

## RESEARCH ARTICLE

## Individualized prediction of risk of ascending aortic syndromes

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## Abstract

## Objectives

Although ascending aortic diameter changes acutely after dissection, recommendation for prophylactic surgery of thoracic aortic aneurysms rely on data from dissected aortas. In this case-control study we aim to identify risk markers for acute and chronic aortic syndromes of the ascending aorta (ACAS-AA). Furthermore, to develop a predictive model for ACAS-AA.

## Methods

We collected data of 188 cases of ACAS-AA and 376 controls standardized to age- and sex of the background population. Medical history and CT-derived aortic morphology were collected. For the dependent outcome ACAS-AA, potential independent risk factors were identified by univariate logistic regression and confirmed in multivariate logistic regression. As post-dissection tubular ascending aortic diameter is prone to expand, this factor was not included in the first model. The individual calculated adjusted odds ratios were then used in ROC-curve analysis to evaluate the diagnostic accuracy of the model. To test the influence of post-ACAS-AA tubular ascending aortic diameter, this was added to the model.

## Results

The following risk factors were identified as independent risk factors for ACAS-AA in multivariate analysis: bicuspid aortic valve (OR 20.41,  $p = 0.03$ ), renal insufficiency (OR 2.9,  $p < 0.01$ ), infrarenal abdominal aortic diameter (OR 1.08,  $p < 0.01$ ), left common carotid artery diameter (OR 1.40,  $p < 0.01$ ) and aortic width (OR 1.07,  $p < 0.01$ ). Area under the curve was 0.88 ( $p < 0.01$ ). Adding post-ACAS-AA tubular ascending aortic diameter to the model, negated the association of bicuspid aortic valve, renal insufficiency, and left common carotid artery diameter. Area under the curve changed to 0.98 ( $p < 0.01$ ).

## Conclusions

A high performing predictive model for ACAS-AA, free of ascending aortic diameter, can be achieved. Furthermore, we have identified abdominal aortic ectasia as an independent risk

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**Abbreviations:** ACAS-AA, acute and chronic aortic syndromes of the ascending aorta; BAV, bicuspid aortic valve; CT, computer tomography; BSA, body surface area; OR, odds ratio; ROC, receiver operating characteristic; AUC, Area under the curve.

factor of ACAS-AA. Integration of potential biomarkers and morphologic variables, derived from undissected aortas, would probably improve the model.

## Introduction

Acute and chronic aortic syndromes of the ascending aorta (ACAS-AA) namely: acute or chronic dissection, rupture, intramural hematoma or penetrating aortic ulcers, are life threatening and require immediate surgery. The prognosis of ACAS-AA is poor as up to 22% of patients die acutely before reaching a hospital [1], and overall in-hospital mortality is 30% [2].

To prevent ACAS-AA, prophylactic surgery is recommended when ascending aortic diameter exceeds 55 mm, with slight modifications if bicuspid aortic valve (BAV) and/or genetic diseases are present [3]. However, recent studies show that most ACAS-AA occur at diameters < 55 mm [2, 4], and some patients do not suffer ACAS-AA regardless of aortic dilatation [2].

The cut-off value of 55 mm is based on data from already dissected aortas. This value has recently been questioned, because ascending aortic diameter expands acutely following dissection [4–7]. However, ascending aortic diameter remains a major indicator for preventive repair, as the relative risk of dissection compared to the background population increases sharply at diameters larger than 45 mm [8]. Consequently, there is a need to explore additional risk factors that can further differentiate the risk of dissection.

Aortic elongation [9] and bovine aortic arch [10] seem to be risk factors for ACAS-AA. Ratios relating aortic diameter to age, body weight and height have been developed, but have not been implemented [11]. The association of supra-aortic vessel diameters have received less attention, as has the presence of abdominal aortic aneurysms or established risk factors for abdominal aortic rupture.

Moreover, diameters of vertebral corpora depend on genetically defined body size. Ratios comparing vertebral corporal diameters to aortic diameter can be easily obtained and might prove useful clinically.

In this paper, we aim to identify risk factors of ACAS-AA, and to develop a predictive multivariate logistic regression model based on computer tomography (CT)-derived aortic variables and medical history.

## Materials and methods

### Setting

We obtained medical records and CT-scans of patients treated at Odense University Hospital, in the department of Cardiac-, Thoracic- and Vascular Surgery and the department of Cardiology, from 01.01.2009 to 01.03.2018. Patients were identified via the patient administrative system, through their social security number. Data was collected retrospectively.

### Participants

**Cases.** We included patients diagnosed with: Acute Stanford type A aortic dissection—symptoms not exceeding 14 days; Chronic Stanford type A aortic dissection—symptoms exceeding 14 days; contained ascending aortic rupture—dissection through all aortic layers except the adventitia; ascending aortic rupture—rupture through all aortic layers; ascending aortic intra mural hematoma—hematoma without a visible intimal dissection flap or inlet;

ascending aortic penetrating aortic ulcers—ulceration into the aortic wall in the basis of an atherosclerotic plaque. We excluded iatrogenic- and traumatic dissections, patients who had not undergone CT-scanning before surgery or death, and patients whose CT-scans or medical history were unobtainable.

We verified the diagnoses through surgical- or autopsy reports if available, otherwise we used radiological reports. If none of the above was available, CT-scans were evaluated according to radiologic features described in the literature [12].

**Controls.** For each case, two controls were included. These were comprised of patients who had undergone CT-scanning of the thorax, and preferably of the abdomen as well, for reasons other than ACAS-AA. To mirror the age distribution of the background population [13], controls were included in age groups with the same distribution. The age-groups begin at 35, and end at older than 85, with five-year intervals. The ratio of men to women was set to 1:1. Finally, to limit possible confounders such as surgery or medication, we collected data from index contacts.

## Variables

The presence of ACAS-AA in the ascending aorta was the dependent variable. Suspected independent variables are summarized in Tables 1 and 2.

**Medical record review.** We gathered data describing weight, height, age, gender, comorbidities, medications, history of illicit drug use, cardiovascular risk factors, family history of aortic disease, predisposing genetic syndromes, laboratory values and blood pressure. Laboratory values and blood pressure were detected at the time of hospitalization for cases, and at the time of index CT-scanning for controls.

Predisposing genetic syndromes included Marfan syndrome, Ehlers-Danlos syndrome type IV, Loeys-Dietz syndrome, and Turner syndrome. Patients with a history of congenital immunosuppression or those with leucopenia (leucocyte levels  $< 4 \times 10^9$  cells/L) and a history of recurrent infections were regarded as chronically immunosuppressed. Autoimmune diseases encompassed Takayasu arteritis, giant cell arteritis, ankylosing spondylitis, morbus Behçet, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, Sjögren's syndrome, Scleroderma, and Hashimoto's thyroiditis. SIRS was defined according to criteria published in an article by Bone et al. [14].

Active -, previous—and never smokers were defined according to self-reporting. Renal insufficiency was defined as  $eGFR < 60$  ml/min/1,73 m<sup>2</sup>. Those treated with an antihypertensive were regarded as having a history of hypertension. Patients treated with antidiabetics or those who had an HBA1c  $> 48$  were regarded as diabetics. Patients with mechanic aortic valves were separated from patients treated with anticoagulant agents for other reasons. Similarly, patients treated with thrombocyte inhibitors due to ischemic stroke were separated from those treated with the same agents for other reasons.

**CT evaluation.** Values were obtained using Siemens syngo.via® image analysis platform. (Siemens Healthcare A/S, Erlangen, Germany).

