Redefining the histopathologic profile of acute aortic syndromes: Clinical and prognostic implications

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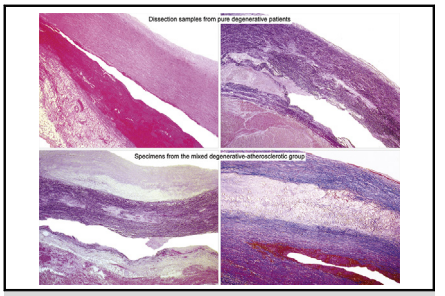
ABSTRACT

Objectives: The study objectives were to describe the aortic histopathologic substrates in patients with type A surgically treated acute aortic syndromes, to provide clinico-pathological correlations, and to identify the possible prognostic role of histology.

Methods: We assessed the aortic wall degenerative or inflammatory alterations of 158 patients according to the histopathologic consensus documents. Moreover, we correlated these histologic patterns with the patients' clinical data and long-term follow-up for mortality, major aorta-related events, and nonaorta-related events (including cardiovascular ones).

Results: We identified 2 histopathologic patterns: 122 patients (77%) with degenerative alterations and 36 patients (23%) with mixed degenerative-atherosclerotic lesions. Patients with mixed alterations were older (mean 69.6 ± 8.7 years vs 62.2 ± 12.4 years, $P = .001$) and more hypercholesterolemic (33.3% vs 13.9%, $P = .017$). The degenerative subgroup showed more intralamellar-mucoid extracellular matrix accumulation (86% vs 66.7%, $P = .017$) and a lower prevalence of translamellar collagen increase (9.8% vs 50%, $P < .001$). Patients with mixed degenerative-atherosclerotic abnormalities more frequently had long-term nonaorta-related events compared with those with degenerative abnormalities alone ($P = .046$); no differences were found between the groups with respect to mortality, major aorta-related events, and cardiovascular nonaorta-related events.

Conclusions: Although degenerative lesions of the medial layer were present in all specimens, substantial atherosclerosis coexisted in approximately one quarter of cases. Patients with mixed degenerative-atherosclerotic abnormalities had a coherent clinical risk profile, a clinical presentation frequently mimicking acute coronary syndrome, and a higher incidence of nonaorta-related events during follow-up. Histopathologic characterization may improve the long-term prognostic stratification of patients after surgical treatment. (J Thorac Cardiovasc Surg 2018;156:1776-85)



Comparison between histologic features of degenerative alterations and atherosclerosis.

Central Message

Patients with relevant atherosclerosis associated with MD were older, hypercholesterolemic, and had more major nonaorta-related events than patients without atherosclerosis.

Perspective

All surgical specimens of type A AAS showed MD, associated with relevant atherosclerosis in one quarter. These patients had a coherent CV risk profile and showed more nonaorta-related events. Atherosclerosis was a probable independent risk factor for nonaorta-related events. Therefore, histology holds a stronger predictive value than clinical data alone.

See Editorial Commentary page 1786.

See Editorial page 1772.

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Abbreviations and Acronyms

AAS = acute aortic syndrome
ACS = acute coronary syndrome
AECVP = Association for European Cardiovascular Pathology
CI = confidence interval
CV = cardiovascular
EFFL = elastic fiber fragmentation/loss
EFT = elastic fiber thinning out
HR = hazard ratio
ICI = intralamellar collagen increase
I-MEMA = intralamellar mucoid extracellular matrix accumulation
LMC = laminar medial collapse
MD = medial degeneration
SCVP = Society for Cardiovascular Pathology
TCI = translamellar collagen increase
T-MEMA = translamellar mucoid extracellular matrix accumulation

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Type A acute aortic syndromes (AAS) are a life-threatening condition that require emergency surgical treatment.[1] Although different inherited and acquired conditions predispose to this dramatic event, our knowledge of the histology of the diseased aortic wall is incomplete. The available clinico-pathological correlation studies are relatively old and tend to examine acute and chronic aortic diseases together.[2-5]

The histopathology underlying type A AAS is generally considered due to degenerative lesions of the aortic medial layer, first identified by Erdheim[6] in 1930 as ''aortic idiopathic (cystic) medial necrosis.'' Recently, however, the Association for European Cardiovascular Pathology (AECVP) and the Society for Cardiovascular Pathology (SCVP) have proposed a revised nomenclature, terminology, grading systems, and diagnostic criteria for aortic diseases in 2 consensus statements on the histopathology of inflammatory[7] and noninflammatory degenerative[8] aortic diseases. We applied these criteria to the analysis of the aortic specimens obtained during surgery, with the aim of providing detailed histopathologic characterization and search for clinico-pathological correlations, including the possible role of histology in prognostic stratification.

MATERIALS AND METHODS

Clinical Setting

Our hospital is the AAS referral center for Bologna and the surrounding metropolitan area (catchment area 1,000,000 inhabitants). Our registry includes all adult (aged >18 years) consecutive patients with a final diagnosis of spontaneous AAS referred to our center between January 1, 2000, and December 31, 2013. Patients with symptoms onset lasting more than 14 days or with traumatic AAS were not included. Median follow-up for alive patients was 4 years (interquartile range, 2.2-6). The study conforms to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee, and patients provided written informed consent.

Pathology

An average of 6 samples were obtained from ascending aortic specimens of patients operated for type A AAS and paraffin embedded (Figure E1). The histologic sections were stained with hematoxylin–eosin and stainings for collagen (Azan–Mallory trichrome) and elastic fibers (Weigert–Van Gieson). The samples were evaluated de novo, blind to clinical data, applying the AECVP/SCVP documents diagnostic criteria.[7,8]

Degenerative aortic medial damage was assessed as overall medial degeneration (MD) resulting from the sum of 6 individual abnormalities: mucoid extracellular matrix accumulation (MEMA), both intralamellar (I-MEMA) and translamellar (T-MEMA); elastic fiber fragmentation/loss (EFFL); elastic fiber thinning out (EFT); laminar medial collapse (LMC); intralamellar collagen increase (ICI); and translamellar collagen increase (TCI). Overall MD was graded as mild, moderate, or severe, considering both severity and distribution of single abnormalities.

Atherosclerotic plaques were described according to the American Heart Association scheme.[9,10] Atherosclerosis was then graded as not significant, mild, moderate, or severe. Only moderate to severe lesions were considered causative of significant medial damage.

Clinical Definitions

Major aorta-related events were defined as rehospitalizations for the following aortic complications in some cases requiring reintervention: organ malperfusion, increasing aortic diameter, progressive false lumen dilation, aortic rupture, redissection, and moderate/severe aortic regurgitation.

Nonaorta-related events were defined as rehospitalizations for other CV causes (including acute coronary syndrome [ACS], congestive heart failure, arrhythmia, cerebrovascular accident, bleeding, and other CV causes) and rehospitalization for non-CV causes, mainly neoplasms and infections.

Sudden death was considered aorta related in cases of aortic rupture documented on postmortem or when preceded by signs or symptoms suggestive of cardiac tamponade or aneurysm rupture. Sudden death was considered cardiac, but not aorta-related, in the remaining cases.

High CV risk included patients with history of coronary artery disease or stroke, or aged more than 40 years with at least 1 CV risk factor (hypertension, hypercholesterolemia, diabetes, current smoking habit). ACS-like electrocardiogram abnormalities were defined as previously described.[11,12] Glomerular filtration rate was estimated using the modified Modification of Diet in Renal Disease equation.[13] Cardiac troponin was measured with a standard assay up to 2010 and with a high-sensitivity assay thereafter.

