Pericardial effusion/tamponade
☐ Aortic valve insufficiency

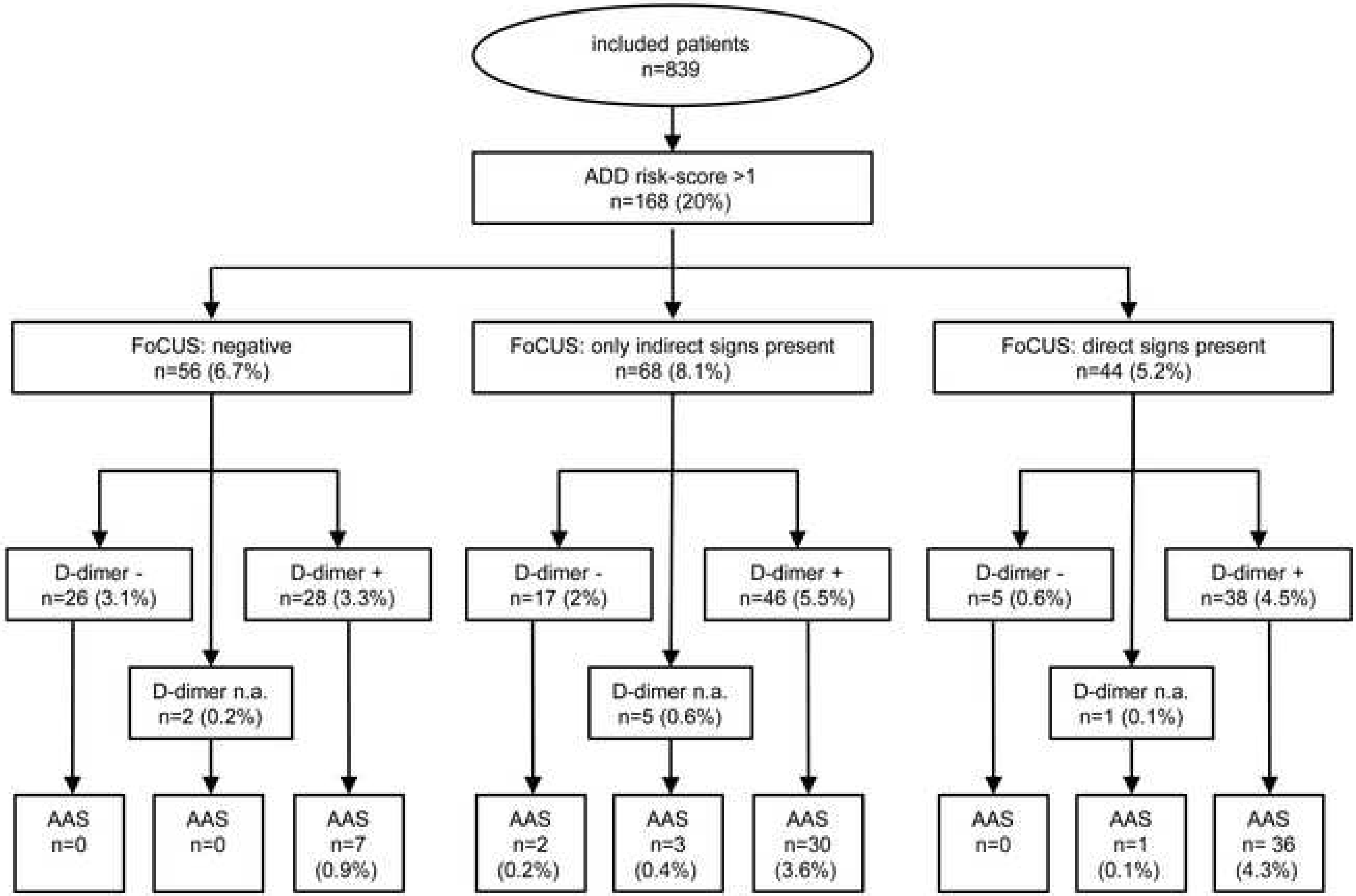
Legend

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

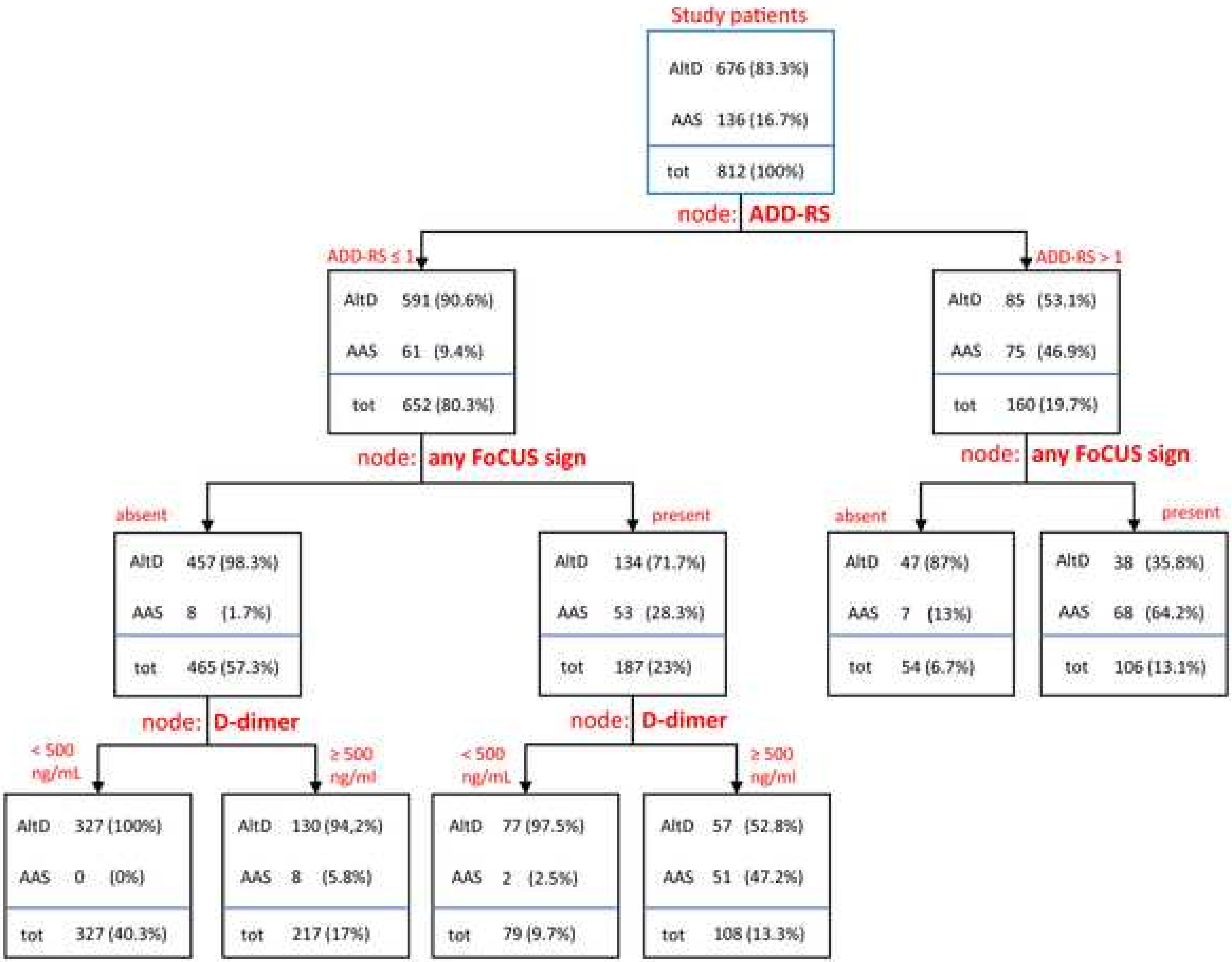
Supplementary files



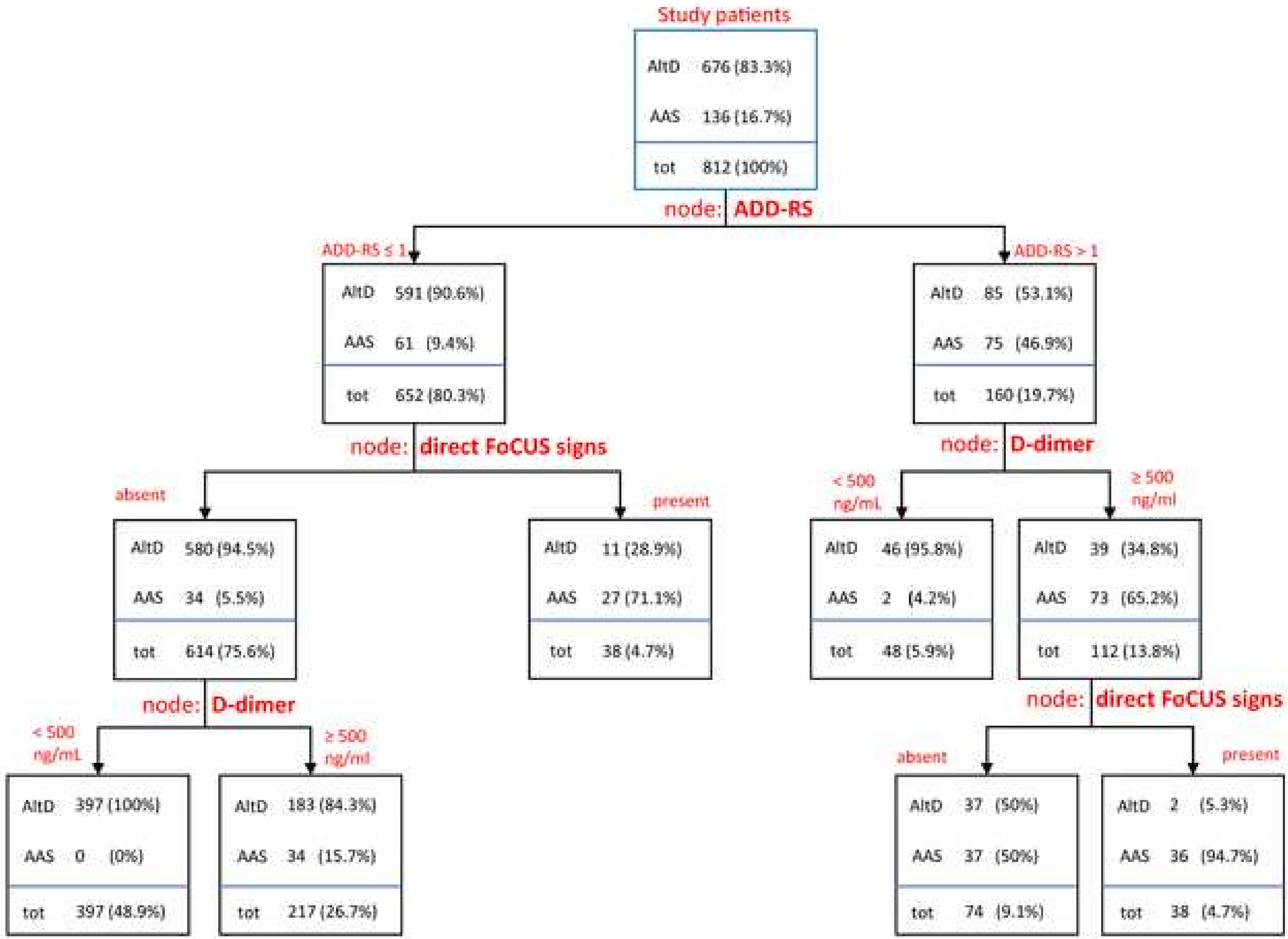
Supplementary files



Supplementary files



Supplementary files



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

FoCUS results	**TP**	**FP**	**TN**	**FN**	**PPV, % (95%CI)**	**NPV, % (95%CI)**	**+LR (95%CI)**	**-LR (95%CI)**
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).

	Sensitivity % (95%CI)			**Specificity % (95%CI)**		
FoCUS results	**Cardiologist**	**Non-cardiologist**	***P***	**Cardiologist**	**Non-cardiologist**	***P***
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.

	P	**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	*0.01*	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	*0.029*	0.016	0.000-0.650
History of ischemic cardiac disease	*0.032*	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	*0.001*	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) ≤1 (low probability of AAS *per* ESC 2014 guidelines).

Diagnostic variable	**% (95% CI)**
n. patients satisfying rule-out criteria	476
AAS	*9*
AltD	*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.

	Diagnostic strategy	Optimism	AUC-ROC
RULE-OUT STRATEGIES	ADD-RS ≤1	0.08%	71.25%
	ADD-RS ≤1 AND direct FoCUS signs absent	0.07%	80.36%
	ADD-RS ≤1 AND FoCUS negative	-0.01%	80.86%
	ADD-RS ≤1 AND direct FoCUS signs absent AND D-dimer negative	-0.03%	79.38%
	ADD-RS ≤1 AND FoCUS negative AND D-dimer negative	0.05%	74.16%
RULE-IN STRATEGIES	ADD-RS > 1	0.06%	71.25%
	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.