Statistical Analysis

Based on preoperative imaging at the index hospitalization, the patients were stratified into 3 groups according to the status of the false lumen: patent, partial thrombosis, and complete thrombosis. The clinical characteristics of each group are presented as frequencies and percentages for the categorical variables and as mean±standard deviation (SD) for the continuous variables. In cases of skewed distributions, the continuous variables are presented as the median and interquartile range (Q1 to Q3, the range between the 25th and the 75th percentile). For categorical variables, between-group differences were analyzed using the chi-squared or 2-sided Fisher's exact test, as appropriate. Continuous variables were compared with an analysis of variance or a Kruskal–Wallis test for data with skewed distributions. Missing data were not defaulted to negative and denominators reflect only those cases reported.

Univariate associations between clinical variables and mortality were calculated using a Cox regression analysis. Independent predictors of mortality were determined using a stepwise Cox proportional-hazards analysis. The initial model used variables with a P value of <0.15 in univariate testing and also included false lumen status. A backward stepwise selection of variables (after adjusting for sex and age) was performed sequentially with a default value for inclusion set at $P<0.05$.

Kaplan–Meier curves were created for the overall patient cohort and stratified according to the false lumen status. Curves were created for survival and for freedom from major adverse events (all-cause mortality, aortic rupture, and reoperation [including endovascular repair]). Between-group differences in survival and freedom from major adverse events were analyzed using the log-rank test.

All data analyses were performed using SPSS version 20 for Windows (SPSS Inc).

Results

Baseline Characteristics, Imaging, Treatment, and Complications

The mean age (±SD) of the 522 patients was 57.9±13.6 years, and 19.6% were aged >70 years (Table 1). The majority of patients (74.9%) were male and had a history of hypertension (70.9%). Other common comorbidities were atherosclerosis (19.1%), previous aortic aneurysm (11.7%), previous open-heart surgery (8.8%), and cardiac catheterization or percutaneous coronary intervention (7.8%). Marfan syndrome was present in 5.8% of the patients, and 30.0% were current smokers. Diabetes mellitus was rare in this patient cohort (4.9%), as were chronic renal insufficiency (3.6%) and chronic obstructive pulmonary disease (4.3%).

Almost a quarter of patients presented with hypotension, shock, or cardiac tamponade. Chest pain was common (85.3%); 15.0% of the patients presented with neurologic deficits, and 28.9% had a pulse deficit.

The mean number (±SD) of imaging studies per patient was 1.8±0.7, with a median (Q1 to Q3) number of studies of 2.0 (1.0 to 3.0). The most frequent procedure was computed tomography, which was performed in 81.0% of the patients, and 78.6% underwent a trans-esophageal echocardiography. Arch vessel involvement occurred in 40.3% of the patients. About one-third of the dissections were confined to the ascending aorta and aortic arch.

Complete arch replacement was performed in 12.3% of cases, and the aortic valve was replaced in 29.9% of patients (Table 2). Deliberate interruption of systemic perfusion was used in 86.0%, with a median (Q1 to Q3) circulatory arrest time of 44 (28 to 97) minutes.

Neurologic complications occurred in one quarter of the patients, acute renal failure in 19.3%, and limb ischemia in 13.4%. Mesenteric ischemia was rare, occurring in only 3.2% of patients.

Clinical Differences According to Preoperative False Lumen Status

Patients with a patent false lumen were on average 3 years younger than those with a partially thrombosed false lumen and 6 years younger than those with complete false lumen thrombosis. There were no differences with regard to previous medical history, presenting symptoms, or clinical findings. Patients with a patent false lumen had fewer imaging studies per patient, with a mean (±SD) of 1.7±0.6, versus 2.0±0.7 for those with partial thrombosis and 2.0±0.8 for those with complete thrombosis ($P=0.006$). Computed tomography was performed more frequently in the patients with partial thrombosis of the false lumen (90.5%) compared to the patients with complete patency or complete thrombosis of the false lumen (79.4% or 75.0%, respectively, $P=0.034$). The distal extension of the dissection was similar between the groups; however, extension merely to the aortic arch occurred more frequently in the partial thrombosis and complete thrombosis groups than in the patent false lumen group (31.8%, 37.5% and 17.1%, respectively, $P=0.005$). The surgical strategy did not differ between the groups.

Aortic Growth and Long-Term Outcome

The median aortic growth rate (Q1 to Q3) was 0.5 (−0.3 to 2.0) mm/year in the aortic arch and 2.0 (0.2 to 4.0) mm/year in the descending thoracic aorta (Table 3). Aortic growth was similar regardless of the degree of preoperative false lumen thrombosis.

Table 1. Patient Characteristics Stratified by False Lumen Status

	All Patients (n=522)	Status of the False Lumen			*P* Value
		Patent (n=414)	Partial Thrombosis (n=84)	Complete Thrombosis (n=24)	
Baseline patient characteristics					
Age, mean±SD	57.9±13.6	57.0±13.6	60.8±13.4	63.3±12.6	0.009*
Age ≥70 years, no./total no. (%)	102/521 (19.6)	73/413 (17.7)	20/84 (23.8)	9/24 (37.5)	0.036
Female gender, no./total no. (%)	131/522 (25.1)	96/414 (23.2)	26/84 (31.0)	9/24 (37.5)	0.12
Marfan syndrome, no./total no. (%)	30/514 (5.8)	25/407 (6.1)	4/83 (4.8)	1/24 (4.2)	0.93
Hypertension, no./total no. (%)	365/515 (70.9)	289/410 (70.5)	60/82 (73.2)	16/23 (69.6)	0.88
Atherosclerosis, no./total no. (%)†	98/513 (19.1)	82/406 (20.2)	10/83 (12.0)	6/24 (25.0)	0.16
Previous aortic dissection, no./total no. (%)	17/512 (3.3)	11/406 (2.7)	4/83 (4.8)	2/23 (8.7)	0.15
Previous aortic aneurysm, no./total no. (%)	60/513 (11.7)	52/407 (12.8)	5/82 (6.1)	3/24 (12.5)	0.21
Current smoking, no./total no. (%)‡	36/120 (30.0)	28/89 (31.5)	7/27 (25.9)	1/4 (25.0)	0.85
Diabetes mellitus, no./total no. (%)	25/513 (4.9)	19/407 (4.7)	5/82 (6.1)	1/24 (4.2)	0.84
COPD, no./total no. (%)	6/140 (4.3)	3/106 (2.8)	3/30 (10.0)	0/4 (0.0)	0.26
Chronic renal insufficiency, no./total no. (%)	5/140 (3.6)	4/106 (3.8)	1/30 (3.3)	0/4 (0.0)	1.00
Previous invasive cardiac procedures					
Open heart surgery, no./total no. (%)	44/499 (8.8)	33/396 (8.3)	8/81 (9.9)	3/22 (13.6)	0.53
Catheterization and/or PCI, no./total no. (%)	32/409 (7.8)	25/326 (7.7)	6/65 (9.2)	1/18 (5.6)	0.86
Clinical presentation					
Abrupt onset of pain, no./total no. (%)	439/498 (88.2)	350/395 (88.6)	67/79 (84.8)	22/24 (91.7)	0.60
Chest pain, no./total no. (%)	434/509 (85.3)	338/402 (84.1)	73/83 (88.0)	23/24 (95.8)	0.25
Migrating pain, no./total no. (%)§	72/478 (15.1)	57/380 (15.0)	12/78 (15.4)	3/20 (15.0)	1.00
Hypotension/shock/tamponade, no./total no. (%)¶	118/509 (23.2)	94/404 (23.3)	18/81 (22.2)	6/24 (25.0)	0.96
First systolic blood pressure (mm Hg), mean±SD	131.8±37.6	132.1±38.2	130.0±36.3	133.4±33.5	0.89
First diastolic blood pressure (mm Hg), mean±SD	73.0±22.0	72.9±21.8	72.7±23.9	74.7±19.3	0.93
Any pulse deficit, no./total no. (%)‖	122/422 (28.9)	102/338 (30.2)	18/68 (26.5)	2/16 (12.5)	0.30
Any neurologic deficit, no./total no. (%)**	77/513 (15.0)	65/405 (16.0)	10/84 (11.9)	2/24 (8.3)	0.49
Abnormal ECG, no./total no. (%)††	311/495 (62.8)	238/388 (61.3)	56/83 (67.5)	17/24 (70.8)	0.41
Diagnostic imaging					
Number of studies per patient, mean±SD	1.8±0.7	1.7±0.6	2.0±0.7	2.0±0.8	0.006
Computed tomography, no./total no. (%)	421/520 (81.0)	327/412 (79.4)	76/84 (90.5)	18/24 (75.0)	0.034
Magnetic resonance imaging, no./total no. (%)	25/492 (5.1)	15/391 (3.8)	8/77 (10.4)	2/24 (8.3)	0.037
Trans-esophageal echocardiography, no./total no. (%)	408/519 (78.6)	324/411 (78.8)	66/84 (78.6)	18/24 (75.0)	0.91
Arch vessel involvement, no./total no. (%)‡‡	183/454 (40.3)	147/357 (41.2)	30/78 (38.5)	6/19 (31.6)	0.66
Widest diameter of ascending aorta (cm), median (Q1 to Q3)§§	5.0 (4.4 to 5.8)	5.0 (4.4 to 5.6)	4.9 (4.1 to 6.0)	5.0 (4.1 to 6.1)	0.94
Widest diameter of descending aorta (cm), median (Q1 to Q3)§§	3.3 (3.0 to 3.7)	3.2 (3.0 to 3.6)	3.5 (3.0 to 4.0)	3.4 (2.9 to 4.0)	0.51

Continued

Table 1. Continued

	All Patients (n=522)	Status of the False Lumen			*P* Value
		Patent (n=414)	Partial Thrombosis (n=84)	Complete Thrombosis (n=24)	
Most distal extension of dissection					
Ascending aorta, no./total no. (%)	59/392 (15.1)	47/310 (15.2)	10/66 (15.2)	2/16 (12.5)	1.00
Aortic arch, no./total no. (%)	80/392 (20.4)	53/310 (17.1)	21/66 (31.8)	6/16 (37.5)	0.005
Left subclavian level, no./total no. (%)	22/392 (5.6)	19/310 (6.1)	3/66 (4.5)	0/16 (0.0)	0.74
Descending thoracic aorta, no./total no. (%)	103/392 (26.3)	86/310 (27.7)	12/66 (18.2)	5/16 (31.2)	0.24
Abdominal aorta, no./total no. (%)	128/392 (32.7)	105/310 (33.9)	20/66 (30.3)	3/16 (18.8)	0.41

SD indicates standard deviation; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; ECG, echocardiogram; ANOVA, analysis of variance.
*Analyzed using ANOVA. Independent T-test between groups: Patent vs partial thrombosis, *P*=0.019. Patent vs complete thrombosis, *P*=0.026. Partial vs complete thrombosis, *P*=0.411.
†Any history of PCI, coronary artery bypass graft surgery, or catheterization demonstrating >70% stenosis in coronary, cerebral, or peripheral vasculature.
‡Tobacco use during the last month.
§Pain changed location.
¶Hypotension defined as systolic blood pressure <100 mm Hg.
‖Diminution or absence of pulse in either right or left carotid, brachial or femoral arteries.
**Paraparesis, paraplegia, stroke, or coma.
††Showing signs of old or new infarction, nonspecific ST-T segment changes, left ventricular hypertrophy or low voltage.
‡‡Any imaging modality showing dissection extending into the brachiocephalic trunk, left common carotid artery or left subclavian artery.
§§Q1 to Q3 denotes interquartile range.