Statistical Analysis

Categoric variables are expressed as number and percentage; continuous variables are expressed as mean ± standard deviation or median and interquartile range. Categoric variables were compared with the chi-square test or Fisher exact test in cases of a small number of events. Shapiro–Wilk W test was performed to assess normality distribution of continuous variables, and then comparisons were performed with the Student *t* test or Mann–Whitney test accordingly. The Kaplan–Meier method

was used to analyze the occurrence of death (log-rank test for curves comparison), and Cox regression analysis was performed to identify predictors of mortality. Major aorta-related events, CV, and other nonaorta-related events were evaluated with cumulative incidence function with death as competing risk (Pepe and Mori test for curves comparison), and competing risk regressions were used to identify long-term predictors. Regarding Cox regression model, proportional-hazards assumption was evaluated on the basis of Schoenfeld residuals. For other events (aorta related, nonaorta related, CV nonaorta related), the proportional-subhazards assumption in competing risk regression was tested ensuring that coefficients were time invariant. All variables tested at the univariable analysis were included in the initial multivariable model, 1-by-1 tested, and eventually excluded according to *P* and chi-square values of the subsequent models. All statistical analyses were performed using Stata/SE 14.2 (StataCorp LP, College Station, Tex).

RESULTS

Study Population and Histopathologic Findings

A total of 257 patients with type A AAS were considered; 218 (85%) underwent surgical treatment during the index hospitalization. Surgical specimens for histology were available for 158 patients who constituted our study population (Figure E2). Baseline histopathologic characteristics are reported in Table 1. Patients with unavailable aortic specimens (60) had similar baseline characteristics to those included in the study (Table E1). All surgical specimens showed MD, and this was severe in 38 patients (24%). The most frequent degenerative abnormalities were EFFL (153 patients, 98.7%), EFT (145 patients, 92.8%), and I-MEMA (129 patients, 81.6%) (Figure 1). Coexisting atherosclerosis (any grade) was documented in 88 patients (55.7%) and was moderate or severe in 36 patients (22.8%). Patients with coexisting moderate-severe atherosclerosis constituted the mixed degenerative-atherosclerotic group, renamed ''mixed'' for simplicity. Therefore, the study population was divided accordingly into 2 groups: 122 patients (77.2%) with exclusively degenerative abnormalities and 36 patients (22.8%) with mixed degenerative-atherosclerotic findings (Figure 2).

Comparing the 2 groups, MEMA, especially intralamellar, was the single abnormality that most characterized the degenerative group; the most frequent alteration in the mixed group was TCI. LMC was found in 61 patients (50%) in the degenerative group and in 14 patients (38.9%) in the mixed group. Among the mixed group, this abnormality was mainly (13/14) present as a dense band of elastic fiber compaction bordering the lower margin of atherosclerotic plaque. In degenerative patients, LMC was usually found in the central areas of the medial layer above or on the same level as the dissection (Figure E3).

Clinical Findings

Baseline clinical characteristics of the study population are reported in Table 2. A total of 147 patients (93%) were diagnosed with acute aortic dissection, and the remaining 11 patients (7%) were diagnosed with intramural hematoma. The mean age of patients was

TABLE 1. Histopathologic findings in the overall population and in the subgroups defined by histology

Variable	Overall (n = 158)	Degenerative (n = 122, 77.2%)	Mixed (n = 36, 22.8%)	*P* value
Atherosclerosis, (%)	88 (55.7)	52 (42.6)	36 (100)	NA
Severe	8 (5.1)	0 (0)	8 (22.2)	NA
Moderate	28 (17.7)	0 (0)	28 (77.8)	NA
Mild	52 (32.9)	52 (42.6)	0 (0)	NA
Not significant	70 (44.3)	70 (57.4)	0 (0)	NA
Degenerative lesions, (%)	158 (100)	122 (100)	36 (100)	1
I-MEMA	129 (81.6)	105 (86)	24 (66.7)	.017
Moderate/severe I-MEMA	93 (58.9)	80 (65.6)	13 (36.1)	.002
T-MEMA	108 (68.4)	88 (72.1)	20 (55.6)	.094
Moderate/severe T-MEMA	108 (68.4)	88 (72.1)	20 (55.6)	.094
Laminar medial collapse	75 (47.5)	61 (50)	14 (38.9)	.325
Dense laminar medial collapse	59 (37.3)	46 (37.7)	13 (36.1)	.982
Elastic fiber thinning out	145 (92.8)	115 (94.3)	30 (83.3)	.08
Moderate/severe elastic fiber thinning out	108 (68.4)	87 (71.3)	21 (58.3)	.205
Elastic fiber fragmentation	153 (98.7)	117 (95.9)	36 (100)	.489
Moderate/severe elastic fiber fragmentation	117 (74)	91 (74.6)	26 (72.2)	.945
Intralamellar collagen increase	117 (74)	93 (76.2)	24 (66.7)	.35
Moderate/severe intralamellar collagen increase	23 (14.6)	17 (13.9)	6 (16.7)	.788
Translamellar collagen increase	30 (19)	12 (9.8)	18 (50)	<.001
Moderate/severe translamellar collagen increase	18 (11.4)	5 (4)	13 (36.1)	<.001
Overall severe degenerative	38 (24)	32 (26.2)	6 (16.7)	.274

NA, Not applicable; *I-MEMA*, intralamellar-mucoid extracellular matrix accumulation; *T-MEMA*, translamellar-mucoid extracellular matrix accumulation.