CT-derived variables were measured in the same manner as a parallel study, performed in the same setting and on the same sample population, the results of which have already been published [6]. In short, the inner-to-inner aortic diameter was measured perpendicular to the vessel axis from the sinotubular junction to the proximal abdominal aorta. The diameters of the supra-aortic vessels were measured as well.

In addition, we measured; the largest infrarenal abdominal aortic diameter in both the mediolateral and anterior-posterior directions; Aortic length—the distance spanning from the sinotubular junction to the corresponding point of the descending aorta in the transverse

**Table 1. Descriptive statistics of independent variables gathered through medical record review, and results of univariate logistic regression analysis, where the presence of acute or chronic aortic syndrome of the ascending aorta is the dependent variable.** Continuous variables are presented with mean  $\pm$  standard deviation, categorical variables with numbers and frequency. “-” = no results due to no/low observations.

Independent variable	Cases	Controls	Univariate analysis results, unadjusted odds ratio (90% Confidence Interval)	p-value
<b>Sex, N (%)</b>				
Men	113 (60.1%)	188 (50%)	1.04 (1.03–1.05)	< 0.01
Women	75 (39.9%)	188 (50%)		
<b>Age (years)</b>	66.33 $\pm$ 13.57	58.13 $\pm$ 14.12	1.51 (1.11–2.02)	0.02
<b>Height (cm)</b>	174.14 $\pm$ 10.35	171.79 $\pm$ 9.72	1.02 (1.01–1.04)	0.01
<b>Weight (kg)</b>	80.00 $\pm$ 19.26	75.42 $\pm$ 16.87	1.01 (1.01–1.02)	< 0.01
<b>BMI (kg/m<sup>2</sup>)</b>	26.21 $\pm$ 4.99	25.52 $\pm$ 4.95	1.02 (0.99–1.05)	0.12
<b>BSA–Dubois formula (m<sup>2</sup>)</b>	1.94 $\pm$ 0.25	1.87 $\pm$ 0.22	3.33 (1.76–6.31)	< 0.01
<b>BSA–Mosteller’s formula (m<sup>2</sup>)</b>	1.95 $\pm$ 0.27	1.88 $\pm$ 0.24	3.00 (1.65–5.46)	< 0.01
<b>Family history of acute or chronic syndrome of the ascending aorta, N (%)</b>	5 (2.7%)	0	1	-
<b>History of, N (%)</b>				
Predisposing genetic syndrome	2 (1.1%)	0	1	-
Abdominal/Descending aortic dissection or rupture	9 (4.7%)	4 (1.0%)	4.67 (1.72–12.7)	0.01
Aortic Coarctation	1 (0.5%)	0	1	-
Bicuspid aortic valve	10 (5.3%)	3 (0.7%)	6.98 (2.34–20.83)	< 0.01
Replaced aortic valve	11 (5.8%)	3 (0.8%)	7.72 (2.61–22.79)	< 0.01
COPD	20 (10.7%)	49 (13.0%)	0.79 (0.5–1.27)	0.42
Polycystic kidney disease	0	3 (0.8%)	1	-
Hypertension	86 (46%)	132 (35.1%)	1.58 (1.17–2.14)	0.01
Diabetes	9 (4.8%)	31 (8.2%)	0.56 (0.29–1.06)	0.14
Peripheral arterial disease	3 (1.6%)	12 (3.2%)	0.49 (0.16–1.44)	0.28
Ischemic heart disease	19 (10.2%)	24 (6.4%)	1.65 (0.97–2.81)	0.11
Cerebrovascular disease	25 (13.3%)	21 (5.5%)	2.60 (1.56–4.34)	< 0.01
Renal insufficiency	70 (37.8%)	44 (11.9%)	4.46 (3.11–6.42)	< 0.01
Chronic immunosuppression	15 (8.0%)	18 (4.8%)	1.73 (0.95–3.14)	0.12
Autoimmune diseases	12 (6.4%)	12 (3.2%)	2.08 (1.04–4.14)	0.08
Pheochromocytoma	0	0	1	-
SIRS within 3 months	15 (8.0%)	46 (12.2%)	0.62 (0.37–1.04)	0.13
Pregnancy	0	0	1	-
<b>Smoking</b>				
<b>Current</b>	61 (35.7%)	177 (47.4%)	0.33 (0.22–0.47)	< 0.01
<b>Former</b>	40 (23.4%)	129 (34.6%)	0.29 (0.19–0.47)	< 0.01
<b>Never</b>	70 (37.2%)	67 (17.8%)	-	-
<b>Medication and Drugs, N (%)</b>				
Statins	43 (23.1%)	71 (18.9%)	1.29 (0.90–1.84)	0.24
Warfarin/NOAC	21 (11.2%)	21 (5.5%)	2.15 (1.26–3.65)	0.01
Oral glucocorticoids	9 (4.8%)	16 (4.3%)	1.14 (0.56–2.31)	0.75
Bronchodilators	20 (10.7%)	55 (14.6%)	0.70 (0.44–1.11)	0.20
Platelet inhibitors	51 (27.0%)	64 (17%)	1.84 (1.29–2.61)	< 0.01
NSAID	6 (3.2%)	16 (4.3%)	0.75 (0.33–1.67)	0.55
Cocaine	0	0	1	-
Amphetamine	0	1 (0.3%)	1	-
<b>Blood pressure (mmHg)</b>				
Systolic	120 $\pm$ 32	138 $\pm$ 22	0.97 (0.96–0.98)	< 0.01

(Continued)

Table 1. (Continued)