On univariate testing, age, preexisting renal failure and aortic aneurysm, presenting with chest or back pain, and the composite of postoperative cerebrovascular accident, coma, or renal failure were significantly associated with death during follow-up (Table 4). In the multiple regression models, only age and the composite of postoperative cerebrovascular accident, coma, or renal failure were statistically significant (Table 5). The preoperative status of the false lumen did not predict death after discharge in the univariate testing or when adjusted for age and gender.

Table 2. Surgical Treatment and In-Hospital Complications

	All Patients (n=522)	Status of the False Lumen			*P* Value
		Patent (n=414)	Partial Thrombosis (n=84)	Complete Thrombosis (n=24)	
Surgical treatment					
Complete arch replacement, no./total no. (%)	60/489 (12.3)	42/385 (10.9)	14/81 (17.3)	4/23 (17.4)	0.20
Descending aortic replacement, no./total no. (%)*	8/490 (1.6)	5/387 (1.3)	2/80 (2.5)	1/23 (4.3)	0.17
Aortic valve replacement, no./total no. (%)	145/485 (29.9)	124/384 (32.3)	16/78 (20.5)	5/23 (21.7)	0.080
Hypothermic circulatory arrest					
HCA used, no./total no. (%)	430/500 (86.0)	342/393 (87.0)	69/84 (82.1)	19/23 (82.6)	0.39
HCA duration (minutes), median (Q1 to Q3)†	44 (28 to 97)	44 (28 to 100)	42 (25 to 80)	46 (33 to 87)	0.52
In-hospital complications (pre- and postoperative)					
Neurologic deficit, no./total no. (%)‡	125/501 (25.0)	98/397 (24.7)	21/81 (25.9)	6/23 (26.1)	0.98
Mesenteric ischemia or infarction, no./total no. (%)	16/496 (3.2)	15/393 (3.8)	1/80 (1.2)	0/23 (0.0)	0.57
Acute renal failure, no./total no. (%)§	97/502 (19.3)	76/397 (19.1)	18/81 (22.2)	3/24 (12.5)	0.60
Limb ischemia, no./total no. (%)	67/499 (13.4)	55/395 (13.9)	11/80 (13.8)	1/24 (4.2)	0.48

HCA indicates hypothermic circulatory arrest.
*Replacement of at least part of the aorta between the left subclavian level and the diaphragm.
†Q1 to Q3 denotes interquartile range.
‡Stroke, coma, or spinal cord ischemia.
§Three-fold increase in serum creatinine, 75% reduction in glomerular filtration rate, serum creatinine ≥354 μmol/L, urine output <0.3 mL/kg per hour over 24 hours or anuria for ≥12 hours.

Table 3. Aortic Growth Rates (mm/year).

	All Patients (n=522)	Status of the False Lumen			*P* Value
		Patent (n=414)	Partial Thrombosis (n=84)	Complete Thrombosis (n=24)	
Aortic arch, median (Q1 to Q3)	0.5 (−0.3 to 2.0)	0.5 (−0.5 to 1.8)	1.7 (0.0 to 4.2)	0.3 (−1.0 to 9.2)	0.24
Descending thoracic aorta, median (Q1 to Q3)	2.0 (0.2 to 4.0)	1.8 (0.4 to 4.0)	2.1 (−0.1 to 4.9)	0.3 (−0.5 to 3.4)	0.29

Q1 to Q3 denotes interquartile range.

Table 4. Univariate Predictors of Long-Term Mortality

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Age	1.04	1.02 to 1.07	0.001
Age ≥70 years	2.96	1.65 to 5.31	<0.001
Female gender	1.24	0.66 to 2.35	0.51
Atherosclerosis*	1.48	0.78 to 2.82	0.23
Patent false lumen†	1.00		
Partially thrombosed false lumen	0.80	0.34 to 1.88	0.60
Completely thrombosed false lumen	0.87	0.21 to 3.61	0.85
Postoperative CVA, coma and/or acute renal failure‡	2.73	1.46 to 5.11	0.002
Postoperative spinal cord ischemia	0.93	0.13 to 6.80	0.95
Presenting diameter ascending aorta	1.02	0.80 to 1.31	0.86
Presenting diameter descending aorta	1.20	0.77 to 1.87	0.42
Chronic renal insufficiency	7.00	1.40 to 34.87	0.018
Previous aortic aneurysm	2.31	1.15 to 4.66	0.019
Peripheral artery disease	6.23	0.75 to 51.88	0.091
Postoperative mesenteric ischemia/infarction	5.66	0.77 to 41.77	0.089
Presenting syncope	0.50	0.20 to 1.27	0.14
Presenting CVA	1.87	0.67 to 5.23	0.23
Surgery on descending aorta	3.02	0.73 to 12.46	0.13
Presenting chest or back pain	0.44	0.21 to 0.92	0.029

CVA indicates cerebrovascular accident.
*Any history of percutaneous coronary intervention, coronary artery bypass graft surgery or catheterization demonstrating > 70% stenosis in coronary, cerebral or peripheral vasculature.
†Patent false lumen is the reference group.
‡Three-fold increase in serum creatinine, 75% reduction in glomerular filtration rate, serum creatinine ≥354 μmol/L, urine output <0.3 mL/kg per hour over 24 hours or anuria for ≥12 hours.

Table 5. Independent Predictors of Long-Term Mortality After Multivariate Model Adjustments

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Female gender	0.90	0.43 to 1.87	0.78
Age ≥70 years	2.34	1.20 to 4.56	0.012
Patent false lumen*	1.00		
Partial thrombosis false lumen	0.78	0.30 to 1.99	0.60
Complete thrombosis false lumen	0.81	0.19 to 3.44	0.78
Postoperative CVA, coma and/or renal failure†	2.62	1.40 to 4.92	0.003

CVA indicates cerebrovascular accident.
*Patent false lumen is the reference group.
†Three-fold increase in serum creatinine, 75% reduction in glomerular filtration rate, serum creatinine ≥354 μmol/L, urine output <0.3 mL/kg per hour over 24 hours or anuria for ≥12 hours.

The Kaplan–Meier curves showed an overall 5-year survival of 84.7% (95% CI; 79.6% to 88.6%; Figure 2). The extent of preoperative false lumen thrombosis did not affect the 5-year survival rates (Figure 3). Nor did thrombosis of the false lumen preoperatively affect freedom of major adverse events (Figure 4).

Discussion

The data included in the present analysis reject the hypothesis that a partially thrombosed false lumen on preoperative imaging was a predictor of an ominous clinical course in patients with surgically treated AAAD.

To our knowledge, the relationship between partial thrombosis of the false lumen and long-term outcome in patients with aortic dissection has been examined in 7 studies.[13–15,17–20] All of these studies have included patients with either type B dissections, postoperative AAAD, or a combination of both. The results have been divergent. Partial thrombosis was identified as an independent predictor for aortic enlargement, aortic-related procedures, or death in 2 studies.[13,14] In the remaining 5 studies,[15,17–20] partial thrombosis was not associated with a worse outcome, faster aortic growth, or higher incidence of aneurysm development compared to complete patency of the false lumen. However, in the

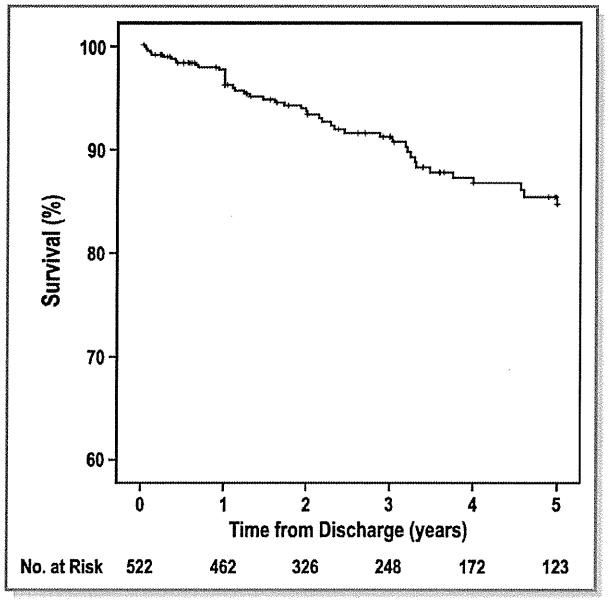

Figure 2. Kaplan–Meier postdischarge survival curve for all patients.

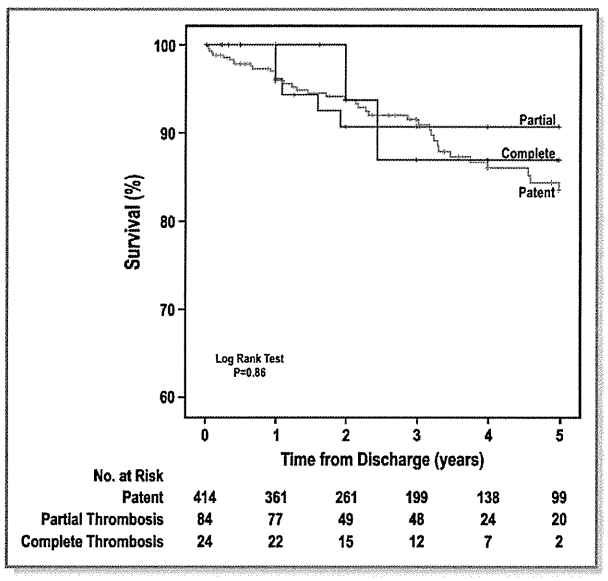

Figure 3. Kaplan–Meier postdischarge survival curves stratified according to the false lumen status.

study by Sueyoshi et al,[15] which compared aortic enlargement across different degrees of false lumen thrombosis in type B dissections, a subset within the partial thrombosis group with a blind pouch in the false lumen (ie, thrombosis covering the potential reentry site) had considerably faster growth rates. This group was small, only accounting for 15% of the patients with partial thrombosis of the false lumen.