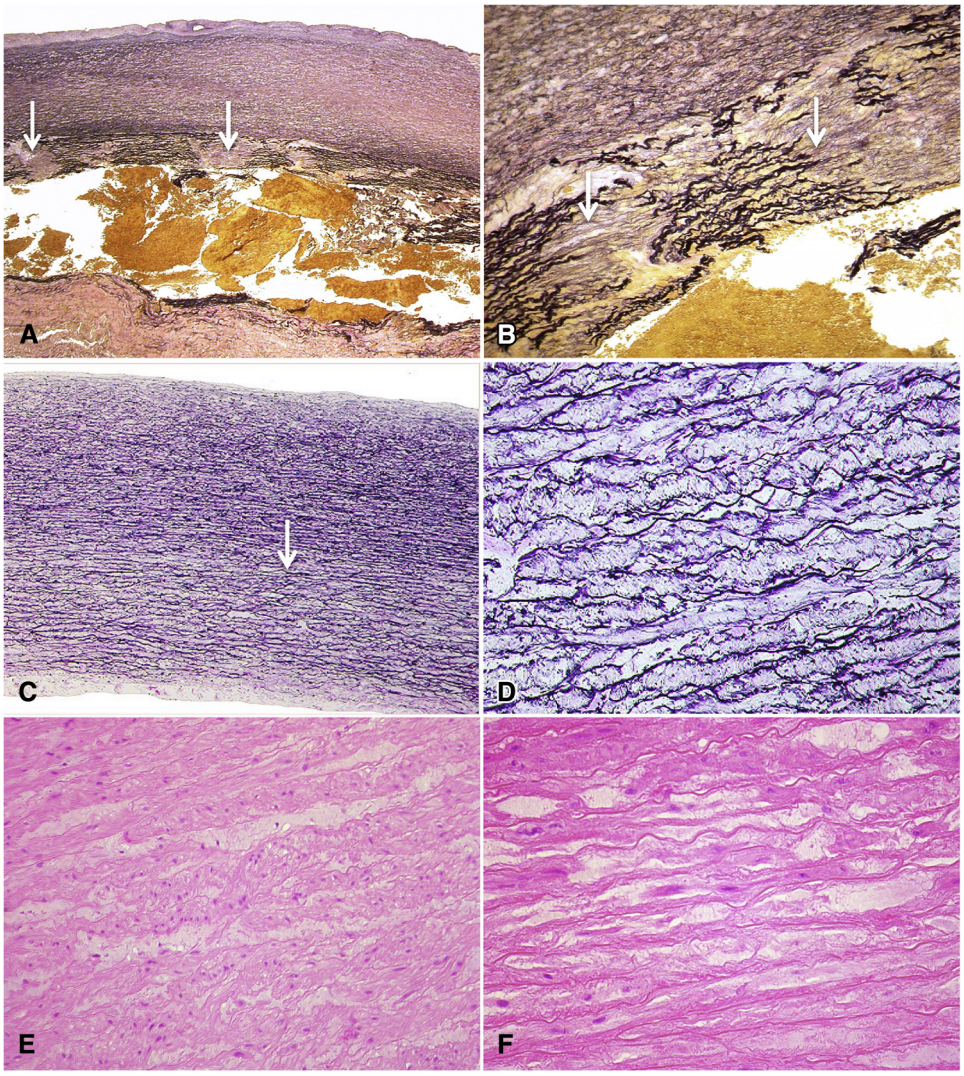

FIGURE 1. Microscopic images illustrating the most frequently found degenerative lesions. A and B, Aortic dissection in a patient with Marfan syndrome showing severe EFFL around the false lumen (*arrows*). A, Weigert Van Gieson, original magnification ×25; (B), detail of elastic fiber fragmentation (*arrows*). Weigert Van Gieson, original magnification ×100. C and D, Full-thickness aortic specimen with an area of elastic fiber rarefaction in the outer medial layer (C, *arrow*: Weigert Van Gieson, original magnification ×25); the detail shows thinning out of elastic fibers and enlarged spaces between them (D, Weigert Van Gieson, original magnification ×400). E and F, Examples of intralamellar-mucoid extracellular matrix accumulation. There is mild (E, ×100) to moderate (B, ×200) enlargement of intralamellar spaces containing bluish-pink mucoid material (hematoxylin–eosin stain).

63.9 years, and 68% were male. Among CV risk factors, hypertension was the most prevalent (114 patients, 72.2%). A history of coronary artery disease and stroke was present in 11 patients (7%) and 5 patients (3.2%), respectively. Marfan syndrome and bicuspid aortic valve coexisted in 2 patients (1.3%) and 6 patients (3.8%), respectively.

Clinico-Pathological Correlations

Patients in the mixed group were older (69.6 ± 8.7 years vs 62.2 ± 12.4 years, $P = .001$) and had a higher prevalence of hypercholesterolemia compared with those in the degenerative group (33.3% vs 13.9%, $P = .017$). In addition, the clinical presentation of patients in the mixed group was more often characterized by chest pain and ACS-like electrocardiogram abnormalities (38.9% vs 19.7%, $P = .032$) (Table 2).

The comparison between patients with dissection (147) and patients with intramural hematoma (10) did not show differences in the histopathologic diagnostic category. However, patients with dissection presented a higher percentage of T-MEMA (70.7% vs 36,4%, $P = .001$), whereas intramural hematoma was strongly associated with atherosclerotic lesions (90.9% vs 53.1%, $P = .023$) (Table E2).

Both patients with a diagnosis of Marfan syndrome were included in the degenerative group with severe MD in 1 case

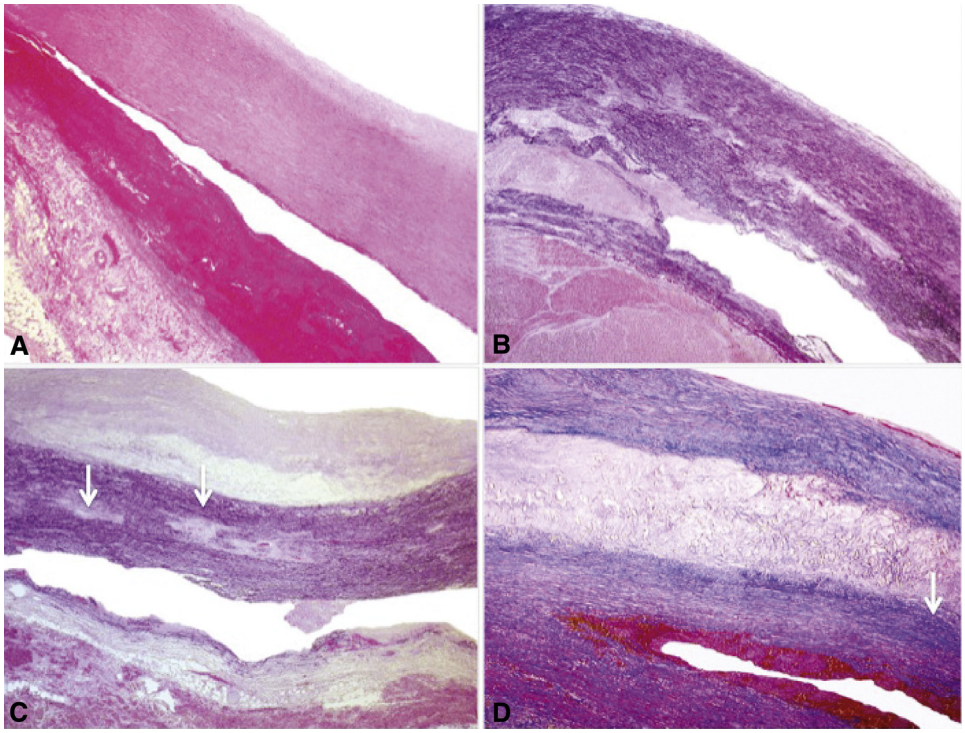

FIGURE 2. A and B, Aortic dissection samples from pure degenerative cases. A, A 45 year-old man with mild MD (hematoxylin–eosin, original magnification ×25). B, A 54-year-old man with bicuspid aortic valve and severe MD (B, Weigert Van Gieson stain, original magnification ×25). C and D, Aortic specimens from the mixed group. The dissection is above the atherosclerotic lesions, and the underlying media shows multifocal elastic fiber fragmentation (C, *arrows*) and translamellar (D, *arrow*) collagen increase (Azan Mallory trichrome, original magnification ×25).

and moderate MD in the other. No atherosclerosis was found in these patients.

Of the 6 patients with bicuspid aortic valve, 5 had purely degenerative abnormalities—3 had moderate degenerative abnormalities, 2 had mild and severe degenerative abnormalities, and 1 had mixed abnormalities (with moderate MD).

Patients with ascending aorta diameter 55 mm or greater at presentation had a more severe overall MD compared with patients with a diameter less than 55 mm (51.7% [15/29] vs 12.3% [7/57], $P < .001$), showing mostly moderate/severe I-MEMA, T-MEMA, and EFT (Table E3).

Patients aged more than 50 years were more frequently found to have atherosclerotic abnormalities (59.8% [82/137] vs 28.6% [6/21], $P = .014$), I-MEMA (83.2% [114/137] vs 71.4% [15/21], $P = .006$), and moderate/severe EFFL (81.7% [112/137] vs 23.8% [5/21], $P < .001$) (Table E4).

Figure 3 shows the prevalence of atherosclerosis according to age, gender, ascending aorta diameter, and AAS subtype according to the DeBakey classification.

Outcome and Prognostic Stratification

In-hospital mortality reached 19% (30 patients) in our population. A total of 45 patients died during follow-up, with an all-cause mortality at 1, 3, and 6 years of 23%, 26%, and 33%, respectively. The cause of death was aorta related in 22 patients (postoperative complications in 21 cases, 1 patient died after reintervention for severe aortic regurgitation during follow-up), CV nonaorta-related in 8 patients (1 for ischemic strokes, 3 for hemorrhagic strokes, 2 for endocarditis on prosthetic valve, 1 for sudden cardiac death, and 1 for cardiogenic shock secondary to ischemic dilated cardiopathy), and non–CV-related in 15 patients (cancer in 4, sepsis in 8, and other causes in 3).

Cumulative incidence of major aorta-related events at 1, 3, and 6 years follow-up was 9%, 16%, and 25%, respectively. Cumulative incidence of nonaorta-related events was 31%, 44%, and 64%, respectively. Cumulative incidence of CV nonaorta-related events was 10%, 17%, and 23%, respectively.