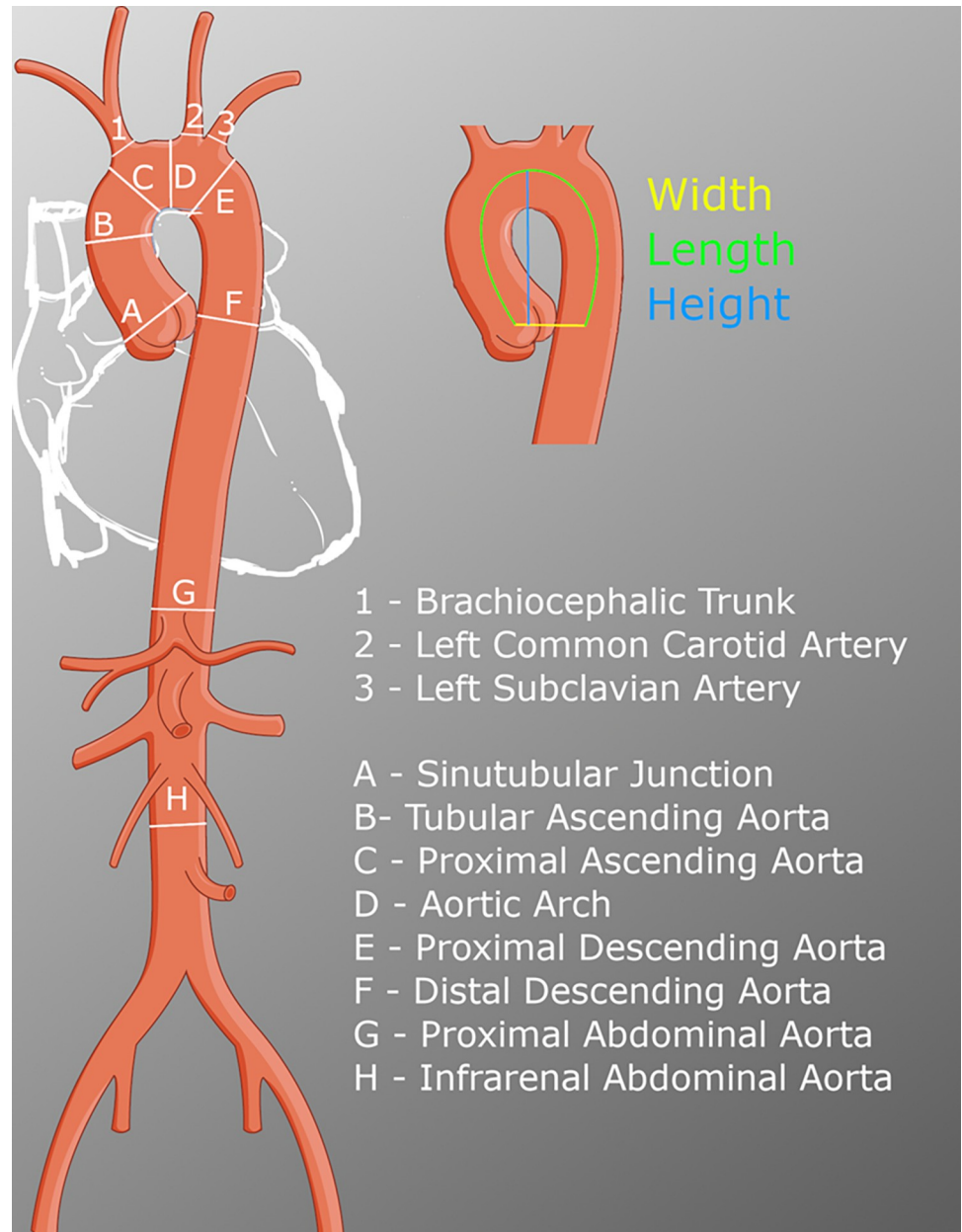
Independent variable	Cases	Controls	Univariate analysis results, unadjusted odds ratio (90% Confidence Interval)	p-value
Diastolic	66 ± 20	81 ± 12	0.94 (0.93–0.95)	< 0.01
Mean arterial pressure	84 ± 22	100 ± 14	0.95 (0.94–0.96)	< 0.01
Pulse pressure	52 ± 23	57 ± 17	0.98 (0.98–0.99)	0.01
<b>Laboratory values</b>				
Hemoglobin (mmol/L)	8 ± 1.14	8 ± 1.01	0.67 (0.58–0.77)	< 0.01
Thrombocytes (10 <sup>9</sup> /L)	205 ± 71.47	296 ± 108	0.98 (0.98–0.99)	< 0.01
Creatinine (μmol/L)	98 ± 46.38	83 ± 88.53	1.01 (1.00–1.01)	0.09
eGFR (ml/min/1.73 m <sup>2</sup> )	69 ± 23.07	86 ± 21.15	0.96 (0.96–0.97)	< 0.01

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Table 2. Descriptive statistics of independent variables, gathered through analysis of computer tomography scans, and results of univariate logistic regression analysis where the presence of acute or chronic aortic syndrome of the ascending aorta is the dependent variable. Continuous variables are presented with mean ± standard deviation, categorical variables with numbers and frequency. “-” = no results due to no/low observations.

Independent variable	Cases	Controls	Univariate analysis results, unadjusted odds ratio (90% Confidence Interval)	p-value
<b>Variations of aortic anatomy, N (%)</b>				
Bovine arch	35 (18.6%)	53 (14.1%)	1.39 (0.94–2.06)	0.16
Isolated vertebral artery	14 (7.4%)	21 (5.6%)	1.36 (0.75–2.44)	0.38
Aberrant right subclavian artery	0	1 (0.3%)	1	-
Right aortic arch	0	0	1	-
<b>Arterial vessel diameters (mm)</b>				
Sinutubular junction	49.31 ± 10.55	31.64 ± 4.55	1.46 (1.38–1.55)	< 0.01
Tubular Ascending Aorta	53.44 ± 10.16	34.92 ± 4.75	1.49 (1.40–1.58)	< 0.01
Ratio to medio-lateral abdominal aortic diameter	0.49 ± 0.23	0.57 ± 0.15	0.01 (0.01–0.03)	< 0.01
Ratio to First Vertebral Corpus	29.5 ± 0.44	19.9 ± 0.15	1.82 (1.66–1.99)	< 0.01
Distal Ascending Aorta	41.78 ± 6.74	31.90 ± 3.89	1.54 (1.45–1.64)	< 0.01
Aortic Arch	31.89 ± 4.60	26.59 ± 3.31	1.44 (1.36–1.52)	< 0.01
Proximal Descending Aorta	29.54 ± 4.35	24.02 ± 3.08	1.54 (1.44–1.64)	< 0.01
Descending Aorta	31.85 ± 5.45	25.37 ± 3.29	1.49 (1.40–1.58)	< 0.01
Proximal Abdominal Aorta	28.18 ± 4.26	23.45 ± 3.23	1.43 (1.35–1.51)	< 0.01
Distal Abdominal Aorta	23.16 ± 4.59	19.14 ± 3.05	1.38 (1.30–1.46)	< 0.01
Infrarenal abdominal Aortic Diameter				
Anterior-posterior	25.14 ± 8.35	19.83 ± 5.59	1.17 (1.12–1.22)	< 0.01
Medio-lateral	25.73 ± 9.74	19.94 ± 5.80	1.16 (1.12–1.20)	< 0.01
Ratio to Third Lumbar Corpus	7.40 ± 2.20	6.00 ± 1.58	1.72 (1.51–1.96)	< 0.01
Brachiocephalic trunk	15.87 ± 2.99	12.54 ± 2.27	1.62 (1.50–1.74)	< 0.01
Left Common Carotid Artery	9.64 ± 2.35	8.10 ± 1.36	1.63 (1.48–1.79)	< 0.01
Left Subclavian Artery	12.67 ± 2.87	11.11 ± 2.16	1.28 (1.21–1.37)	< 0.01
<b>Other (mm)</b>				
Aortic length	224.15 ± 26.91	185.56 ± 30.61	1.04 (1.03–1.05)	< 0.01
Aortic width	98.04 ± 15.93	78.37 ± 13.39	1.09 (1.07–1.11)	< 0.01
Aortic height	80.56 ± 12.69	68.63 ± 13.1	1.07 (1.05–1.08)	< 0.01
Aortic Tortuosity	2.33 ± 0.43	2.39 ± 0.38	0.67 (0.45–0.98)	0.08
Diameter of First Thoracic Vertebral Corpus	18.23 ± 1.98	17.58 ± 1.81	1.20 (1.11–1.30)	< 0.01
Diameter of Third Lumbar Vertebral Corpus	33.50 ± 3.45	33.20 ± 3.30	1.02 (0.98–1.07)	0.33
Estimated ascending aortic diameter	34.79 ± 1.30	33.68 ± 1.37	1.57 (1.4–1.77)	< 0.01

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**Fig 1. Illustrates the level at which aortic and other vessel diameter and morphology was measured.** This figure was created using adapted material from Smart Servier Medical Art, [smart.servier.com](https://smart.servier.com).

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plane; Aortic width—the direct distance between the sinotubular junction and the corresponding point of the descending aorta in the transverse plane; Aortic height—the distance between the most superior point of the aortic centerline to the transverse level at which the aortic width was measured, in a 90 degree angle; Anterior to posterior diameters of the first thoracic and third lumbar vertebral corporal bodies, perpendicular to the vertebral corporal axis. Finally, anatomic supra-aortic vessel variation was noted. Locations of aortic measurements are illustrated in Fig 1.