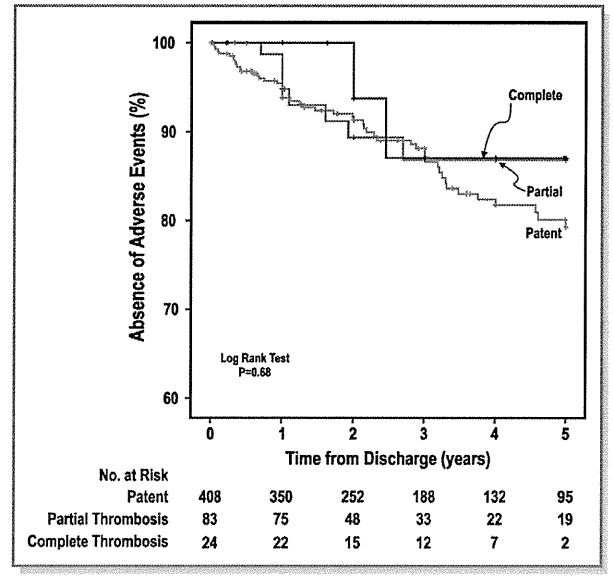

Figure 4. Kaplan–Meier curves of postdischarge freedom from major adverse events (all-cause mortality, aortic rupture and reoperation, including endovascular repair), stratified according to the false lumen status.

Results from previous studies on type B dissections and postoperative AAAD cannot readily be extrapolated to our data, as we examined the influence of preoperative false lumen thrombosis in AAAD. In addition, the fact that partial thrombosis of the false lumen seems to be unfavorable in type B dissections does not necessarily imply that this is the case in postoperative AAAD. The notion that an operated AAAD with a persistent false lumen in the descending aorta mirrors a type B dissection is not intuitive. In AAAD, the primary entry tear is typically located in the ascending aorta, whereas the area just distal to the subclavian artery is the predilection site in type B dissections.[21,22] This region is also most prone to dilation and rupture in the chronic phase.[20] By surgically removing the primary entry tear, the pathological process of an AAAD is fundamentally changed. Residual intimal tears, which maintain flow in the false lumen and remain distal after type A dissection repair, might have a different impact on flow and pressure dynamics compared to that associated with the primary entry in type B dissections. In fact, a residual primary entry tear independently predicts the need for reintervention in patients with operated AAAD only.[17] Moreover, patients with a patent false lumen distally to AAAD repair have better outcomes compared to type B dissections, which is potentially related to the size and location of intimal tears.[23] It is also to be noted, that the one study supporting partial thrombosis as a negative predictor in surgically treated AAAD[14] is based on 27 patients with a particularly high mortality of 60% at 5 years.

We observed that the degree of false lumen thrombosis appeared to increase with age. It is unknown why older

patients are more likely to have spontaneous complete thrombosis of the false lumen, but blood coagulability increases with age.[24] The group with complete thrombosis was small: 24 patients (4.6% of the total patient cohort). Traditionally, complete thrombosis of the false lumen has been thought to be a prerequisite for healing of the aorta postdissection, as flow and pressurization of the false lumen are thought to contribute to late dilation and rupture. Accordingly, one could expect lower mortality during follow-up in this setting. Our data did not show that there was any survival benefit associated with complete false lumen thrombosis. Because of the small number of patients, even in the IRAD database, adjusted comparisons with this group lacked statistical power. Of great practical importance, however, is that there are no definitive clinical epidemiological data supporting the traditional view that a persistent blood-flow in the false lumen is a definitive negative predictor for outome.[25] Thus, an extensive procedure with arch replacement and intraoperative stentgrafting of the descending aorta[3,4] has little support as a routine procedure in AAAD. Such an extensive operation is also at odds with the acceptable overall long-term survival rate of 85% at 5 years in surgically treated AAAD in the IRAD database.

The imaging characteristics in our material warrant further attention. Patients with partial or complete thrombosis of the false lumen were subjected to more imaging studies compared to those with no thrombosis of the false lumen. It could be argued that partial or complete thrombosis of the false lumen is more likely to be diagnosed with an increasing number of different imaging modalities and that a given portion of the patients who were categorized as having patent lumens may have actually had some degree of thrombosis. Conversely, diagnosing aortic dissection itself can be challenging, more so when there is no flow in the false lumen. In the case of a "classic" aortic dissection with flow in the false lumen and a clearly visible intimal flap, the diagnosis is straightforward. When the false lumen is void of flow, establishing the diagnosis can be difficult, particularly by echocardiography. Additional imaging is required in such circumstances.

A key aspect in the interpretation of our data is that the status of the false lumen was established once (at presentation, ie, before surgery). The main goal of surgery in AAAD is to prevent lethal complications, such as rupture, cardiac tamponade, and malperfusion. A secondary goal is to resect the entry tear and redirect the blood flow to the true lumen. Resection of the primary tear and aortic reconstruction will alter flow in the false lumen and might promote thrombosis. Thus, our classification (based on aortic morphology at presentation), may be altered postoperatively. However, a distal false lumen remains patent in as many as 79% of patients following the initial repair.[9,10,26–29]

Strengths and Limitations of the Study

The main strength of the study is that it included >500 patients in an orderly, prespecified manner during a limited time period. However, IRAD is an observational registry and selection bias is possible. Furthermore, follow-up data were not available for more than half of the survivors. As a result, our data might not be representative of the entire IRAD patient population but might represent a selection from the centers with the most systematic patient registration and follow-up.

Information on preoperative false lumen status was lacking for 40% of the AAAD patients in IRAD. In cases of iatrogenic dissections that occur during elective or emergency cardiac surgery for other reasons, preoperative imaging will not be relevant. Also, when a patient with AAAD present with cardiac tamponade, cardiac arrest, or other critical conditions, preoperative imaging will in many cases be limited to a screening echocardiography, and details regarding false lumen thrombosis will not be available.

Imaging techniques may have varied among the centers. Misclassification of false lumen status was possible as the imaging data were collected and reviewed at each participating center before the start of the study and were not reevaluated in a core laboratory. Likewise, patients with a completely thrombosed false lumen might have been excluded and patients with an intramural hematoma might have been included, as this distinction can be challenging. Furthermore, traditional first-pass imaging of the aorta might have overestimated the degree of thrombosis in the false lumen.[30]

We were unable to provide cause-of-death data and the distribution of aortic-related and nonaortic-related death could be different between the groups.

Conclusions

The present study revealed that preoperative partial thrombosis of the false lumen in surgically treated AAAD in the IRAD database was not an independent risk factor for aortic enlargement, intervention, or death in the follow-up period. The AAAD survivors had favorable prognoses, but the factors that influence aortic dilation and rupture following acute aortic dissections are still incompletely understood. New imaging techniques, for example, based on flow-dynamics[31] and/or bioimaging[32,33] can hopefully improve our ability to predict an ominous outcome in patients with aortic dissection.

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Disclosures

None.

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the use of iliofemoral access for transcatheter aortic valve insertion. Although the aneurysm diameter in this patient did not meet criteria for repair (>5.5 cm), the use of a bifurcated aortic stent graft allowed more aggressive dilation of the aortic bifurcation in a controlled fashion to achieve larger luminal diameter. It is unclear whether the technique would work in patients with nonaneurysmal arteries, and vascular surgery consultation should be obtained before such intervention. Further cautious evaluation of the technique is warranted before more widespread use.

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Hybrid Repair of Subclavian-Axillary Artery Aneurysms and Aortic Arch Aneurysm in a Patient With Marfan Syndrome

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A patient with Marfan syndrome who had previously undergone a Cabrol procedure and thoracoabdominal aortic replacement had enlarging, symptomatic aneurysms in the subclavian-axillary artery and aortic arch. Both vessels were replaced with prosthetic grafts. A thoracic endoprosthesis was inserted bridging the aortic arch graft and the previously implanted descending aorta graft. Another stent graft was placed, bridging the axillary artery and a branch of the aortic arch graft. All the stent graft landing zones were within grafts, avoiding contact between the endoprostheses and fragile aortic wall. The aneurysms were excluded from the circulation, and the patient had no serious complications.

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Aneurysms of the subclavian or axillary artery are rare [1]. Large aneurysms have generally been treated with open surgical resection and placement of a prosthetic graft [2], but the sternotomy or lateral thoracotomy necessitated by this invasive procedure sometimes results in injury to the nerves or vessels [3]. Patients with Marfan syndrome probably have increased rates of morbidity and mortality after this operation, although this has not yet been clearly established [4]. Endovascular treatment of subclavian artery lesions is a less aggressive approach, and reduced death and complication rates and good patency outcomes have been reported with a variety of endovascular methods, devices, and access routes [4, 5]. However, the use of endovascular therapy in patients with Marfan syndrome is controversial because of the risk of possible adverse effects on the fragile aortic wall of the radial force exerted by stent grafts. We describe a case in which a hybrid procedure was used to repair subclavian-axillary and aortic arch aneurysms in a patient with Marfan syndrome.

A 49-year-old man with Marfan syndrome presented with a pulsatile mass in the right axilla and supraclavian region and numbness in the right arm that he first noticed 2 months earlier. Twenty-three years earlier, he had undergone a Cabrol procedure to treat an acute type A aortic dissection. Two years later, he had an elective repair of a dissection-related thoracoabdominal aortic aneurysm that included placement of a prosthetic graft. Approximately 9 years later, a pseudoaneurysm developed at the anastomosis of the prosthesis to the intercostal arteries. The graft was replaced with another synthetic graft, attached with the use of a side-to-end anastomosis, and the intercostal arteries were reconstructed. At about the same time, computed tomographic angiography (CTA) showed that the patient had an aneurysm of the right subclavian artery (maximum diameter, 3 cm). No intervention was performed, but the patient began to have routine annual CTA evaluations of the lesion. Approximately 12 years later, the patient underwent a mitral valve replacement and coronary artery bypass grafting. He had no symptoms associated with the aneurysm in the right subclavian artery for more than 15 years before the development of the pulsating mass and numbness.