Figures 4 and 5 show the 6-year clinical outcome according to histopathologic characteristics. Patients with mixed degenerative atherosclerotic abnormalities more frequently had nonaorta-related events during follow-up compared with those with degenerative abnormalities alone (Pepe and Mori test, $P = .046$) (Figure 5). No differences were found between these 2 subgroups with respect to mortality (34 deaths among degenerative patients and 11 among mixed patients at the end of follow-up, log-rank

TABLE 2. Clinical findings in the overall population and in the subgroups according to histology

Variable	Overall (n = 158)	Degenerative (n = 122, 77.2%)	Mixed (n = 36, 22.8%)	*P* value
Aortic dissection, (%)	147 (93)	115 (94.3)	32 (88.9)	.459
Intramural hematoma, (%)	11 (7)	7 (5.7)	4 (11.1)	.273
Plaque rupture-ulceration, (%)	0 (0)	0 (0)	0 (0)	1
DeBakey type I, (%)	111 (70.3)	89 (73)	22 (61.1)	.247
Patients' characteristics, (%)				
Age (y), mean ± SD	63.9 ± 12	62.2 ± 12.4	69.6 ± 8.7	.001
Male gender	108 (68.4)	80 (65.6)	28 (77.8)	.238
Hypertension (history)	114 (72.2)	84 (68.9)	30 (83.3)	.136
Hypercholesterolemia	29 (18.4)	17 (13.9)	12 (33.3)	.017
Diabetes	6 (3.8)	6 (4.9)	0 (0)	.337
Current smoke	31 (19.6)	23 (18.9)	8 (22.2)	.639
Marfan syndrome	2 (1.3)	2 (1.6)	0 (0)	1
Bicuspid aortic valve	6 (3.8)	5 (4.1)	1 (2.8)	1
Aortic coarctation	0 (0)	0 (0)	0 (0)	1
Known thoracic-abdominal aortic aneurysm (surgically treated or not)	13 (8.2)	8 (6.6)	5 (13.9)	.174
Previous AAS	2 (1.3)	1 (0.8)	1 (2.8)	.404
Previous stroke	5 (3.2)	4 (3.3)	1 (2.8)	1
Coronary artery disease (history)	11 (7)	6 (4.9)	5 (13.9)	.127
Clinical features at presentation, (%)				
Systolic blood pressure (mm Hg), mean ± SD	134.5 ± 37.3	132.6 ± 37.3	141.1 ± 37.1	.231
Back pain	56 (35.4)	42 (34.4)	14 (38.9)	.769
Chest pain	117 (74.1)	88 (72.1)	29 (80.6)	.426
Migratory pain	16 (10.1)	10 (8.2)	6 (16.7)	.203
Abdominal pain	35 (22.2)	27 (22.1)	8 (22.2)	1
CVA at presentation	5 (3.2)	5 (4.1)	0 (0)	.589
Peripheral pulse deficit	36 (22.3)	25 (20.5)	11 (30.6)	.257
Shock within 12h of admission	28 (14.3)	24 (19.7)	4 (11.1)	.322
ACS-like ECG + chest pain	38 (24.1)	24 (19.7)	14 (38.9)	.032
ACS-like ECG	48 (30.4)	32 (26.2)	16 (44.4)	.06
Aortic diameters (mm) on imaging at presentation				
Valsalva sinuses, median (IQR)	44 (40-48) (47/158)	45 (40-47) (31/122)	43 (40-48) (16/36)	.955
Ascending aorta, median (IQR)	51 (46-56) (86/158)	50 (45-56) (62/122)	52 (47-56) (24/36)	.794
Aortic arch, median (IQR)	32 (31-39) (27/158)	33 (30-34) (18/122)	31 (31-41) (9/36)	.661
Descending aorta, median (IQR)	32 (27-38) (29/158)	33 (27-38) (21/122)	31 (28-39) (8/36)	.961
Laboratory findings				
GFR (mL/min/1.73 m^2), median (IQR)	67 (53-82) (141/158)	67 (54-85) (108/122)	60 (51-77) (33/36)	.371
Troponin positivity	33.3% (35/105)	38.8% (31/80)	16% (4/25)	.05
Disease complications, (%)				
Pleural effusion	25 (15.8)	20 (16.4)	5 (13.9)	.801
Pericardial effusion	64 (40.5)	49 (40.2)	15 (41.7)	.975
Periaortic effusion	13 (8.2)	8 (6.6)	5 (13.9)	.174
Moderate/severe aortic regurgitation	61 (38.6)	44 (36.1)	17 (47.2)	.311
Cardiac tamponade	19 (12)	15 (12.3)	4 (11.1)	1
Coronary ostia involvement	16 (10.1)	12 (9.8)	4 (11.1)	.761

SD, Standard deviation; *AAS*, acute aortic syndrome; *CVA*, cerebrovascular accident; *ACS*, acute coronary syndrome; *ECG*, electrocardiogram; *IQR*, interquartile range; *GFR*, glomerular filtration rate.

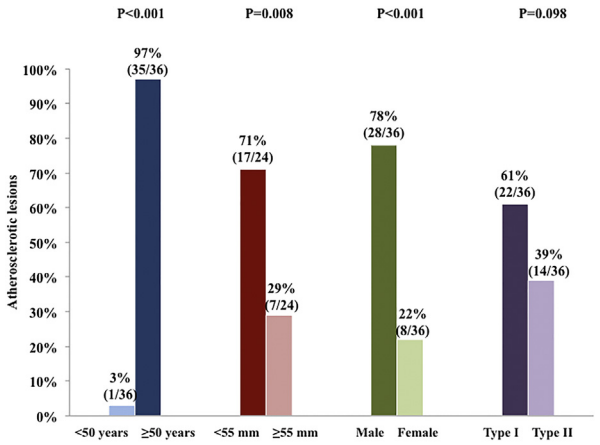

FIGURE 3. Prevalence of atherosclerotic lesions according to age, ascending aorta diameter, gender, and DeBakey subtype.

test, $P = .574$), major aorta-related events (19 events among degenerative patients and 10 events among mixed patients at the end of follow-up, Pepe and Mori test, $P = .407$), and CV nonaorta-related events (19 events among degenerative patients and 10 events among mixed patients at the end of follow-up, Pepe and Mori test, $P = .202$).

Tables 3 and 4 report the major clinical and histologic incremental risk factors for 6-year mortality and for 6-year nonaorta-related events. Age (hazard ratio [HR], 1.03 for each 1-year increase; 95% confidence interval [CI, 0.99-1.06]; $P = .069$, borderline significance) and glomerular filtration rate less than 60 mL/min/1.73 m^2 at presentation (HR, 2.33; 95% CI, 1.24-4.4; $P = .009$) were independent predictors of mortality (Table 3). Nonaorta-related events were analyzed in detail, and no differences were found according to the patients' CV risk profile (Figure E4). Hypertension (sub-HR, 1.79; 95% CI, 1.01-3.21; $P = .047$) and the coexistence of atherosclerotic lesions together with degenerative abnormalities (sub-HR, 1.65; 95% CI, 0.96-2.84; $P = .068$, borderline significance) were found to be independent risk predictors for nonaorta-related events (Table 4).

DISCUSSION

This is the first study to provide a detailed description of the histopathologic findings of aortic specimens and their clinico-pathological correlation from a large unselected cohort of patients with type A AAS, applying the classification and diagnostic criteria from the recent AECVP/SCVP consensus statements.[7,8] The main findings of the study are as follows: (1) Although degenerative lesions of the medial layer were present in all specimens, substantial atherosclerosis coexisted in approximately one quarter. (2) Patients with mixed degenerative-atherosclerotic abnormalities had a coherent clinical risk profile, with a more frequent presentation mimicking ACS and a long-term follow-up characterized by nonaorta-related events, including coronary and cerebrovascular events. (3) Histopathologic characterization could help the long-term prognostic stratification of patients after surgical treatment.