**Calculated data.** Body surface area (BSA) was calculated using Mosteller's and Duboi's formulae. Tortuosity was defined as the ratio between aortic length and width. We calculated



the ratio of the anterior-posterior infrarenal abdominal aortic diameter relative to the diameter of the third lumbar vertebral corpus multiplied by 10 to make the results interpretable. Finally a calculated estimate of ascending aortic diameter derived from a study by Obel et al. [15], was calculated. This estimate relies on age, BSA and sex.

### Statistical analysis

We used STATA 16.1® (STATA Corp, College Station, TX 77845, USA) to analyze all data. Missing data was ignored. Through univariate logistic regression analysis, we identified potential risk factors associated to the dependent variable using  $p < 0.10$ . The identified risk factors were then included in multivariate logistic regression analysis.

To reduce collinearity in multivariate analysis, we included the risk factor with the highest odds ratio (OR) in univariate analysis from factors that described the same aspect, e.g., BMI, height and BSA. If in doubt we ran the model with the competing variables and chose that which yielded the highest performing multivariate model. Thus, the following variables were excluded from multivariable analysis: age, sex, height, weight, BMI, BSA, creatinine levels, aortic length, aortic height, aortic tortuosity, distal abdominal aortic diameter, left subclavian artery diameter, anterior-posterior infrarenal abdominal aortic diameter and its derived calculated variables.

ACAS-AA can influence blood pressure, hemoglobin—and thrombocyte levels. Bleeding or dissection extending to the aortic valve can lower blood pressure. Bleeding can also influence hemoglobin and thrombocyte levels. These variables were therefore excluded from multivariate analysis. Considering the expected high abundance of smokers in the control group, history of smoking was also excluded.

In already published results from a parallel study on this population, our results have shown that diameters increase significantly from the sinotubular junction to the proximal abdominal aorta, as well as in the brachiocephalic trunk, after acute dissection [6]. Therefore, we excluded the following CT-derived variables from multivariate regression analysis: sinotubular junction aortic diameter, tubular ascending aortic diameter and its derived calculated variables, distal ascending aortic diameter, aortic arch diameter, proximal descending aortic diameter, descending aorta diameter, and proximal abdominal aortic diameter. However, to test the influence of including tubular ascending aortic diameter to the multivariate model, we made an additional model where it was included.

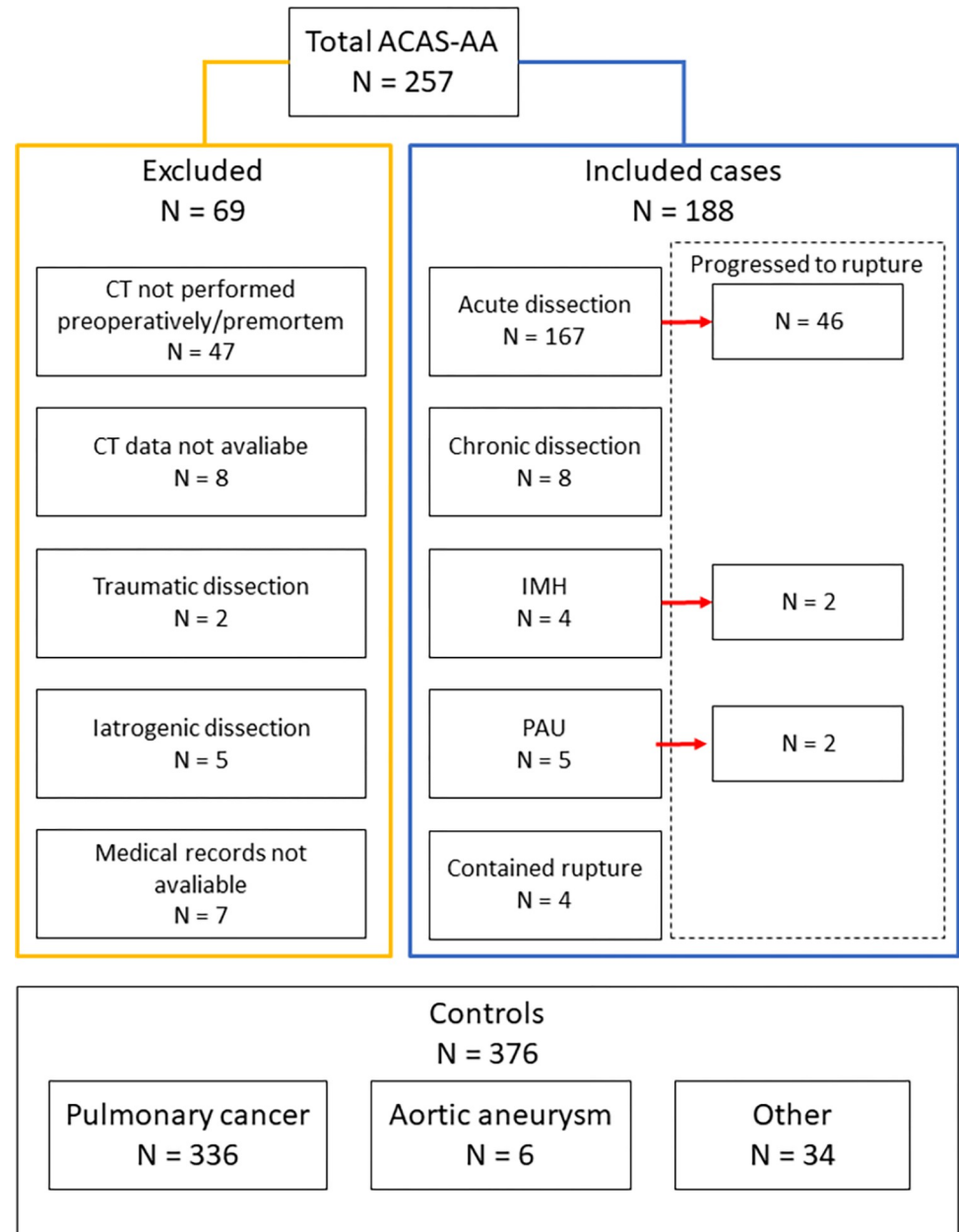
Independent risk factors in multivariate analysis were defined by  $p < 0.05$ . The diagnostic accuracy of the models were evaluated using receiver operating characteristic (ROC) curve analysis including area under the curve (AUC). Using STATA generated individual sensitivity and specificity, we calculated Youden index. The highest calculated Youden index was then used to determine the optimal sensitivity and specificity for the models.

### Ethical permission

The project received approval from the Department of Patient Safety at the National Board of Health (3-3013-2124/1), and the data protection agency. It was reported to our department's internal database, in compliance with The Danish Code of Conduct. Data was stored in a Red-Cap database. Scientific ethical approval and informed consent were not required by the ethics committee as no new patient contact or intervention took place.

### Results

We included 188 cases, and excluded 69 out of a total of 257 reported ACAS-AA cases. Of the excluded ACAS-AA patients, 47 did not undergo CT-scanning prior to operation or death, 8 did not have available CT data, 2 suffered from traumatic ACAS-AA, 5 suffered from



**Fig 2. Inclusion and exclusion of cases and controls.** n = number, ASAC-AA = Acute and chronic aortic syndromes of the ascending aorta, CT = computer-tomography scan, IMH = intramural hematoma, PAU = penetrating aortic ulcer. Other = patients with recurrent spontaneous pneumothorax or benign pulmonary tumors.