CTA showed a subclavian artery aneurysm (4-cm diameter) and two axillary artery aneurysms (maximum diameters, 3.3 cm proximally and 2.5 cm distally). The subclavian artery aneurysm had a proximal neck, and there were necks between the three aneurysms (Fig 1). The aortic arch was dilated (5-cm diameter). We decided to repair the aneurysms by using a hybrid procedure because the procedure would be performed without thoracotomy and injury to the nerves and vessels.

A 10-mm–diameter Dacron graft (Hemashield; Boston Scientific, Natick, MA) was inserted into the axillary artery through a subclavian incision, and each end of the device was anastomosed to an aneurysm neck in an end-to-end fashion (Fig 2). A total arch replacement was performed through a median sternotomy by using a

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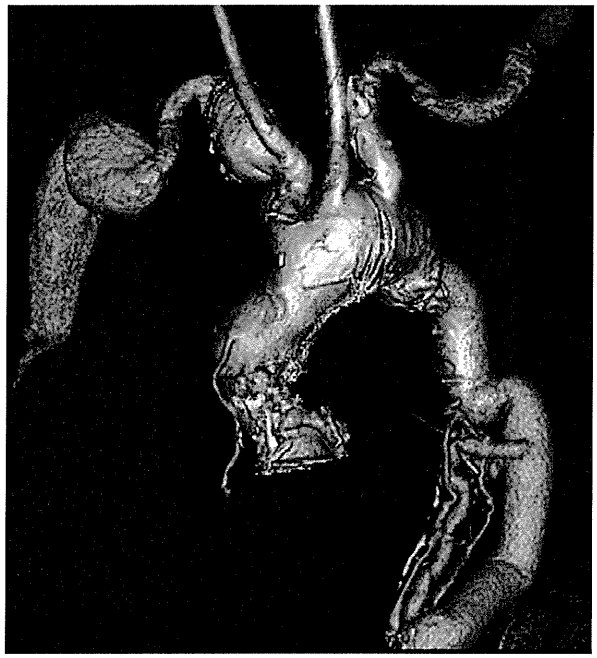

Fig 1. Baseline computed tomographic scan shows a subclavian-axillary artery aneurysm and dilation of the aortic arch. The prosthetic graft that was inserted previously to replace the middle portion of the descending thoracic aorta shows tortuosity.

Dacron graft (Hemashield) with four branches and the elephant trunk technique. A moderately hypothermic cardiopulmonary bypass (25°C) and selective antegrade brain perfusion were used during this procedure.

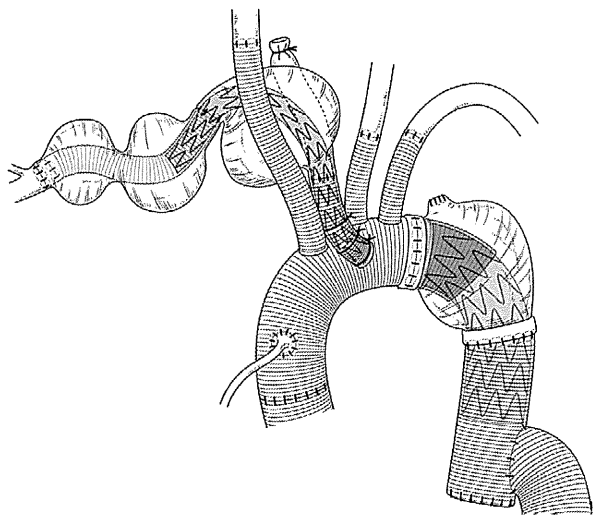

Fig 2. Diagram of the hybrid repair. The right axillary artery was replaced with a Dacron graft. The entire aortic arch was replaced with a four-branched Dacron graft. An endoprosthesis was placed in a bridging position between the aortic arch graft and the graft in the descending aorta. Another endoprosthesis was placed between the graft that replaced the axillary artery and one branch of the four-branched graft.

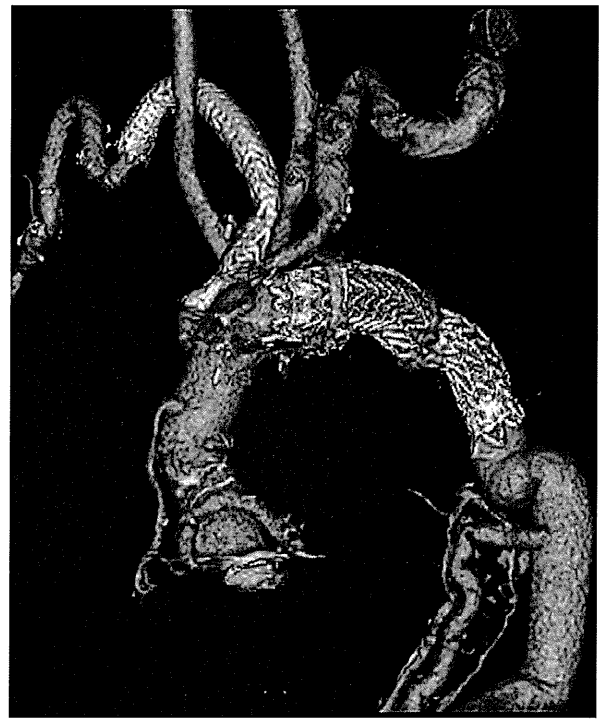

Fig 3. Computed tomographic scan obtained after the hybrid repair shows that all bypasses are patent and that the aneurysms are completely excluded from the blood flow.

The right common carotid artery was ligated, and an anastomosis was created between the vessel and one branch of the four-branched Dacron graft. Another branch of the graft was anastomosed to the neck of the subclavian artery aneurysm. A 28 mm × 15 cm stent graft (Gore TAG Thoracic Endoprosthesis; W.L. Gore and Associates, Flagstaff, AZ) was inserted through a branch of the four-branched graft and placed in a bridging position between the prosthetic graft in the aortic arch and that in the descending aorta. The proximal landing zone for the stent graft was just distal to the origin of the side branches. Two segments of a 12-mm–diameter endoprosthesis (contralateral legs of a bifurcated Excluder AAA device; W.L. Gore and Associates) were inserted into the Dacron graft that had replaced the axillary artery and were deployed in the branch of the graft that was anastomosed to the brachiocephalic artery.

The patient recovered fully from the operation, without any serious perioperative complications, and he remains well 1 year later. CTA performed 6 months after the procedure showed that all bypasses were patent and that the aneurysms were completely excluded from the blood flow (Fig 3).

Comment

Endovascular techniques have been used to treat aneurysms with a variety of causes. Using stent grafts to provide a bridge between the necks of synthetic grafts

proximally and distally may be safer than performing multiple thoracotomies in patients with Marfan syndrome. However, it has been suggested that stent grafts should not be deployed in either the abdominal or thoracic aorta in patients with this syndrome or another connective tissue disease [6].

In our patient with Marfan syndrome, a right subclavian-axillary artery aneurysm, and an aortic arch aneurysm, we used a hybrid repair. Before placing endoprostheses in the right subclavian artery and aortic arch, we performed an open surgical procedure to replace the arch with a synthetic graft. Therefore, the proximal and distal landing zones for the stent grafts were within prostheses, which avoided possible injury to the aortic wall caused by the radial force applied by stent grafts.

Our patient had previously undergone repair of a pseudoaneurysm at the anastomosis to the intercostal arteries. The procedure involved reconstruction of the middle portion of the Dacron graft present in the descending aorta by replacement of another synthetic graft with the use of a side-to-end anastomosis. Moreover, a femorofemoral bypass was performed concomitantly with the dissection of the aorta. Because of these factors, we decided to avoid delivering a stent graft in a retrograde direction—that is, through the femoral artery to the aortic arch. Instead, we replaced the aortic arch with a branched Dacron graft (elephant trunk technique) and then deployed a thoracic stent graft in an antegrade manner, through a branch of the Dacron graft. The elephant trunk thus served as the proximal neck for the stent graft, whereas the graft in the descending aorta served as the distal neck. Because a graft that extended from the aortic root (including the aortic valve) to the ascending aorta and a graft that extended from the descending aorta to the abdominal aorta were already in place, our procedure resulted in replacement of the entire aorta with prostheses.

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Spontaneous Triple Coronary Artery Dissection

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Multivessel spontaneous coronary artery dissection (SCAD) is extremely rare, and to the best of our knowledge, triple-vessel dissection has been reported in only 7 patients to date. We present the successful surgical treatment of the triple coronary artery dissection in a 57-year-old man. The patient had aortic valve replacement simultaneously. Triple SCAD is a rare and life-threatening condition, and long-term results are necessary for an optimum treatment approach. It should be kept in mind that triple SCAD may be more common and fatal than thought, as uninvestigated cases of sudden death could mask the true incidence and prognosis of triple SCAD.

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Spontaneous coronary artery dissection (SCAD) is a rare condition that has been found to be associated with various pathophysiologic situations, such as pregnancy, postpartum, collagen diseases, cocaine abuse, severe hypertension, smoking, oral contraceptives, heavy exercise, or vasospasm. Approximately 70% of patients have dissection in a single coronary artery, and the left anterior descending artery is the most involved one [1]. Multivessel dissection is extremely rare, and triple-vessel dissection has been reported in only 7 patients to date. In this report, we present the successful surgical treatment of spontaneous dissection of each three coronary arteries in a patient without cardiovascular disease history and analyze previously reported triple SCAD cases.

A 57-year-old man was admitted to our emergency department with sudden onset of constricting chest pain. The physical examination was unremarkable except for a diastolic heart murmur on the left sternal border; electrocardiography showed nonspecific ST-segment changes as negative T waves on lead V1, flattened T waves on leads V2 through 4, and minimally depressed ST-segment on leads V5 and 6. Echocardiography was performed, and global hypokinesia of the left ventricle and severe aortic regurgitation was seen; the ascending aorta and the root of the aorta were normal; and the left ventricle ejection fraction was calculated as 35% using the modified Simpson formula. The patient was diagnosed as having acute coronary syndrome and taken to the catheterization laboratory immediately.