The histopathologic substrate of our cohort was heterogeneous because of the variable combination, quantitatively and qualitatively, of degenerative and atherosclerotic lesions. All patients showed MD abnormalities: Almost all cases had elastic fiber abnormalities, including both thinning out and fragmentation; MEMA was present as I-MEMA in more than 80% of patients and as T-MEMA (an expression of a more severe mucopolysaccharide accumulation) in 68.4%; collagen increase was present with a heterogeneous distribution: intralamellar in 74% and translamellar (ie, fibrosis) in 19% of cases. It is noteworthy that more than 50% of patients had some degree of atherosclerosis associated with degenerative lesions. Approximately one quarter of patients had moderate/severe atherosclerosis, which the AECVP/SCVP statement[7] considers a cause of significant aortic wall damage with consequent weakness.

The comparison between exclusively degenerative or mixed subgroups reveals differences in the distribution of mucoid accumulation and fibrosis. I-MEMA was the most typical lesion in purely degenerative patients, whereas translamellar collagen was distinctly increased in the mixed group. Of note, one third of major atherosclerotic plaques was accompanied by a thick band of medial laminar collapse, which, together with TCI, can probably be considered a final response to the atherosclerotic plaque penetrating more deeply into the media. Elastic fiber alterations were present in the purely degenerative and mixed groups in equal measure, probably due to the heterogeneity of various causative conditions, including the aging process. Our only 2 patients with Marfan syndrome and 5 of 6 patients with bicuspid aortic valve had moderate/severe degenerative lesions, in line with the findings of previous studies.[14,15]

Unlike previously published similar series,[2-5] our study included exclusively patients with AAS. The first 2 published series evaluating clinico-pathological features of the ascending aorta described 63[2] and 339 patients[3] who underwent surgery for aneurysm or dissection of the ascending aorta. Compared with our population, the patients in these series were younger, with a higher prevalence of connective tissue disorders and a lower prevalence of severe atherosclerosis. MD was the most common histopathologic finding, and an inverse relationship between the severity of MD and age was found.[3] A more recent study describing 513 patients[4] found that connective tissue disorders were most frequently associated with MD, followed by aging, and no association between bicuspid aortic valve and MD was found. Severe atherosclerosis was described in an exiguous number of patients. Again, it should be noted that the population in this series was younger compared with

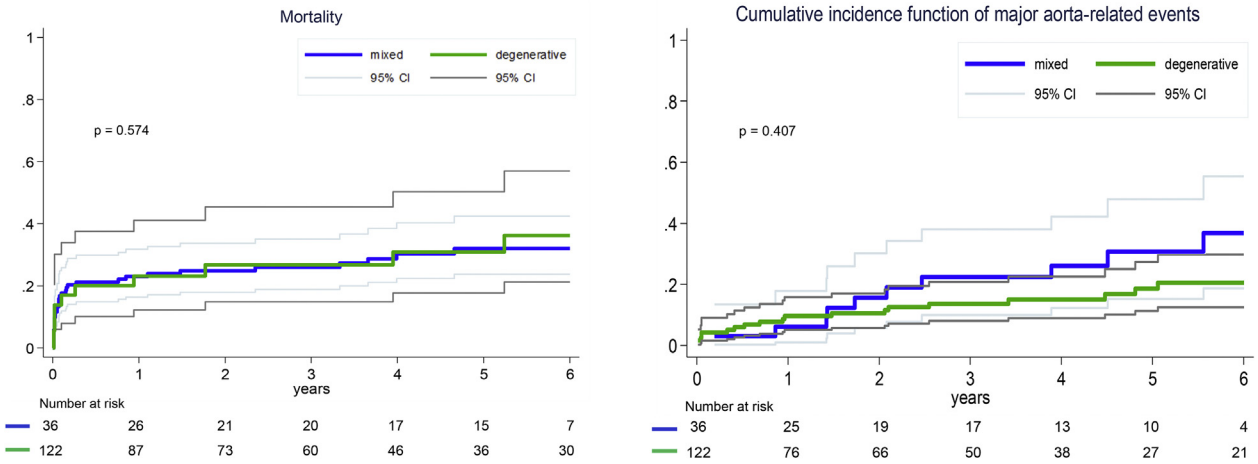

FIGURE 4. Mortality (*left*) and major aorta-related events (*right*) of patients with type A AAS with degenerative (122 patients, *green line*) versus mixed (36 patients, *blue line*) histologic abnormalities. *CI*, Confidence interval.

ours and that both aneurysms and dissections were considered. A further study on 338 surgical specimens, including a few patients with Marfan, found that MD was a common, age-related, and nonspecific histologic pattern in aortic aneurysms and dissections.[5] Atherosclerosis was present in only 10% of patients and was more frequently associated with aneurysms than dissections.

In our study, atherosclerosis was more frequent than previously described, and this is probably due to the older age of our patients. On the other hand, clinical and epidemiologic characteristics of our study population were similar to those of the largest "real world registry" International Registry of Acute Aortic Dissection.[16] In particular, mean age (63.9 years), prevalence of male gender (~68.4%), hypertension (72.2%), and bicuspid aortic valve (3.8%) were similar, whereas Marfan syndrome was less frequent (1.3% vs 4.7%) probably because of the prophylactic surgery strategy adopted in our network.

As expected, patients with atherosclerotic lesions had a higher CV risk profile. In particular, they were older, male, and hypercholesterolemic. Of note, atherosclerotic lesions were more frequent in patients with a diameter of the ascending aorta less than 55 mm and in type I AAS compared with type II (borderline significance) (Figure 3).

The long-term outcome of patients with associated atherosclerosis is characterized by high probability of nonaorta-related events, including coronary and cerebrovascular events and infectious complications, even if no association with overall mortality was shown. As demonstrated by other studies, renal function and age (borderline significance in our work) were found to be risk factors for mortality.[17] Notably, along with

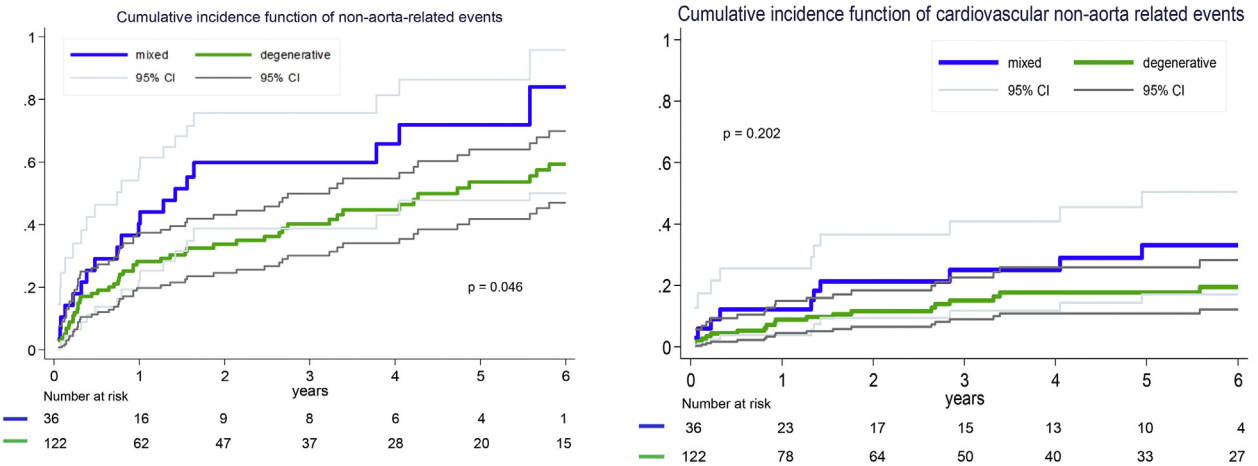

FIGURE 5. Nonaorta-related events (*left*) and CV non–aorta-related events (*right*) of patients with type A AAS with degenerative (122 patients, *green line*) versus mixed (36 patients, *blue line*) histologic abnormalities. *CI*, Confidence interval.