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iatrogenic ACAS-AA, and 7 had no available medical records. Consequently, 376 controls were included. The control group included 336 patients diagnosed with pulmonary cancer, 6 with ascending aortic aneurysms, and 34 with benign pulmonary tumors or recurrent spontaneous pneumothorax, as detailed in Fig 2. Tables 1 and 2 summarize all variables, descriptive statistics, and results of univariate regression analysis.

The following variables were included in multivariate analysis: BAV; aortic width; renal insufficiency; history of aortic valve surgery;—hypertension,—cerebrovascular disease,—auto-immune disease and abdominal/descending aortic dissection or rupture; use of anticoagulants,



**Table 3. Result of multivariate logistic regression analysis model were the presence of acute and chronic aortic syndromes of the ascending aorta is the dependent variable.** Renal insufficiency was defined as eGFR < 60. Aortic width is the direct distance from the sinutubular junction to the corresponding point of the descending aorta in the transverse plane. OR = Odds ratio, CI = confidence interval.

Independent variable	Model one		Model two	
	OR (CI)	P-value	OR (CI)	P-value
<b>History of</b>				
Abdominal/descending aortic dissection or rupture	1.01 (0.14–7.18)	0.98	4.41 (0.27–71.658)	0.49
Bicuspid aortic valve	20.41 (2.14–194.44)	< 0.01	0.69 (0.03–14.19)	0.81
Replaced aortic valve	3.5 (0.74–16.38)	0.11	16.26 (0.98–268.99)	0.051
Hypertension	0.57 (0.31–1.06)	0.07	0.54 (0.20–1.49)	0.24
Cerebrovascular disease	1.69 (0.67–4.24)	0.26	2.81 (0.60–13.06)	0.18
Renal insufficiency	2.9 (1.53–5.47)	< 0.01	3.01 (0.99–7.77)	0.051
Autoimmune disease	2.09 (0.73–5.93)	0.16	6.86 (1.62–5.05)	< 0.01
<b>Use of</b>				
Warfarin/NOAC	1.49 (0.59–3.79)	0.39	0.92 (0.17–5.04)	0.93
Platelet inhibitors	0.86 (0.42–1.78)	0.69	0.67 (0.19–2.34)	0.53
Infrarenal medio-lateral abdominal aortic diameter	1.08 (1.03–1.13)	< 0.01	1.10 (1.03–1.17)	< 0.01
Left common carotid artery diameter	1.40 (1.21–1.63)	< 0.01	1.02 (0.86–1.39)	0.42
Aortic width	1.07 (1.05–1.09)	< 0.01	0.94 (0.94–1.02)	0.45
First Thoracic Vertebral Corporal diameter	0.88 (0.76–1.02)	0.10	0.87 (0.67–1.12)	0.28
Estimated ascending aortic diameter	0.99 (0.78–1.25)	0.93	0.78 (0.52–1.18)	0.24
Tubular ascending aortic diameter	-	-	1.66 (1.47–1.87)	< 0.01

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use of platelet inhibitors; medio-lateral abdominal aortic diameter; LCCA diameter, diameter of first thoracic corporal body; calculated estimate of ascending aortic diameter.

Identified independent risk markers by multivariate analysis were (model one): BAV (OR 20.41, 95% CI 2.14–194.44,  $p < 0.01$ ), renal insufficiency (OR 2.9, 95% CI 1.53–5.47,  $p < 0.01$ ), medio-lateral infrarenal abdominal aortic diameter (OR 1.08, 95% CI 1.03–1.13,  $p < 0.01$ ), LCCA diameter (OR 1.4, 95% CI 1.21–1.63,  $p < 0.01$ ), and aortic width (OR 1.07, 95% CI 1.05–1.09,  $p < 0.01$ ).

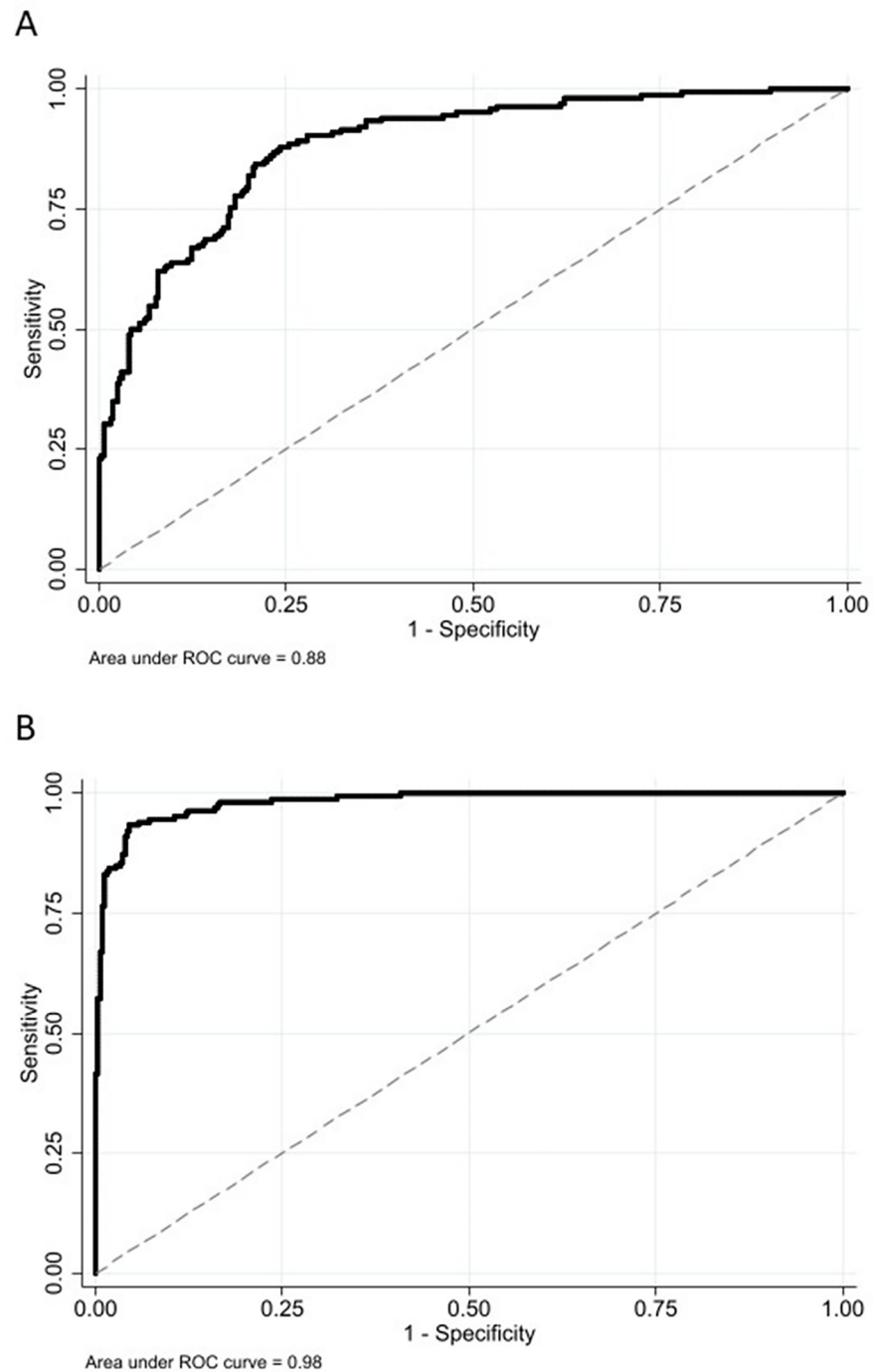
The following variables were significantly associated with the independent variable when tubular ascending aortic diameter was included (model two): autoimmune disease (OR 6.86, 95% CI 1.62–5.05,  $p < 0.01$ ), medio-lateral infrarenal abdominal aortic diameter (OR 1.10, 95% CI 1.03–1.17,  $p < 0.01$ ) and tubular ascending aortic diameter (OR 1.66, 95% CI 1.47–1.87,  $p < 0.01$ ). Table 3 demonstrates the results of both models.