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EDITORIAL

Targeting Transforming Growth Factor-β Signaling in Aortopathies in Marfan Syndrome

Daigo Sawaki, MD; Toru Suzuki, MD

Marfan syndrome (MFS) is characterized by mutations in the fibrillin-1 gene and dysregulation of transforming growth factor-β (TGFβ) signaling, which is phenotypically associated with gradual weakening of connective tissue throughout the body, including the lungs, bones and cardiovascular system.[1] A primary cause of mortality in MFS patients reaching adolescence or adulthood is aortic rupture or dissection. Surgery is generally performed to remove the affected portion of the aorta, but more than half of patients who have had their aortas repaired require additional surgery or manifest aortic rupture because of expansion of the unrepaired regions of the aorta over time.[2] At present, measures to identify patients exhibiting progressive expansion or re-expansion of the aorta after surgery is a topic of importance. On medical therapy, β-blockers have been historically used as the anchoring agent. The renin-angiotensin system (RAS) has also recently been implicated in the pathogenesis of Marfan aortopathy, with initial experiments showing prevention of aortic root expansion in a mouse model of MFS using RAS blockade,[3] which was followed by studies in human patients that showed similar results.[4,5] These findings were welcomed with enthusiasm as a pharmacological solution for MFS, and have prompted several human clinical trials, which are presently ongoing to determine the possible benefit of RAS blockade in aortopathy in MFS patients.[6] TGFβ signaling has also received attention as a key factor in the aortopathy of MFS patients, as not only the canonical regulatory pathway involving downstream Smad proteins but also a non-canonical pathway involving ERK and JNK kinases has been recently described as implicated in MFS pathology upon activation of the TGFβ pathway.[7,8] Moreover, circulating levels of TGFβ have received attention because they are not only elevated in patients with MFS aortopathy but are also responsive to pharmacological treatment, thus suggesting their possible use as a sur-

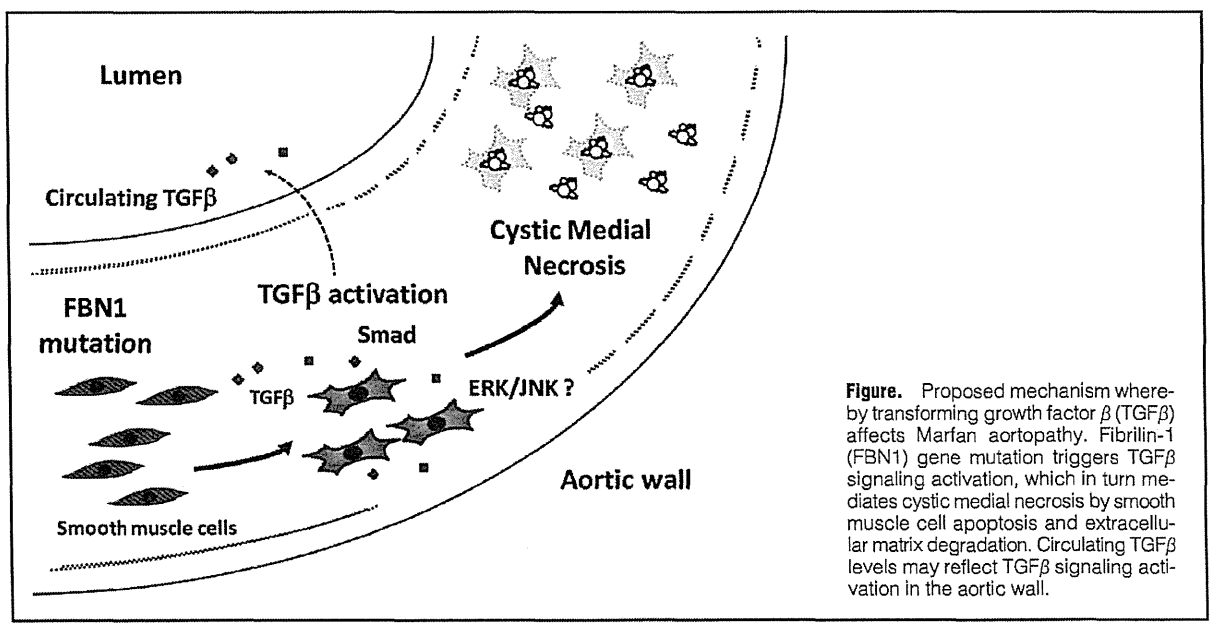

Figure. Proposed mechanism whereby transforming growth factor β (TGFβ) affects Marfan aortopathy. Fibrilin-1 (FBN1) gene mutation triggers TGFβ signaling activation, which in turn mediates cystic medial necrosis by smooth muscle cell apoptosis and extracellular matrix degradation. Circulating TGFβ levels may reflect TGFβ signaling activation in the aortic wall.

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rogate biomarker for the aortic remodeling process.[9] However, there remains a paucity of data linking the severity of aortic wall destruction, histologically increased focal TGFβ activation and elevated circulating TGFβ levels in human cases of Marfan aortopathy.

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In this issue of the Journal, Kim and colleagues[10] report on their investigation of aortic tissue injury, such as cystic medial degeneration and cellular apoptosis, and Smad2 phosphorylation in MFS patients, in addition to TGFβ levels in both the peripheral blood and aortic tissue. They demonstrate an association between circulating levels of active TGFβ-1 and the severity of aortic remodeling (cystic medial degeneration and Smad2 phosphorylation in aneurysmal aortic layers) in MFS patients.

One of the noteworthy features of this study is that, for the first time, an association between pathologic aortic remodeling and both TGFβ signaling in the aortic wall and circulating levels in MFS patients are shown (**Figure**). Activation of the Smad2 pathway had been previously reported as common to both syndromic and non-syndromic aneurysms of the human ascending aorta (including MFS as well as degenerative aneurysm and bicupsid aortic valve patients), but that previous study only reported pathologically increased Smad2 phosphorylation and expression levels of TGFβ in the diseased aortic wall and did not determine the association between these phenomena and the degree of aortic wall remodeling/destruction or circulating TGFβ levels.[11]

Another feature of the present study is the patient cohort. Investigated patients had not been treated with antihypertensive drugs for more than 2 weeks, which provided the condition of minimal concomitant effects by the various drugs and agents used in this syndrome that may affect TGFβ signaling and MFS pathogenesis. This, however, does imply that patients were basically medically untreated and thus points to an unconventional cohort for present standards of care. Further, the authors report on the degree and relationship between Smad phosphorylation and TGFβ signaling at the histologic level in Asian subjects, as racial differences in MFS phenotype and circulating TGFβ levels had been reported.[12] MFS patients with aortic dissection were also shown to exhibit more severe cystic medial degradation, and increased circulating or aortic TGFβ levels. Although this finding is descriptive and not necessarily causal, it describes an association between the severity of aortic remodeling and circulating TGFβ levels.

Several issues remain unanswered in the application, in the real world, of circulating TGFβ levels as a surrogate biomarker to monitor disease activity or therapeutic efficacy in MFS or other aortopathic patients, in addition to the technical difficulties that lead to false-positive results (eg, method of blood sampling). One is that it is still unclear is whether circulating TGFβ levels are truly associated with dilation of the aorta, which is of clinical importance. The present study showed a dilated aorta with an average width of 59 mm at the sinus of Valsalva regardless of circulating TGFβ levels. Lack of correlation between the z value (an indicator of aortic root expansion) and circulating TGFβ level, despite reduction in the level by pharmacological intervention, has also been reported.[9] Another issue is the need to better understand the relative contribution of TGFβ and its downstream signaling molecules in aneurysmal formation in the Marfan aorta.

Collectively, circulating TGFβ levels may be associated with progression of aortic remodeling as reflected by activated Smad (phosphorylation) protein on histopathologic analysis. Importantly, however, other mechanisms, including Smad-independent pathways and/or inflammatory processes, might also contribute to clinical aneurysmal dilatation, rupture or dissection.[13]

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Review article

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Diagnosis of acute aortic syndromes

Imaging and beyond

Introduction

Acute aortic syndromes encompass a spectrum of related conditions, ranging from aortic dissection (AoD) to intramural hematoma (IMH) and penetrating atherosclerotic ulcer (PAU). From a physiological standpoint, these conditions commonly result from disruption of the structural integrity of the aortic wall [1, 2, 3]. Beyond the typical presentation of rest-onset chest pain, patients with AoD may present with nonspecific symptoms, such as neurological deficits, syncope, or cramping abdominal pain [4]. Clinical variability can make diagnosis challenging, with symptomatic heterogeneity relating to distribution of aortic involvement. Failure to promptly recognize and treat acute aortic syndrome may result in progressive aortic injury, end-organ compromise, and hemodynamic instability, thereby, adding to the potential morbidity and mortality risks of these serious conditions [4, 5, 6].

This review provides an overview of established and emerging approaches for assessment of acute aortic syndromes, with focus on imaging and biomarkers. Diagnostic options are discussed in the context of consensus guidelines, including relative benefits offered by individual tests towards the goal of comprehensive evaluation and risk assessment of patients with known or suspected acute aortic syndrome.

Imaging

Aortic dissection

AoD typically results from a tear in the aortic intima, an index event that causes blood extravasation with separation of the aortic wall layers (i.e., intima, media, and adventitia). AoD is generally classified as acute if presentation occurs within 2 weeks of symptom onset, subacute if it occurs within 2–6 weeks, and chronic if more than 6 weeks have elapsed [1, 2, 3, 4].

Anatomic location of AoD is a key determinant of clinical outcome and is widely used to guide management (◘ Fig. 1a). The Stanford classification categorizes AoD involving the ascending aorta as *type A*, and AoD confined to the aortic arch or descending aorta (i.e., distal to the left subclavian artery) as *type B*. The DeBakey classification categorizes AoD based on site of origin of the intimal tear—*type I* originates in the ascending aorta and extends distally (i.e., aortic arch or beyond), *type II* is confined to the ascending aorta, and *type III* involves the descending aorta (i.e., distal to the left subclavian artery) [1, 2].

Tab. 1 Relative strengths of imaging modalities for acute aortic syndromes

	TTE	TEE	MRI	CT
Imaging factors				
Comprehensive aortic assessment	+	++	+++	+++
Tomographic (3D reconstruction)	–	–	+++	+++
Functional	+++	+++	++	+
Tissue characterization	–	–	+++	+++
Clinical factors				
Portability	+++	++	–	–
Patient access/monitoring	+++	+++	+	++
Rapidity	++	++	++	+++
Non-contrast	+++	+++	+	+
Radiation exposure	+++	+++	+++	+

3D three-dimensional, TTE transthoracic echocardiography, TEE transesophageal echocardiography, MRI magnetic resonance imaging, CT computed tomography.