TABLE 3. Risk factors for 6-year mortality of surgically treated patients with type A acute aortic syndrome

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (for each 1-y increase)	1.03 (1.01-1.06)	.019	1.03 (0.99-1.06)	.069
Male gender	0.95 (0.51-1.78)	.897		
Hypertension (history)	1.16 (0.59-2.31)	.653		
Hypercholesterolemia	1.22 (0.58-2.54)	.587		
Diabetes	2.03 (0.62-6.59)	.237		
Current smoke	0.67 (0.28-1.58)	.365		
Marfan-BAV	0.33 (0.04-2.46)	.285		
DeBakey type I	1.9 (0.47-1.71)	.75		
GFR <60 mL/min/1.73 m^2 at presentation	2.66 (1.43-4.95)	.002	2.33 (1.24-4.40)	.009
Degenerative-atherosclerotic lesions	1.07 (0.54-2.11)	.839		
Atherosclerosis (for each 1-point increase according to AHA classification)	1.12 (0.98-1.29)	.083		

Harrell's C = 0.65; goodness of fit test (score test) = 0.553; AIC = 382; BIC = 388. *HR*, Hazard ratio; *CI*, confidence interval; *BAV*, bicuspid aortic valve; *GFR*, glomerular filtration rate; *AHA*, American Heart Association.

hypertension, the presence of atherosclerotic abnormalities was a probable risk factor for nonaorta-related events. Therefore, the knowledge of the histopathologic substrate underlying AAS may provide additional information to the level of risk derived from patients' clinical characteristics alone.

Study Limitations

Because of the monocentric nature of our work, the size of the study population and relative events are not comparable with international registries. Twenty-seven percent of aortic specimens among surgically treated patients did not reach the histology laboratory because of logistic reasons. Marfan syndrome was less frequent in our study than in other series probably because of the prophylactic surgery strategy adopted in our network. Although the description of the histopathologic spectrum, according to the current AECVP/SCVP classification, in patients with type A AAS provides robust and new information, the impact of clinico-pathological correlations is inevitably limited by the relatively small study population and the few events during follow-up. Last, because of the retrospective nature of this study and the emergency clinical setting, availability of laboratory data and imaging details—both at presentation and during follow-up—is limited.

CONCLUSIONS

The new AECVP/SCVP classification allows a comprehensive description of aortic wall abnormalities, provides a standardized characterization of MD, and represents a

TABLE 4. Risk factors for 6-year nonaorta-related events of surgically treated patients with type A acute aortic syndrome

Variable	Univariable analysis		Multivariable analysis	
	SHR (95% CI)	*P* value	SHR (95% CI)	*P* value
Age (for each 1-y increase)	1.01 (0.98-1.03)	.426		
Male gender	0.87 (0.54-1.44)	.611		
Hypertension (history)	1.94 (1.09-3.46)	.023	1.79 (1.01-3.21)	.047
Hypercholesterolemia	0.97 (0.49-1.94)	.954		
Diabetes	0.32 (0.03-2.82)	.309		
Current smoker	0.86 (0.45-1.64)	.651		
Marfan-BAV	0.69 (0.25-1.88)	.472		
DeBakey type I	0.84 (0.51-1.42)	.534		
GFR <60 mL/min/1.73 m^2 at presentation	0.67 (0.39-1.15)	.151		
Degenerative-atherosclerotic lesions	1.83 (1.09-3.07)	.022	1.65 (0.96-2.84)	.068
Atherosclerosis (for each 1-point increase according to AHA classification)	1.06 (0.95-1.18)	.245		

AIC = 585.9; BIC = 592.1. *SHR*, Sub-hazard ratio; *CI*, confidence interval; *BAV*, bicuspid aortic valve; *GFR*, glomerular filtration rate; *AHA*, American Heart Association.

useful tool for nosography, clinico-pathological correlations, and prognostic information in patients with type A AAS. Full knowledge of the histopathologic details of patients who underwent surgery for AAS can lead to better planning of long-term follow-up, especially regarding preventive strategies for nonaorta-related events.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: acute aortic syndromes, clinico-pathological correlations, long-term follow-up

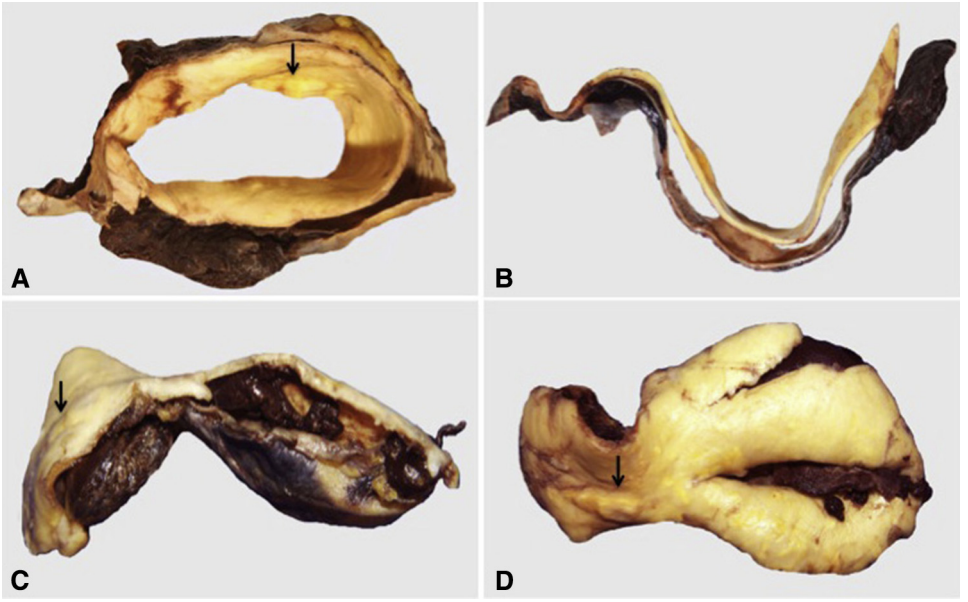

FIGURE E1. Specimens of type A aortic dissection. A, Dissection involves 75% of circumference and the false lumen contains thrombosis; atherosclerotic plaques are visible in the intima (*arrow*). B, Aortic sample where dissection is more extensive (90% of circumference) and the aortic wall is extremely thinned. C and D, Extensive dissection and irregular intimal surface due to some whitish-yellow plaques (*arrow*).

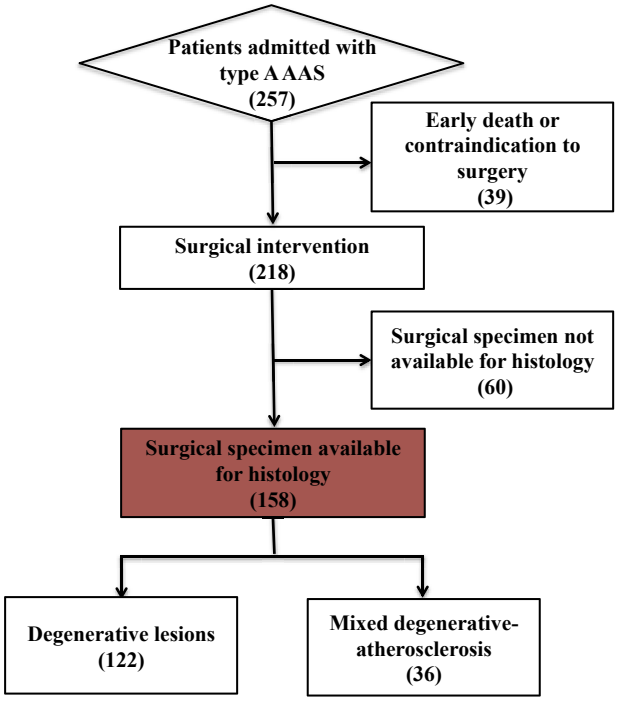

FIGURE E2. Study flowchart. *AAS*, Acute aortic syndrome.