ROC curve analysis of model one yielded an estimated AUC of 0.88 ( $p < 0.01$ ), for which highest calculated Youden index was 0.63, yielding an optimal sensitivity and specificity of 87% and 75%, respectively. For model two the estimated AUC was 0.98 ( $p < 0.01$ ), the highest calculated Youden index was 0.88, with optimal sensitivity and specificity of 93% and 95%, respectively. ROC curve analysis for both models are illustrated in Fig 3.

Considering the results published by McClure et al. [16], the cumulated life risk of ACA-S-AA in a Danish population aged 40 years or more, is approximately 0.2%. Using our models, positive predictive value would equal 0.6% and 3.59% in model one and two, respectively. Consequently, to prevent one event of ACAS-AA, 166 elective repairs are needed using model one, and 27 using model two.

## Discussion

In this case-control study, we explored the differences between patients suffering from acute or chronic syndromes of the ascending aorta, and a control group. Variables explored were



**Fig 3. Receiver operating characteristic curve analysis of multivariate logistic regression models, where presence of acute and chronic aortic syndromes of the ascending aorta is the dependent variable.** The independent variables in "A" are BAV, aortic width, renal insufficiency, use of anticoagulants, use of platelet inhibitors, medio-lateral abdominal aortic diameter, left common carotid artery diameter, diameter of first thoracic corporal body, calculated estimate of ascending aortic diameter, and history of aortic valve surgery, hypertension, cerebrovascular disease, autoimmune disease and abdominal/descending aortic dissection or rupture. The independent variables in "B" are the same as A with the addition of tubular ascending aortic diameter.

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derived from medical history and CT-scans, and tested with univariate logistic regression analysis. The association of potential risk factors was then confirmed with multivariate regression analysis. Finally, we developed two predictive models using multivariate logistic regression analysis. Model one excludes ascending aortic diameter, and model two does not.

In consistency with the literature [3, 17–20], results from the univariate analysis shows that patients suffering from ACAS-AA were more likely to be older, males, with higher BSA and frequency of cardiovascular disease,—hypertension, and use of warfarin and platelet inhibitors. Morphologically, ACAS-AA patients had larger aortic and supra-aortic vessel diameters, and longer, wider thoracic aortas.

Furthermore, our data shows that ACAS-AA patients suffer more frequently from renal insufficiency than controls. Results from population-based studies have estimated the prevalence of chronic kidney disease in patients suffering from aortic dissections to range from 8.5%– 20.4% [21]. Cases in this project had a relatively higher prevalence of renal insufficiency (37.8%), but this result might be different if the excluded cases are considered.

Identified independent risk factors for ACAS-AA in multivariate analysis model one were BAV, renal insufficiency, abdominal aortic ectasia, LCCA diameter and aortic width. The addition of tubular ascending aortic diameter to the multivariate analysis, in model two, negated the association of morphologically derived variables except abdominal aortic diameter. The association of renal insufficiency ceased, although the OR confidence interval remained largely positive. Lastly, autoimmune disease was an independent risk factor in model two, but not in model one.

The presence of BAV is a well-established risk factor for ACAS-AA [22, 23]. The task force for the diagnosis and treatment of aortic diseases of the European Society of Cardiology recommends prophylactic surgical intervention in patients with BAV and ascending aortic aneurysms equal to or exceeding 50 mm [22]. While the American College of Cardiology/American Heart Association task force guideline for the management of patients with valvular heart disease recommends surgical interventions if ascending aortic aneurysms equal to or exceeds 55 mm [23].

Chronic kidney disease is an established risk factor for atherosclerotic cardiovascular diseases [24]. Atherosclerotic lesions in the aorta can provide the bases for ulceration and subsequent intramural hematoma and rupture [22]. However, only four cases were diagnosed with intramural hematoma and five with penetrating aortic ulcer in this project. Interestingly, a recent study has found that lipid metabolism index, inflammatory factor index and M1 macrophage content, were significantly higher in patients diagnosed with dissection and atherosclerotic disease compared to patients with atherosclerotic disease [25]. These findings could suggest a link between progressing atherosclerotic disease, aortic wall degradation and increased risk of ACAS-AA.

Chronic kidney disease patients have similar characteristics to patients who suffer from ACAS-AA, such as increasing age, male gender, hypertension and higher frequency of cardiovascular diseases [24]. Nonetheless, these factors were accounted for in multivariate analysis, directly or indirectly through calculated estimated ascending aortic diameter. To the best of our knowledge, a direct association between renal insufficiency and ACAS-AA has not been reported previously.

The association of infrarenal abdominal aortic ectasia, LCCA and increased aortic width could point to a generalized pathology of the great vessels rather than one localized to the ascending aorta. Underlying systemic—and genetic diseases, as well as family history of ascending aortic disease are already established risk factors for ACAS-AA [3] and may contribute to the systemic ectasia of the great vessels.

Local inflammatory diseases, such as Takayasu arteritis or giant cell arteritis, are known risk factor for development of thoracic aortic aneurysms and ACAS-AA [3, 26]. The increased

risk has also been described for systemic inflammatory diseases, such as Sjögrens syndrome or systemic lupus erythematosus [27, 28]. Thus, there seems to be some evidence suggesting that systemic inflammatory processes can induce local conditions in the aortic wall that favor ectasia and ACAS-AA.

We did not find an association between bovine aortic arch and ACAS-AA, the presence of which has consistently been shown to be associated with ascending aortic aneurysms [29–31], however the reported association to ACAS-AA has been heterogenic [10, 30, 32–35]. Similarly, we did not find an association of isolated vertebral artery to ACAS-AA. To the best of our knowledge this has yet to be investigated in other studies.

Numerous variables have been reported as direct or indirect risk factors of ACAS-AA and thoracic aortic aneurysms [3, 17, 36, 37]. These include aortitis, polycystic kidney disease, pheochromocytoma, right subclavian artery, right aortic arch, coarctation of the aorta, genetic predisposing diseases, pregnancy, use of illicit drugs, family history of aortic disease and chronic corticosteroid. Our data did not show an association of these with ACAS-AA. Some of these variables are rare in the setting of ACAS-AA. In larger settings, these risk factors might yield significant associations with ACAS-AA.

Due to data protection rights, the control group could only consist of patients treated at our respective departments. To be included, a control must have undergone CT-scanning of the thorax and preferably the abdomen. Due to the lack of screening programs for aortic ectasia, we could not include healthy controls. Therefore, the control group consisted largely of patients suffering from pulmonary cancer. These patients suffer more frequently from chronic obstructive pulmonary disease and have a history of smoking. This could explain the seemingly protective association of smoking in univariate analysis. Interestingly, in recently published DANCAVAS studies by Obel et al., smoking was associated as a protective marker for development of ascending aortic aneurysms [15, 38]. A direct protective association to ACAS-AA is however yet to be reported.

Aortic dimensions might differ in pulmonary cancer patients compared to healthy controls. Recently, an association between increasing severity of COPD and emphysema to thoracic aortic ectasia, has been reported [39]. However, the mean tubular ascending aortic diameter in the control group was similar to the reported 30–34 mm diameter in healthy subjects [40, 41].