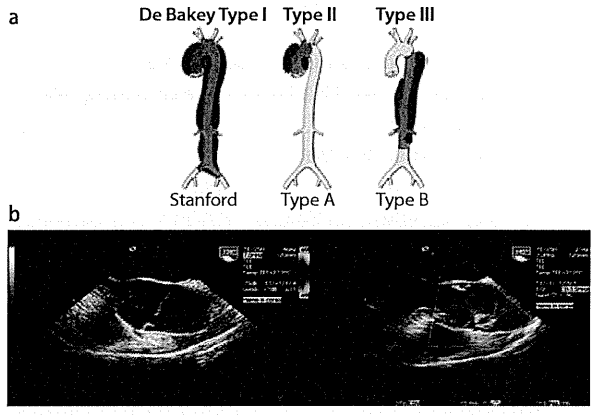

Fig. 1 ▲ Aortic Dissection. **a** DeBakey and Stanford classification systems. The DeBakey system (*top*) classifies AoD into three types based on site of origin and extent: type I originates in the ascending aorta and propagates at least to the aortic arch, type II originates and is confined to the ascending aorta, and type III originates in the descending aorta but occasionally extends in an antegrade or retrograde direction. The Stanford system (*bottom*) classifies AoD into two types: type A involves the ascending aorta, and type B is confined to the aortic arch or descending aorta. (Reproduced with permission. Modified from [42]). **b** Transesophageal echocardiography: Type A aortic dissection: intimal flap with entry tear close to the right anterior Valsalva sinus without (*left panel*) and with (*right panel*) color Doppler. (Courtesy of Rodolfo Citro, MD, Heart Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy)

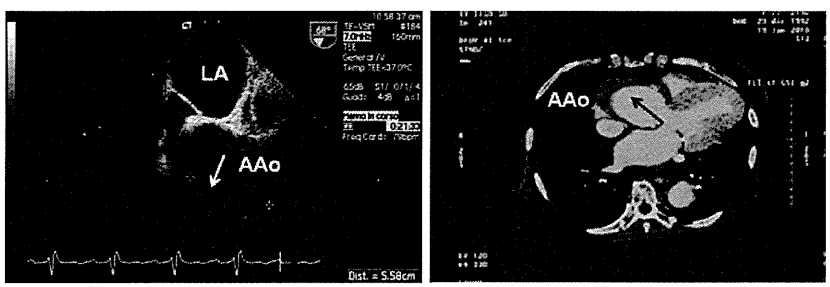

Fig. 2 ▲ Intramural hematoma. Transesophageal echocardiography (*left*) reveals ascending aortic aneurysm and aortic wall thickening (*arrow*) without accompanying dissection flap or false lumen. Contrast-enhanced computed tomography (*right*) demonstrates crescentic aortic wall thickening (*arrow*), a hallmark of intramural hematoma. (Courtesy of Rodolfo Citro, MD, Heart Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy). *AAo* ascending aorta, *LA* left atrium

Both the Stanford and DeBakey classification systems can readily be applied to imaging (◘ **Fig. 2**). In consensus guidelines, there is a lack of agreement as to which system is better [1, 2]. Prompt surgical intervention is usually indicated for AoD involving the ascending aorta (Stanford type A, DeBakey types I or II), whereas medical management with β-blockade and adjunctive blood pressure control is reserved for AoD localized to the aortic arch or descending aorta (Stanford type B, DeBakey type II). Endovascular stenting is an alternative management strategy for dissections involving the descending thoracic aorta. Patient-specific decisions regarding surgical/interventional vs. medical management are influenced by ancillary considerations, such as cardiovascular/hemodynamic stability and end-organ compromise [1, 2].

Diagnostic performance of imaging in AoD can vary depending on technology used, institutional expertise, and exam quality. Given the acute nature of AoD and the importance of early treatment, prospective randomized comparisons of imaging modalities are difficult. In a recent meta-analysis, encompassing 1139 patients from 16 studies, pooled sensitivity (98–100%) and specificity (95–100%) were similar between transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI) [7]. Transthoracic echocardiography (TTE) has generally been reported to yield lower sensitivity for AoD diagnosis, with better performance for type A (78–87%) compared to type B (29–40%) AoD [1, 2, 8, 9]. According to data from the International Registry of Acute Aortic Dissection (IRAD), multimodality imaging is employed in approximately two thirds of patients being evaluated for AoD [5, 9], highlighting the importance of follow-up testing if clinical suspicion remains high despite an initially negative or equivocal diagnostic imaging result.

From an individual patient standpoint, decisions as to which modality should be used for AoD are influenced by imaging and clinical considerations. A comparison of the relative strengths of major noninvasive imaging modalities is shown in ◘ **Tab. 1**. In addition to their general strengths, it is also important to recognize that test performance can vary between patients and institutions. Imaging expertise is critically important to optimize quality and maximize test performance. The common imaging challenges that may affect aortic assessment, as well as the strategies that can be employed to contend with them are outlined in ◘ **Tab. 2**. As a general principle, multimodality imaging should be strongly considered when image quality is suboptimal or clinical suspicion for acute aortic syndrome persists after an initial negative test result.

The remainder of this section details key clinical and imaging considerations for imaging tests commonly used to assess AoD.

Echocardiography

TTE is widely used as a general screening test for patients with cardiovascular disease, including individuals with known or suspected AoD [10]. Major advantages include wide availability, bedside portability, absence of ionizing radiation, and no need for contrast administration (of particular

benefit in the context of AoD, a condition associated with impaired renal perfusion). TTE is well suited to assess cardiac complications of AoD, such as aortic regurgitation and pericardial effusion/tamponade [1, 2, 10].

TTE provides immediate and reliable assessment of cardiac structure and function, but its ability to comprehensively assess the aorta is limited. Quality can vary depending on patient body habitus and sonographer expertise. Imaging of the descending thoracic aorta is often challenging because of its relative distance from the sonographic probe, rendering TTE suboptimal for the assessment of AoD in this region.

TEE enables physician-guided imaging in close proximity to the thoracic aorta and provides high spatial and temporal resolution images in discrete aortic segments. Clinical advantages of TEE are counterbalanced by its invasive nature, which is dissatisfying for patients with low pretest probability for AoD, and may be contraindicated in patients with high pretest probability in whom hemodynamic instability prohibits sedation and endoscopy. Image artifacts due to reverberation may mimic AoD, appearing as a linear mobile density within the ascending aorta. Assessment of mobility (i.e., AoD manifests independent mobility from surrounding structures), location (i.e., AoD does not transect the aortic wall), and Doppler flow pattern (i.e., differential flow on either side of the dissection flap) are useful criteria for distinguishing AoD from an image artifact [1]. TEE may occasionally be suboptimal for imaging the distal ascending aorta/proximal arch because of interference by tracheal air shadowing, as well as the abdominal aorta because of the distance from the imaging probe, emphasizing the need for alternative imaging in some individuals [1, 2, 10].

Computed tomography and magnetic resonance imaging

Tomographic imaging—whether by CT or MRI—provides comprehensive assessment of the aorta and its branch vessels. Tomographic imaging also enables double oblique reformatting for identification of AoD origin and accurate assessment of aortic size [11, 12], all major prognostic indices in patients with aortic disease. In addition to direct aortic assessment, both CT and MRI are well suited to assess complications of AoD, including pericardial or pleural effusions. Tomographic imaging is particularly useful for patients with prior aortic interventions, as it enables integrated visualization of both native aortic segments and prosthetic materials. Accelerated sampling methods have reduced test times for both CT and MRI, allowing rapid imaging of patients with known or suspected AoD. ECG gating techniques improve temporal resolution and reduce blurring of the aortic root, a relatively mobile region that can be difficult to assess on non-gated imaging.

Beyond their common advantages, it is important to consider the relative strengths of each tomographic imaging modality in the context of clinical considerations. MRI entails no radiation exposure and is well suited for serial assessment of at-risk patients. Using phase velocity encoded imaging techniques, MRI can directly measure aortic flow and thereby assess adjunctive complications such as aortic regurgitation. However, MRI is performed in a highly controlled setting, with most scanners employing closed bore systems that make rapid patient access difficult—a key disadvantage for unstable or claustrophobic patients. Additionally, MRI is prohibited in patients with ferromagnetic and/or magnetically activated implants (including most cardiac pacemakers and defibrillators), and image artifacts can interfere with assessment of vascular stents [13]. Gadolinium-based contrast agents are contraindicated in patients with advanced renal im-

Abstract · Zusammenfassung

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Diagnosis of acute aortic syndromes. Imaging and beyond

Abstract

Acute aortic syndromes are fatal medical conditions including classic acute aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Given the nonspecific symptoms and signs, a high clinical index of suspicion followed by an imaging study, namely transesophageal echocardiography, computed tomography, and magnetic resonance imaging (sensitivity 98–100% and specificity 95–100%), is a *conditio sine qua non* for prompt diagnosis of acute aortic syndromes. This article provides an overview of established and emerging approaches for the assessment of acute aortic syndromes, with focus on imaging and biomarkers. In this regard, D-dimer levels (cut-off: 500 ng/ml) may be useful to rule out aortic dissection, if used within the first 24 h after symptom onset.

Keywords

Acute aortic syndromes · Aortic dissection · Cardiac imaging techniques · D-dimer · Congenital abnormalities

Diagnose des akuten Aortensyndroms. Bildgebung und mehr

Zusammenfassung

Das akute Aortensyndrom ist eine letale Erkrankung und umfasst beispielsweise die klassische akute Aortendissektion, das intramurale Hämatom und das penetrierende atherosklerotische Ulkus. Angesichts der unspezifischen Symptome sind bei starkem klinischem Verdacht bildgebende Untersuchungen, also transösophageale Echokardiographie, Computertomographie und Magnetresonanztomographie (Sensitivität: 98–100%, Spezifität: 95–100%), eine Conditio sine qua non für die zügige Diagnose eines akuten Aortensyndroms. In der vorliegenden Übersichtsarbeit wird ein Überblick über etablierte und neue Ansätze zur Beurteilung des akuten Aortensyndroms gegeben, dabei liegt der Schwerpunkt auf Bildgebung und Biomarkern. Diesbezüglich ist möglicherweise die Bestimmung des D-Dimer-Spiegels (Grenzwert: 500 ng/ml) zum Ausschluss einer Aortendissektion hilfreich, wenn sie innerhalb der ersten 24 h nach Symptombeginn durchgeführt wird.