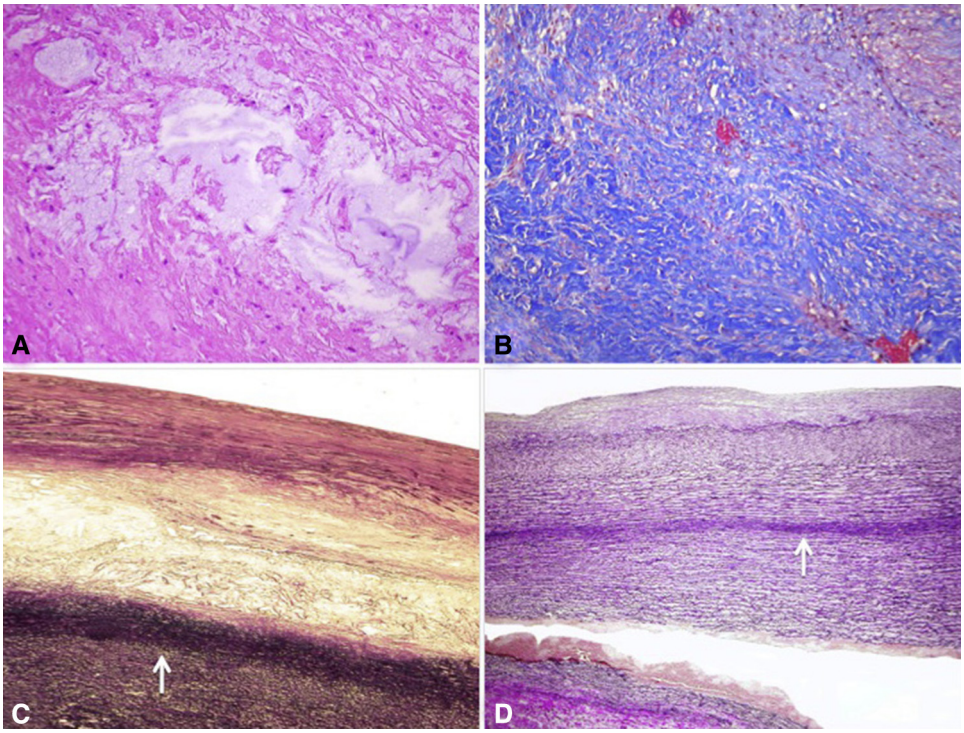

FIGURE E3. A, Severe focus of translamellar mucoid extracellular matrix accumulation in a degenerative group patient (hematoxylin–eosin stain, original magnification ×200). B, Medial fibrosis (ie, translamellar collagen increase), a distinctive lesion of the mixed group (Azan Mallory trichrome, original magnification ×200). C and D, laminar medial collapse. In the mixed group, this lesion was frequently found as a dense band of elastic fiber compaction bordering the lower margin of atherosclerotic plaques (C, *arrow*; Weigert Van Gieson, original magnification ×100); in degenerative patients, the lesion was frequently seen in the central areas of the medial layer above or on the same plane of the dissection (*arrow*) (Weigert Van Gieson, original magnification ×100).

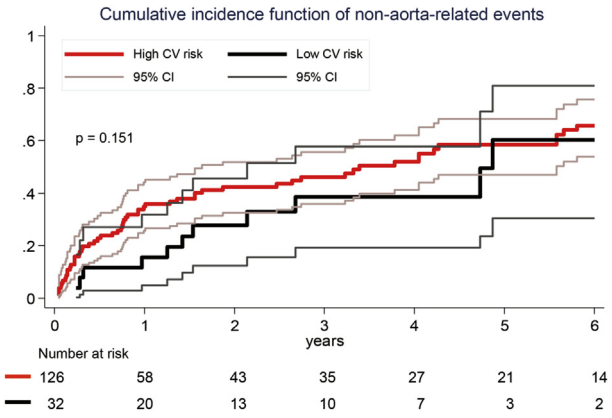

FIGURE E4. The 6-year nonaorta-related events of type A AAS according to patients' CV risk profile. High CV risk means patients with history of coronary artery disease or stroke, or aged 40 years or older with at least 1 CV risk factor (hypertension, hypercholesterolemia, diabetes, current smoker). *CI*, Confidence interval.

TABLE E1. Surgically treated patients with type A acute aortic syndrome with available versus unavailable surgical specimen for histology

Variable	Overall (n = 218)	Specimen available (n = 158, 72.5%)	Specimen unavailable (n = 60, 27.5%)	*P* value
Aortic dissection, (%)	198 (90.8)	147 (93)	51 (85)	.116
Intramural hematoma, (%)	18 (8.3)	11 (7)	7 (11.7)	.276
Plaque rupture-ulceration, (%)	2 (0.9)	0 (0)	2 (3.3)	.074
DeBakey type I, (%)	147 (67.4)	111 (70.3)	36 (60)	.2
Patients' characteristics, (%)				
Age (y), mean ± SD	64.4 ± 12.1	63.9 ± 12	65.5 ± 12.4	.385
Men	148 (67.9)	108 (68.4)	40 (66.7)	.939
Hypertension (history)	157 (72)	114 (72.2)	43 (71.7)	.922
Hypercholesterolemia	43 (19.7)	29 (18.4)	14 (23.3)	.526
Diabetes	9 (4.1)	6 (3.8)	3 (5)	.709
Current smoke	37 (17)	31 (19.6)	6 (10)	.107
Marfan syndrome	3 (1.4)	2 (1.3)	1 (1.7)	1
Bicuspid aortic valve	7 (3.2)	6 (3.8)	1 (1.7)	.676
Aortic coarctation	0 (0)	0 (0)	0 (0)	1
Known thoracic-abdominal aortic aneurysm (surgically treated or not)	19 (8.7)	13 (8.2)	6 (10)	.788
Previous AAS	3 (1.4)	2 (1.3)	1 (1.7)	1
Previous stroke	9 (4.1)	5 (3.2)	4 (6.7)	.263
Coronary artery disease (history)	15 (6.9)	11 (7)	4 (6.7)	1
Clinical features at presentation, (%)				
Systolic blood pressure (mm Hg), mean ± SD	134.7 ± 38.4	134.5 ± 37.3	135.1 ± 41.9	.932
Back pain	81 (37.2)	56 (35.4)	25 (41.7)	.489
Chest pain	161 (73.9)	117 (74.1)	44 (73.3)	.948
Migratory pain	24 (11)	16 (10.1)	8 (13.3)	.477
Abdominal pain	48 (22)	35 (22.2)	13 (21.7)	.916
CVA at presentation	9 (4.1)	5 (3.2)	4 (6.7)	.263
Peripheral pulse deficit	48 (22)	36 (22.3)	12 (20)	.975
Shock within 12 of admission	39 (17.9)	28 (14.3)	11 (18.3)	.926
ACS-like ECG + chest pain	50 (22.9)	38 (24.1)	12 (20)	.649
ACS-like electrocardiogram	62 (28.4)	48 (30.4)	14 (23.3)	.389
Aortic diameters (mm) in first imaging examination				
Valsalva sinuses, median (IQR)	42 (40-47) (64/218)	44 (40-48) (47/158)	40 (36-43) (17/60)	.019
Ascending aorta, median (IQR)	50 (46-55) (123/218)	51 (46-56) (86/158)	50 (46-54) (37/60)	.454
Aortic arch, median (IQR)	34 (31-40) (42/218)	32 (31-39) (27/158)	37 (34-41) (15/60)	.253
Descending aorta, median (IQR)	35 (29-41) (49/218)	32 (27-38) (29/158)	40 (31-50) (20/60)	.059
Laboratory findings				
GFR (mL/min/1.73 m^2), median (IQR)	67 (54-81) (195/218)	66 (53-82) (141/158)	70 (57) (54/60)	.65
Troponin positivity	32% (41/128)	33.3% (35/105)	26.1% (6/23)	.625
Disease complications, (%)				
Pleural effusion	37 (17)	25 (15.8)	12 (20)	.595
Pericardial effusion	89 (40.8)	64 (40.5)	25 (41.7)	.999
Periaortic effusion	26 (11.9)	13 (8.2)	13 (21.7)	.012
Moderate/severe aortic regurgitation	86 (39.4)	61 (38.6)	25 (41.7)	.797
Cardiac tamponade	28 (12.8)	19 (12)	9 (15)	.651
Coronary ostia involvement	21 (9.6)	16 (10.1)	5 (8.3)	.801

AAS, Acute aortic syndrome; *ACS*, acute coronary syndrome; *CVA*, cerebrovascular accident; *ECG*, electrocardiogram; *GFR*, glomerular filtration rate; *IQR*, interquartile range; *SD*, standard deviation.