The strength of model one is its' reliance on surrogate markers of aortic ectasia that do not increase in diameter following dissection [6]. However, even with an AUC just shy of 90%, the model is not sufficient in selecting eligible patients from the background population for preventive repair, due to the low prevalence of ACAS-AA.

Model two is more accurate, with AUC close to 100%, and numbers needed to treat far lower than that of model one. However, the accuracy of such a model is questionable as post-ACAS-AA diameters have been shown to over-estimate pre-ACAS-AA conditions [4–7].

## Limitations

Although all cases of ACAS-AA in the region of Southern Denmark are transferred to the mentioned departments at Odense University Hospital, selection bias may have occurred. Incorrect diagnosis, death before diagnosis or death before CT-scanning has probably excluded some patients from the study. We attempted to limit further selection bias by standardizing the inclusion procedure to manuals approved by all authors. Validation of data was not possible due to the project's retrospective setting, and some variables may be erroneously underreported. Furthermore, a control group composed of healthy individuals would have provided more accurate results.

CT-derived variables were gathered by a single investigator to ensure uniform measurement, and limit information bias. We attempted to limit confounding factors by including all described risk factors and many potential risk factors. However, not all variables were included in multivariable analysis as discussed, and therefore some confounding factors may be unaccounted for. There may also have been unidentified risk factors not included in the model. Therefore, the risk of residual confounding can't be excluded.

## Conclusion

ACAS-AA is a complex syndrome, with both local and systemic risk factors, and predictive models for ACAS-AA should reflect this complexity. We have shown that a high performing predictive model, free of ascending aortic diameter, can be achieved. Furthermore, we have identified abdominal aortic ectasia as an independent risk factor of ACAS-AA. Integration of potential biomarkers and morphologic variables, derived from undissected aortas, would probably improve such a model.

## Author Contributions

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**Funding acquisition:** Qais Waleed Saleh.

**Investigation:** Qais Waleed Saleh.

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**Resources:** Axel Cosmus Pyndt Diederichsen, Jes Sanddal Lindholt.

**Software:** Axel Cosmus Pyndt Diederichsen, Jes Sanddal Lindholt.

**Supervision:** Axel Cosmus Pyndt Diederichsen, Jes Sanddal Lindholt.

**Writing – original draft:** Qais Waleed Saleh.

**Writing – review & editing:** Qais Waleed Saleh, Axel Cosmus Pyndt Diederichsen, Jes Sanddal Lindholt.

## References

1. Olsson C, Thelin S, Stahle E, Ekblom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation*. 2006; 114(24):2611–8. <https://doi.org/10.1161/CIRCULATIONAHA.106.630400> PMID: 17145990
2. LeMaire SA, Russell L. Epidemiology of thoracic aortic dissection. *Nat Rev Cardiol*. 2011; 8(2):103–13. <https://doi.org/10.1038/nrcardio.2010.187> PMID: 21173794
3. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr., et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of

- Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010; 55(14):e27–e129. <https://doi.org/10.1016/j.jacc.2010.02.015> PMID: 20359588
4. Pape LA, Tsai TT, Isselbacher EM, Oh JK, O’Gara P T, Evangelista A, et al. Aortic diameter  $\geq 5.5$  cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2007; 116(10):1120–7. <https://doi.org/10.1161/CIRCULATIONAHA.107.702720> PMID: 17709637
  5. Rylski B, Blanke P, Beyersdorf F, Desai ND, Milewski RK, Siepe M, et al. How does the ascending aorta geometry change when it dissects? *J Am Coll Cardiol*. 2014; 63(13):1311–9. <https://doi.org/10.1016/j.jacc.2013.12.028> PMID: 24509277
  6. Saleh QW, Diederichsen ACP, Lindholt JS. Ascending Aortic Diameter after Dissection Does Not Reflect Size before Dissection. *EJVES Vascular Forum*. 2020; 49:20–2. <https://doi.org/10.1016/j.ejvsf.2020.09.003> PMID: 33089224
  7. Yamauchi T, Takano H, Takahashi T, Masai T, Sakaki M, Shirakawa Y, et al. Equations estimating the pre-dissected diameter of the ascending aorta for acute type A aortic dissection. *Ann Thorac Surg*. 2019.
  8. Paruchuri V, Salhab KF, Kuzmik G, Gubernikoff G, Fang H, Rizzo JA, et al. Aortic Size Distribution in the General Population: Explaining the Size Paradox in Aortic Dissection. *Cardiology*. 2015; 131(4):265–72. <https://doi.org/10.1159/000381281> PMID: 25997607
  9. Kruger T, Sandoval Boburg R, Lescan M, Oikonomou A, Schneider W, Vohringer L, et al. Aortic elongation in aortic aneurysm and dissection: the Tubingen Aortic Pathoanatomy (TAIPAN) project. *Eur J Cardiothorac Surg*. 2018. <https://doi.org/10.1093/ejcts/ezx503> PMID: 29373683
  10. Moorehead PA, Kim AH, Miller CP, Kashyap TV, Kendrick DE, Kashyap VS. Prevalence of Bovine Aortic Arch Configuration in Adult Patients with and without Thoracic Aortic Pathology. *Ann Vasc Surg*. 2016; 30:132–7. <https://doi.org/10.1016/j.avsg.2015.05.008> PMID: 26166538
  11. Lavall D, Schafers HJ, Bohm M, Laufs U. Aneurysms of the ascending aorta. *Dtsch Arztebl Int*. 2012; 109(13):227–33. <https://doi.org/10.3238/arztebl.2012.0227> PMID: 22532815
  12. Abbas A, Brown IW, Peebles CR, Harden SP, Shambrook JS. The role of multidetector-row CT in the diagnosis, classification and management of acute aortic syndrome. *Br J Radiol*. 2014; 87(1042):20140354. <https://doi.org/10.1259/bjr.20140354> PMID: 25083552
  13. Denmark S. Population at the First Day of the Quarter by Region, Sex, Age, Marital Status and Time [Available from: <https://www.statbank.dk/statbank5a/selectout/print.asp?pxfile=D:\ftproof\LocalUser\statbank\statbank5a\Temp\201842911317219215234FOLK1A.px&outfile=D:\ftproof\LocalUser\statbank\statbank5a\Temp\201842911317219215234FOLK1A&FileformatId=20&Queryfile=201842911317219215234FOLK1A&PLanguage=1&MainTable=FOLK1A&MainTablePretext=Population%20at%20the%20first%20day%20of%20the%20quarter%20by%20region,%20sex,%20age%20and%20marital%20status&potsize=16&Buttons=5&TableStyle=>
  14. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *Chest*. 1992; 101(6):1644–55. <https://doi.org/10.1378/chest.101.6.1644> PMID: 1303622
  15. Obel LM, Diederichsen AC, Steffensen FH, Frost L, Lambrechtsen J, Busk M, et al. Population-Based Risk Factors for Ascending, Arch, Descending, and Abdominal Aortic Dilations for 60-74-Year-Old Individuals. *Journal of the American College of Cardiology*. 2021; 78(3):201–11. <https://doi.org/10.1016/j.jacc.2021.04.094> PMID: 34266574
  16. McClure RS, Brogly SB, Lajkosz K, Payne D, Hall SF, Johnson AP. Epidemiology and management of thoracic aortic dissections and thoracic aortic aneurysms in Ontario, Canada: A population-based study. *J Thorac Cardiovasc Surg*. 2018; 155(6):2254–64.e4. <https://doi.org/10.1016/j.jtcvs.2017.11.105> PMID: 29499864
  17. Kim JB, Spotnitz M, Lindsay ME, MacGillivray TE, Isselbacher EM, Sundt TM 3rd., Risk of Aortic Dissection in the Moderately Dilated Ascending Aorta. *J Am Coll Cardiol*. 2016; 68(11):1209–19. <https://doi.org/10.1016/j.jacc.2016.06.025> PMID: 27609684
  18. Saeyeldin AA, Velasquez CA, Mahmood SUB, Brownstein AJ, Zafar MA, Ziganshin BA, et al. Thoracic aortic aneurysm: unlocking the "silent killer" secrets. *Gen Thorac Cardiovasc Surg*. 2017. <https://doi.org/10.1007/s11748-017-0874-x> PMID: 29204794
  19. Ardellier FD, D’Ostrevy N, Cassagnes L, Ouchchane L, Dubots E, Chabrot P, et al. CT patterns of acute type A aortic arch dissection: longer, higher, more anterior. *Br J Radiol*. 2017; 90(1078):20170417. <https://doi.org/10.1259/bjr.20170417> PMID: 28830228
  20. Krüger T, Forkavets O, Veseli K, Lausberg H, Vöhringer L, Schneider W, et al. Ascending aortic elongation and the risk of dissection. *Eur J Cardiothorac Surg*. 2016; 50(2):241–7. <https://doi.org/10.1093/ejcts/ezw025> PMID: 26984982