Schlüsselwörter

Akutes Aortensyndrom · Aortendissektion · Kardiale Bildgebungsverfahren · D-Dimer · Kongenitale Anomalien

Tab. 2 Imaging challenges in aortic assessment

	Finding	Etiology	Typical location	Potential solutions
TTE	Acoustic shadowing/impaired aortic visualization	Distance from sonographic probe	Aortic arch, descending aorta	Acquire images using suprasternal (for arch) or subcostal (for mid descending aorta) views
TEE	Linear artifact mimicking dissection	Tracheal interference (air shadowing)	Distal arch, proximal descending aorta	Assess mobility pattern (artifact typically transects wall, demonstrates phasic mobility) Assess Doppler flow pattern (dissection typically manifests differential flow between true/false lumen, possible communication at dissection origin)
MRI	Repetitive "ghosting" artifact obscuring aorta or mimicking dissection, blurred vessel contours	Respiratory motion Cardiovascular motion	Nonspecific (typically diffuse)	Accelerated data sampling (i.e., parallel or single shot imaging) Respiratory gating Integrated MR angiography interpretation with noncontrast (i.e., fast spin-echo, steady-state free precession) imaging
	Impaired visualization of prosthetic material (i.e., aortic stents)	Susceptibility Radiofrequency shielding	Localized to prosthetic material (i.e., within or adjacent to stent)	Modify pulse sequence parameters (i.e., increase flip angle, decrease echo time) Alter pulse sequences used use of fast spin-echo pulse sequences (if feasible)
CT	Impaired visualization of prosthetic material (i.e., stents)	Beam hardening artifact (blooming effect)	Localized to prosthetic material (i.e., within or adjacent to stent)	High resolution, multidetector CT scanners (i.e., for reduced voxel size) Modify scanning parameters (i.e., increase tube voltage) Modify data filtering (i.e., use edge enhancing ["sharp"] convolution kernals) Adjust workstation settings for stent interpretation (i.e., width ~1500 HU, center ~300 HU)

TTE transthoracic echocardiography, TEE transesophageal echocardiography, MRI magnetic resonance imaging, CT computed tomography.

pairment because of the risk for nephrogenic systemic fibrosis. Non-contrast MRI techniques, such as fast spin-echo and steady-state free precession, may be useful for aortic assessment of patients with renal dysfunction [14].

For CT angiography, both ionizing radiation and contrast-associated nephrotoxicity are substantial concerns, especially in patients requiring serial testing. Radiation dose reduction can be achieved through use of prospective ECG gating and dose modulation techniques [15]. CT offers several advantages that are especially pertinent to patients with known or suspected AoD. Relatively open scanner environments facilitate patient tolerance of the exam as well as rapid patient access, if necessary. Current generation multidetector CT can provide submillimeter spatial resolution—facilitating detailed assessment of aortic anatomy. Multidetector CT also enables coronary assessment, thereby, providing useful information for patients requiring coronary re-implantation in the context of aortic graft placement. Prosthetic material is well visualized on CT [13], enabling assessment of vessel integrity in patients with prior surgical interventions. These advantages may explain findings from the IRAD study, which reported that CT was the most commonly used initial imaging test for suspected acute AoD (63%), followed by echocardiography (32%) and MRI (1%) [9].

Intramural hematoma

IMH, a potential precursor to AoD [16], reflects hemorrhage of the vasa vasorum into the aortic media, with resultant separation of the vessel wall (intima and media). Clinical differentiation between IMH and acute AoD can be challenging, emphasizing the need for reliable imaging to distinguish between these diagnoses.

Echo, CT, and MRI have all been used to diagnose IMH. An imaging hallmark is crescentic or circumferential aortic wall thickening in the absence of an identifiable dissection flap (**Fig. 2**). IMH location may vary, making comprehensive aortic imaging necessary when this diagnosis is being considered.

Tissue characterization imaging—as offered by CT and MRI—may also enable assessment of vascular properties beyond those discernable solely on the basis of IMH morphology. IMH typically manifests higher signal intensity than intraluminal blood on non-contrast CT and absence of enhancement (i.e., low signal intensity) on contrast-enhanced imaging. Focal regions of intramural contrast uptake have been reported in some cases [17, 18], with variability possibly due to differences in IMH acuity or tissue composition. MRI tissue characterization can similarly demonstrate IMH, with delayed post-contrast (T1-weighted) imaging particularly useful for demonstrating thrombotic components [19, 20]. Complementary MRI approaches, such as T2*-weighted imaging, have been used to detect intramyocardial hemorrhage following acute myocardial infarction [21]. This approach also holds potential for assessing intravascular hemorrhage in the context of IMH. However, IMH may be small in size (i.e., focal), thereby, requiring high spatial resolution imaging to be detected. Aortic mobility imposes a further technical challenge, emphasizing the need for good temporal resolution, which may be difficult to achieve when counterbalanced with spatial resolution requirements. These imaging challenges may explain the limited application of tissue characterization approaches for diagnostic and prognostic assessment of IMH. Complementary MRI approaches include phase contrast and cine imaging, each of which may be helpful to exclude focal dis-

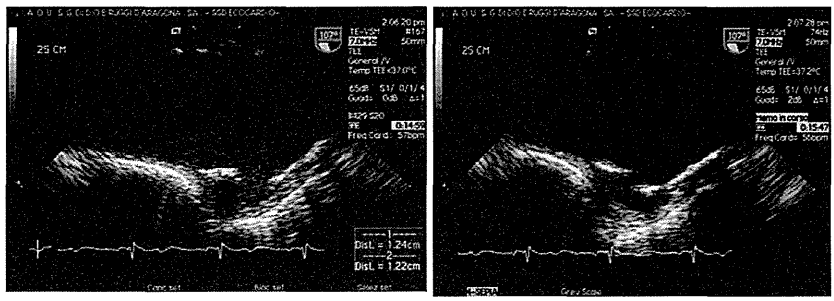

Fig. 3 ▲ Penetrating atherosclerotic ulcer. Transesophageal echocardiography: ulcer-like formation in the inferior wall of the aortic arch with disruption of the internal elastic lamina before (*left panel*) and after (*right panel*) contrast agent administration. (Courtesy of Rodolfo Citro, MD, Heart Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy)

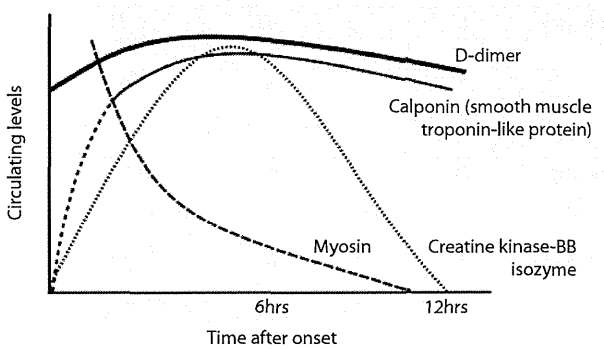

Fig. 4 ◀ Time course of biomarker elevation following acute aortic dissection. Note the rapid and prolonged elevation of D-dimer in relation to other potential biomarkers

section flap and absence of flow in association with IMH.

Penetrating atherosclerotic ulcer

PAU is identifiable by the presence of an ulcerated plaque that extends into the medial layer of the aortic wall. Exposure of the media to pulsatile blood flow may induce structural instability, with subsequent risk of PAU progression to AoD or IMH or even free rupture. Presenting symptoms can mimic IMH or AoD, emphasizing the role of noninvasive imaging for diagnostic assessment of acute aortic syndromes.

PAU typically appears as an *ulcer-like* formation on imaging (◘ **Fig. 3**), with irregularly contoured luminal indentation. These features can be demonstrated on echo, as well as both CT and MRI. However, the latter two modalities offer several benefits of particular utility for PAU. First, both tomographic methods provide three-dimensional imaging—a feature particularly useful for demonstrating PAU in the presence of aortic tortuosity and associated altered geometry. Second, imaging is typically performed with administration of intravascular contrast agents, which improve delineation of the luminal borders and facilitate assessment of plaque ulceration.

Some reports have suggested that MRI is superior to CT for the diagnosis of PAU [22]. However, these conclusions were derived from early imaging technology and can be questioned in the light of current generation multidetector CT, which can provide submillimeter spatial resolution. Similar to IMH, tissue characterization imaging by MRI and CT holds the potential to offer new insights into the pathophysiology of PAU. Both MRI and CT allow for tissue characterization of atherosclerotic plaques [23, 24], a feature that is particularly attractive for the assessment of aortic plaque composition in the context of PAU. However, as with IMH, in vivo application of tissue characterization imaging has been limited, possibly due to technical challenges related to both spatial and temporal resolution. Further advances in MRI and CT technologies may facilitate broader clinical application of tissue characterization approaches for the assessment of acute aortic syndromes.

Biomarkers

Smooth muscle

Smooth muscle is predominantly found in the aortic media, which is injured during onset and evolution of AoD, leading to circulatory release of cellular proteins. This phenomenon has led to investigation of several smooth muscle biomarkers for acute aortic syndromes.

Smooth muscle myosin heavy chain was among the first biomarkers found to be elevated in patients with AoD. Studies showed marked elevations in the setting of acute AoD, with a dynamic range of nearly 20-fold higher levels in patients presenting early after symptom onset [25]. Smooth muscle myosin offered favorable discrimination and diagnostic accuracy, but elevations were transient (i.e., 3–6 h) after AoD onset, similar to myoglobin in acute myocardial infarction [25, 26]. This phenomenon creates a narrow time window of use, a substantial limitation for use of this biomarker in routine clinical practice.

Creatine kinase, which includes both muscle (M-) and brain (B-) isozymes, has also been investigated as a biomarker for AoD. The MM-type isozyme is widely used for detection of skeletal muscle damage, as is the MB-isozyme for detection of ischemic heart disease. Studies measuring the BB-isozyme, which is selective for neurological and smooth muscle, showed marked elevations following AoD, with peak levels approximately 6 h after onset [27]. However, the short time course and lack of specificity of this biomarker are substantial limitations to clinical use.

Calponin, a troponin counterpart of smooth muscle, has also been investigated as a biomarker for AoD. Similar to troponin in the setting of myocardial infarction, a particular benefit of calponin concerns its prolonged elevation. In comparison to creatinine kinase-BB, calponin has a longer time course, remaining elevated throughout the first 24 h following AoD based on an initial assay [28]. The time course of calponin elevation in relation to other biomarkers for acute AoD is illustrated in ◘ **Fig. 4**.