TABLE E2. Histopathologic characteristics according to type of acute aortic syndrome

Variable	Overall (n = 158)	Dissection 93% (n = 147)	Intramural hematoma 7% (n = 11)	*P* value
Atherosclerosis, (%)	88 (55.7)	78 (53.1)	10 (90.9)	.023
Severe	8 (5.1)	6 (4.1)	2 (18.2)	.098
Moderate	28 (17.7)	26 (17.7)	2 (18.2)	1
Mild	52 (32.9)	46 (31.3)	6 (54.5)	.179
Not significant	70 (44.3)	69 (46.9)	1 (9.1)	.023
Degenerative lesions, (%)	158 (100)	147 (100)	11 (100)	NA
I-MEMA	129 (81.6)	121 (82.3)	8 (72.7)	.425
Moderate/severe I-MEMA	93 (58.9)	90 (61.2)	3 (27.3)	.051
T-MEMA	108 (68.4)	104 (70.7)	4 (36.4)	.001
Moderate/severe T-MEMA	108 (68.4)	104 (70.7)	4 (36.4)	.001
Laminar collapse	75 (47.5)	69 (46.9)	6 (54.5)	.757
Dense laminar collapse	59 (37.3)	54 (36.7)	5 (45.4)	.747
Elastic fiber thinning out	145 (92.8)	134 (91.2)	11 (100)	.601
Moderate/severe elastic fiber thinning out	108 (68.4)	102 (69.4)	6 (54.5)	.326
Elastic fiber fragmentation	153 (98.7)	143 (97.3)	10 (90.9)	.306
Moderate/severe elastic fiber fragmentation	117 (74)	110 (74.8)	7 (63.6)	.477
Intralamellar collagen increase	117 (74)	107 (72.8)	10 (90.9)	.291
Moderate/severe intralamellar collagen increase	23 (14.6)	19 (12.9)	4 (36.4)	.056
Translamellar collagen increase	30 (19)	27 (18.4)	3 (27.3)	.438
Moderate/severe translamellar collagen increase	18 (11.4)	16 (10.9)	2 (18.2)	.363
Degenerative group	122 (77.2)	115 (78.2)	7 (63.6)	.274
Mixed group	36 (22.8)	32 (21.8)	4 (36.4)	.274
Oveall severe degenerative	38 (24)	36 (24.5)	2 (18.2)	1

I-MEMA, Intralamellar-mucoid extracellular matrix accumulation; *NA*, not applicable; *T-MEMA*, translamellar-mucoid extracellular matrix accumulation.

TABLE E3. Histopathologic findings according to aortic diameter at presentation

Variable	Overall (n = 86)	Ascending aorta ≥55 mm (n = 29, 33.7%)	Ascending aorta <55 mm (n = 57, 66.3%)	*P* value
Atherosclerosis, (%)	45 (52.3)	15 (51.7)	30 (52.5)	.882
Severe	6 (7)	2 (6.9)	4 (7)	1
Moderate	18 (20.9)	5 (17.2)	13 (22.8)	.779
Mild	21 (24.4)	8 (27.6)	13 (22.8)	.791
Not significant	41 (47.7)	14 (48.3)	27 (47.4)	.882
Degenerative lesions, (%)	86 (100)	29 (100)	57 (100)	1
I-MEMA	62 (72.1)	24 (82.8)	38 (66.7)	.187
Moderate/severe I-MEMA	40 (46.5)	19 (65.5)	21 (36.8)	.022
T-MEMA	51 (59.3)	23 (79.3)	28 (49.1)	.014
Moderate/severe T-MEMA	51 (59.3)	23 (79.3)	28 (49.1)	.014
Laminar medial collapse	29 (33.7)	12 (41.4)	17 (29.8)	.406
Dense laminar medial collapse	25 (29.1)	11 (37.9)	14 (24.6)	.298
Elastic fiber thinning out	77 (89.5)	26 (89.7)	51 (89.5)	.729
Moderate/severe elastic fiber thinning out	26 (30.2)	22 (75.9)	4 (7)	<.001
Elastic fiber fragmentation	82 (95.3)	29 (100)	53 (93)	.358
Moderate/severe elastic fiber fragmentation	57 (66.3)	23 (79.3)	34 (59.6)	.114
Intralamellar collagen increase	62 (72.1)	23 (79.3)	39 (68.4)	.418
Moderate-severe intralamellar collagen increase	13 (15.1)	5 (17.2)	8 (14)	.754
Translamellar collagen increase	16 (18.6)	5 (17.2)	11 (19.3)	1
Moderate-severe translamellar collagen increase	10 (11.6)	3 (10.3)	7 (12.3)	1
Degenerative group	62 (72.1)	22 (75.9)	40 (70.2)	.763
Mixed group	24 (27.9)	7 (24.1)	17 (29.8)	.622
Overall severe degenerative	21 (24.4)	15 (51.7)	7 (12.3)	<.001

I-MEMA, Intralamellar-mucoid extracellular matrix accumulation; *T-MEMA*, translamellar-mucoid extracellular matrix accumulation.

TABLE E4. Histopathologic findings in patients aged more than 50 years versus patients aged 50 years or less

Variable	Overall (n = 158)	Age >50 y (n = 137, 86.7%)	Age ≤50 y (n = 21, 13.3%)	*P* value
Atherosclerosis, (%)				
Severe	8 (5.1)	8 (5.8)	0 (0)	.598
Moderate	28 (17.7)	27 (19.7)	1 (4.8)	.127
Mild	52 (32.9)	47 (34.3)	5 (23.8)	.457
Not significant	70 (44.3)	55 (40.1)	15 (71.4)	.014
Degenerative lesions, (%)				
I-MEMA	129 (81.6)	114 (83.2)	15 (71.4)	.006
Moderate/severe I-MEMA	93 (58.9)	81 (59.1)	12 (57.1)	1
T-MEMA	108 (68.4)	91 (66.4)	17 (80.9)	.184
Moderate/severe T-MEMA	108 (68.4)	91 (66.4)	17 (80.9)	.216
Laminar medial collapse	75 (47.5)	68 (49.6)	7 (33.3)	.240
Dense laminar medial collapse	59 (37.3)	53 (38.7)	6 (28.6)	.471
Elastic fiber thinning out	145 (92.8)	129 (94.2)	16 (76.2)	.787
Moderate/severe elastic fiber thinning out	108 (68.4)	96 (70.1)	12 (57.1)	.313
Elastic fiber fragmentation	153 (98.7)	132 (96.3)	21 (100)	.374
Moderate/severe elastic fiber fragmentation	117 (74)	112 (81.7)	5 (23.8)	<.001
Intralamellar collagen increase	117 (74)	104 (75.9)	13 (61.9)	.187
Moderate-severe intralamellar collagen increase	23 (14.6)	19 (13.9)	4 (19)	.513
Translamellar collagen increase	30 (19)	28 (20.4)	2 (9.5)	.371
Moderate-severe translamellar collagen increase	18 (11.4)	17 (12.4)	1 (4.8)	.471
Degenerative group	122 (77.2)	102 (74.5)	20 (95.2)	.047
Mixed group	36 (22.8)	35 (25.5)	1 (4.8)	.047
Overall severe degenerative	38 (24)	31 (22.6)	7 (33.3)	.284

I-MEMA, Intralamellar-mucoid extracellular matrix accumulation; *T-MEMA*, translamellar-mucoid extracellular matrix accumulation.