21. Johansen KL, Garimella PS, Hicks CW, Kalra PA, Kelly DM, Martens S, et al. Central and peripheral arterial diseases in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International*. 2021; 100(1):35–48. <https://doi.org/10.1016/j.kint.2021.04.029> PMID: 33961868
22. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. *European Heart Journal*. 2014; 35(41):2873–926. <https://doi.org/10.1093/eurheartj/ehu281> PMID: 25173340
23. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *The Journal of Thoracic and Cardiovascular Surgery*. 2014; 148(1):e1–e132. <https://doi.org/10.1016/j.jtcvs.2014.05.014> PMID: 24939033
24. Vallianou NG, Mitesh S, Gkogkou A, Geladari E. Chronic Kidney Disease and Cardiovascular Disease: Is there Any Relationship? *Curr Cardiol Rev*. 2019; 15(1):55–63. <https://doi.org/10.2174/1573403X14666180711124825> PMID: 29992892
25. Liu X, Liu J, Li Y, Zhang H. The correlation between the inflammatory effects of activated macrophages in atherosclerosis and aortic dissection. *Annals of Vascular Surgery*. 2022. <https://doi.org/10.1016/j.avsg.2022.03.027> PMID: 35395377
26. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Ann Intern Med*. 1995; 122(7):502–7. <https://doi.org/10.7326/0003-4819-122-7-199504010-00004> PMID: 7872584
27. Tsai Y-D, Chien W-C, Tsai S-H, Chung C-H, Chu S-J, Chen S-J, et al. Increased risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan. *BMJ Open*. 2018; 8(9):e022326. <https://doi.org/10.1136/bmjopen-2018-022326> PMID: 30244213
28. Corominas H, Tsokos M, Quezado M, Tsokos GC. Aneurysm of the ascending aorta in systemic lupus erythematosus: Case report and review of the literature. *Eur J Rheumatol*. 2017; 4(2):133–5. <https://doi.org/10.5152/eurjrheum.2017.17066> PMID: 28638687
29. Hornick M, Moomiaie R, Mojibian H, Ziganshin B, Almuwaqqat Z, Lee ES, et al. 'Bovine' aortic arch—a marker for thoracic aortic disease. *Cardiology*. 2012; 123(2):116–24. <https://doi.org/10.1159/000342071> PMID: 23037917
30. Brownstein AJ, Bin Mahmood SU, Saeyeldin A, Velasquez Mejia C, Zafar MA, Li Y, et al. Simple renal cysts and bovine aortic arch: markers for aortic disease. *Open Heart*. 2019; 6(1):e000862. <https://doi.org/10.1136/openhrt-2018-000862> PMID: 30774963
31. Malone CD, Urbania TH, Crook SES, Hope MD. Bovine aortic arch: A novel association with thoracic aortic dilation. *Clinical Radiology*. 2012; 67(1):28–31. <https://doi.org/10.1016/j.crad.2011.04.004> PMID: 22070947
32. Mylonas SN, Barkans A, Ante M, Wippermann J, Böckler D, Brunkwall JS. Prevalence of Bovine Aortic Arch Variant in Patients with Aortic Dissection and its Implications in the Outcome of Patients with Acute Type B Aortic Dissection. *Eur J Vasc Endovasc Surg*. 2018; 55(3):385–91. <https://doi.org/10.1016/j.ejvs.2017.12.005> PMID: 29338980
33. Dumfarth J, Peterss S, Kofler M, Plaikner M, Ziganshin BA, Schachner T, et al. In DeBakey Type I Aortic Dissection, Bovine Aortic Arch Is Associated With Arch Tears and Stroke. *Ann Thorac Surg*. 2017; 104(6):2001–8. <https://doi.org/10.1016/j.athoracsur.2017.05.026> PMID: 28811002
34. Wanamaker KM, Amadi CC, Mueller JS, Moraca RJ. Incidence of aortic arch anomalies in patients with thoracic aortic dissections. *J Card Surg*. 2013; 28(2):151–4. <https://doi.org/10.1111/jocs.12072> PMID: 23488580
35. Tapia GP, Zhu X, Xu J, Liang P, Su G, Liu H, et al. Incidence of branching patterns variations of the arch in aortic dissection in Chinese patients. *Medicine (Baltimore)*. 2015; 94(17):e795. <https://doi.org/10.1097/MD.0000000000000795> PMID: 25929931
36. Kamel H, Roman MJ, Pitcher A, Devereux RB. Pregnancy and the Risk of Aortic Dissection or Rupture: A Cohort-Crossover Analysis. *Circulation*. 2016; 134(7):527–33. <https://doi.org/10.1161/CIRCULATIONAHA.116.021594> PMID: 27492904
37. Hsue PY, Salinas CL, Bolger AF, Benowitz NL, Waters DD. Acute aortic dissection related to crack cocaine. *Circulation*. 2002; 105(13):1592–5. <https://doi.org/10.1161/01.cir.0000012524.44897.3a> PMID: 11927528
38. Obel L, Lindholt J, Leetmaa T, Dahl J, Møller J, Steffensen F, et al. Individual, expected diameters of the ascending aorta and prevalence of dilations in a study-population aged 60–74 years: a DANCAVAS substudy. 2020:1–10.
39. Fujikura K, Albini A, Barr RG, Parikh M, Kern J, Hoffman E, et al. Aortic enlargement in chronic obstructive pulmonary disease (COPD) and emphysema: The Multi-Ethnic Study of Atherosclerosis (MESA)

COPD study. *International Journal of Cardiology*. 2021; 331:214–20. <https://doi.org/10.1016/j.ijcard.2021.02.017> PMID: 33587941

40. Mao SS, Ahmadi N, Shah B, Beckmann D, Chen A, Ngo L, et al. Normal thoracic aorta diameter on cardiac computed tomography in healthy asymptomatic adults: impact of age and gender. *Acad Radiol*. 2008; 15(7):827–34. <https://doi.org/10.1016/j.acra.2008.02.001> PMID: 18572117
41. Paruchuri V, Salhab KF, Kuzmik G, Gubernikoff G, Fang H, Rizzo JA, et al. Aortic Size Distribution in the General Population: Explaining the Size Paradox in Aortic Dissection. *Cardiology*. 2015; 131(4):265–72. <https://doi.org/10.1159/000381281> PMID: 25997607