Tab. 3 Potential biomarkers for diagnosis of acute aortic dissection

Biomarker Author	Cases/Ctrl	Stanford A/B	Cut-off	Type of assay	Symptom onset (h)	Sensitivity (%)	Specificity (%)
D-dimer (µg/ml)							
Suzuki et al. [35]	87/133	64/23	>0.5	Immunoassay	24	96.6	46.6
Sbarouni et al. [36]	18/29	13/5	>0.7	ELISA	4–60	94	59
Ohlmann et al. [37]	94/94	67/27	>0.4	Turbidimetric	29	99	34
Hazui et al. [38]	29/49	29/0	>0.9	Latex agglutination	4	93.1	80
Akutsu et al. [39]	30/48	12/18	>0.5	Latex agglutination	4.5	100	54
Eggebrecht et al. [40]	16/48	6/10	>0.62	Latex agglutination	16	100	73
Weber et al. [41]	24/35	12/12	>0.5	Turbidimetric	24	100 [a]	69
SSMMHC (µg/l)							
Suzuki et al. [26]	95/131	45/50	2.5	Enzyme immuno-assay	<3	90.0 [b]	98 [c]
Basic calponin (ng/ml)							
Suzuki et al. [28]	59/158	43/15	159 [d]	Immunoassay	6	63	73
MMP-9 (ng/ml)							
Sangiorgi et al. [31]	13/10	9/4	3-fold higher [e]	ELISA	3	NA	NA
TGF-β (ng/ml)							
Suzuki et al. [33]	28/–	20/8	5-fold higher [f]	Immunoassay	24	NA	NA
CK-BB isozyme (IU/l)							
Suzuki et al. [27]	10/20	–/–	17-fold higher [g]	Electrophoresis	12	NA	NA

CK creatine kinase, **Ctrl** controls, **MMP** matrix metalloproteinases, **SSMMHC** smooth-muscle myosin heavy-chain protein, **TGF** transforming growth factor, **NA** not available. [a]D-dimer values tended to be higher in more extended aortic dissection, [b]sensitivity 72.4% and 30.3% at <6 h and >6 h from symptom onset, respectively, [c]specificity was 83% compared to patients with acute myocardial infarction, [d]optimal value determined from ROC curve analyses, [e]29.3±16.1 ng/ml for type A group and 16.7±2.1 ng/ml for type B group vs 7.74±1.6 ng/ml for ctrl, $p<0.03$, [f]24.5±12.9 ng/ml for aortic dissection patients (28.5±14.7 ng/ml for type A, 14.4±6.1 ng/ml for type B) vs 5.4±2.8 ng/ml for ctrl, [g]3.4 for aortic dissection patients vs 0.2 IU/l for ctrl

Taken together, these data demonstrate the potential of smooth muscle proteins as biomarkers of acute AoD. Further industrial developments are necessary for these assays to become clinically available.

Structural and inflammatory indices

Several markers of vascular integrity or systemic inflammation have been tested for AoD. Elastin, a structural vessel wall protein, has been shown to increase following AoD [29]. However, dynamic range is limited (i.e., less than a two-fold increase compared with normal controls), making reliable clinical use questionable. C-reactive protein, a nonspecific inflammatory marker, has also been shown to increase after acute AoD [30]. Re-elevation and retarded recovery of C-reactive protein levels may reflect instability of intramural thrombus or hematoma (defined as enlargement of localized contrast filling, transition to classic dissection, or expansion of hematoma in the aortic wall) and/or thrombosis within the false lumen [25]. Matrix metalloproteinases (MMP), enzymes involved in aortic remodeling, are also elevated in acute AoD, namely the subunit MMP-9 [31]. Further research is needed to clarify their potential role in AoD.

Circulating transforming growth factor-beta (TGF-β) has received particular attention as it may serve as a biomarker for aortic remodeling in patients with Marfan syndrome [32]. Fibrillin-1, the protein that is defective in Marfan syndrome, regulates TGF-β activity. TGF-β is bound in a complex form to fibrillin-1, which is disrupted upon pathogenic insult. This causes release and activation of the TGF-β molecule, resulting in activation of vascular cell signaling cascades that induce aortic remodeling. Further study is needed to test the clinical utility of TGF-β in a broad range of aortopathies. However, circulating TGF-β levels have been shown to be markedly elevated in patients with acute AoD [33], suggesting that TGF-β may potentially serve as a biomarker for conditions other than Marfan syndrome.

D-dimer

At present, D-dimer is the only biomarker that is clinically available and adequately sensitive to detect AoD. D-dimer, a fibrin fragment released in coagulopathic disorders, is routinely used to diagnose pulmonary embolism (PE). As shown in ◘ **Fig. 4**, D-dimer elevation occurs early after AoD and is prolonged in relation to other biomarkers. This feature is of particular clinical utility as it provides an increased time frame during which D-dimer can be used to identify patients with AoD.

Several studies have shown D-dimer to be elevated in the setting of AoD (◘ **Tab. 3**) [26, 27, 28, 31, 33, 34, 35, 36, 37, 38, 39, 40, 41]. Clinical utility has been tested in the IRAD substudy on biomarkers (IRAD-Bio) [35], which used suspicion of AoD as an entry criterion for both patients and controls, thereby, enabling D-dimer to be tested in a setting similar to routine clinical practice. IRAD-Bio encompassed 220 patients with clinical-

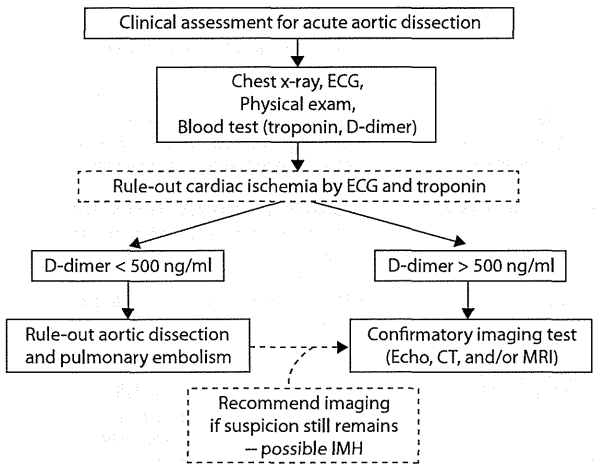

Fig. 5 ◀ Proposed diagnostic algorithm for patients with suspected aortic dissection. D-dimer testing is integrated with imaging and clinical evaluation. *CT* computed tomography, *IMH* intramural hematoma, *MRI* magnetic resonance imaging

ly suspected AoD. Results showed that, within the first 24 h of symptom onset, a D-dimer threshold of 500 ng/ml (commonly used for ruling out PE) can be used to discriminate between patients with and without confirmed AoD. Stratification based on D-dimer was maximal during the first 6 h after symptom onset, suggesting that AoD is associated with rapid and substantial D-dimer elevations. Not only was it possible to *rule out* AoD based on low D-dimer levels, but findings suggested that use of a higher threshold (1600 ng/ml) enabled AoD to be *ruled in*, thereby, supporting both the positive and negative predictive value of D-dimer. One caveat concerns the fact that IRAD-Bio included a small number of patients with PE, emphasizing the need for further study to test the utility of D-dimer among diverse patient cohorts. In summary, current data suggest that D-dimer may be helpful in assessing patients with suspected AoD. Since the same lower threshold can be applied to PE and AoD, this single test can be used to exclude both conditions in certain patients, a feature that is particularly advantageous from the standpoint of simplicity and cost-effectiveness. Notably, the IRAD-Bio study was comprised of patients with suspected AoD—caution is needed in extrapolating these data to patients with generalized chest pain. With the appropriate understanding in use and interpretation, D-dimer can be useful for evaluating chest pain syndromes in which marked elevations of this biomarker prompt consideration of further testing for acute AoD and/or PE.

Proposed algorithm for clinical decision-making

A proposed diagnostic algorithm that may be helpful in guiding evaluation of patients with suspected AoD is outlined in ◘ **Fig. 5**. While the algorithm integrates imaging and biomarker testing (D-dimer, troponin), clinical assessment assumes a primary role. To this end, clinical risk stratification using an "aortic dissection detection" (ADD) scoring tool has been included in recent US (ACC/AHA) consensus guidelines [1]. This tool has also been validated in patients with AoD: when tested in the IRAD registry, the ADD risk score yielded a diagnostic sensitivity of 95.7% for AoD. Among the 4.3% of patients with no clinical markers for AoD (ADD score =0), nearly half (48.6%) that underwent chest X-ray had evidence of widened mediastinum—lending support to the concept that clinical history should be integrated with imaging or other testing when assessing for suspected AoD [5].

Regarding biomarkers, cardiac troponin and D-dimer can help to guide assessment. If possible, both indices should be checked with a point-of-care test that yields prompt results. Troponin, interpreted adjunctively with electrocardiography, can identify evidence of myocardial infarction/ischemia, which may constitute the primary cause of chest pain symptoms or occur as a secondary consequence of AoD (i.e., impaired coronary perfusion). In cases with D-dimer levels >500 ng/ml, an imaging test should be performed promptly for further evaluation. In patients with D-dimer levels >1600 ng/ml, suspicion for AoD or PE should be high, with subsequent management guided by clinical findings and imaging results. In cases with D-dimer levels <500 ng/ml, imaging (i.e., CT, MRI, or TEE) should still be considered if clinical suspicion for AoD persists despite normal biomarker results. Indeed, normal D-dimer levels have been reported among patients with IMH or AoD with thrombosed false lumen [35], highlighting the importance of comprehensive evaluation for patients with suspected acute aortic syndromes.

Conclusion

The diagnosis of acute aortic syndrome can be made with similar accuracy using different imaging techniques such as TEE, CT or MRI depending on the availability of the technique, experience of the imaging staff, and clinical patient's condition. However, multimodality imaging should be strongly considered when image quality is suboptimal or clinical suspicion for acute aortic syndrome persists even after an initial negative test. The measurement of specific biomarkers is intriguing as an initial strategy for the diagnosis of acute aortic syndrome. D-dimer levels (cut-off: 500 ng/ml) may be useful to rule out AoD if used within the first 24 h after symptom onset. Further studies are necessary to test the comparative utility of variable imaging and biomarker-guided algorithms among large cohorts of patients with known or suspected acute aortic syndrome.

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