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

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Glossary of abbreviations:

AAS: acute aortic syndrome

ACS: acute coronary syndrome

AECVP: Association for European Cardiovascular Pathology

AHA: American Heart Association

BAV: bicuspid aortic valve

CAD: coronary artery disease

CI: confidence interval

CV: cardiovascular

EFFL: elastic fibre fragmentation/loss

EFT: elastic fibre thinning out

GFR: glomerular filtration rate

HR: hazard ratio

ICI: intralamellar collagen increase

I-MEMA: intralamellar mucoid extracellular matrix accumulation

IRAD: International Registry of Acute Aortic Dissection

LMC: laminar medial collapse

MD: medial degeneration

MDRD: modification of diet in renal disease

MFS: Marfan syndrome

SCVP: Society for Cardiovascular Pathology

SD: standard deviation

SHR: sub-hazard ratio

TCI: translamellar collagen increase

T-MEMA: translamellar mucoid extracellular matrix accumulation

ABSTRACT

Objectives: 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 and/or inflammatory alterations of 158 patients according to the histopathologic consensus documents. Moreover, we correlated these histologic patterns with the patients' clinical data as well as long-term follow-up for mortality, major aorta-related events, and non-aorta-related events (including cardiovascular ones).

Results: We identified two histopathologic patterns: 122 (77%) patients with degenerative alterations and 36 (23%) with mixed degenerative-atherosclerotic lesions. Patients with mixed alterations were older (mean 69.6±8.7 vs. 62.2±12.4, p=0.001) and more hypercholesterolemic (33.3% vs. 13.9%, p=0.017). The degenerative subgroup showed more Intralamellar-Mucoid Extracellular Matrix Accumulation (86% vs. 66.7%, p=0.017), and a lower prevalence of Translamellar Collagen Increase (9.8% vs. 50%, p<0.001). Patients with mixed degenerative-atherosclerotic abnormalities more frequently had long-term non-aorta-related events compared to those with degenerative abnormalities alone (p=0.046); no differences were found between the groups with respect to ~~long-term~~ mortality, major aorta-related events and cardiovascular non-aorta-related events.

Conclusion: Although degenerative lesions of the medial layer were present in all specimens, substantial atherosclerosis coexisted in nearly a quarter of cases. Patients with mixed degenerative-atherosclerotic abnormalities had a coherent clinical risk profile, a clinical presentation frequently mimicking ACS and a higher incidence of non-aorta-related events during follow-up. So, histopathologic characterization may improve the long-term prognostic stratification of patients following surgical treatment.

Keywords: acute aortic syndromes, clinico-pathological correlations, long-term follow-up.

INTRODUCTION

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 Ehrdheim in 1930 as "aortic idiopathic (cystic) medial necrosis" **(6)**. 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 two consensus statements on the histopathology of inflammatory **(7)** and non-inflammatory 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.

METHODS

Clinical setting

Our Hospital is the AAS referral centre for Bologna and the surrounding metropolitan area (catchment area 1000000 inhabitants).

Our registry includes all adult (>18 years) consecutive patients with a final diagnosis of spontaneous AAS referred to our centre between January 1st 2000 and December 31st 2013. Patients with symptom onset >14 days or with traumatic AAS were not included. Median follow-up for alive patients was 4 years (interquartile range 2.2-6 years). The study conforms to the principles

outlined in the Declaration of Helsinki, was approved by the local ethics committee and patients provided written informed consent.

Pathology

An average of six samples were obtained from ascending aortic specimens of patients operated for type A AAS and paraffin embedded **(supplementary figure 1)**. The histologic sections were stained with Hematoxylin-Eosin and stainings for collagen (Azan-Mallory trichrome) and elastic fibres (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 fibre fragmentation/loss (EFFL); elastic fibre 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 (AHA) 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 re-hospitalizations for the following aortic complications in some cases requiring re-intervention: organ malperfusion, increasing aortic diameter, progressive false lumen dilation, aortic rupture, re-dissection, moderate/severe aortic regurgitation.

Non-aorta-related events were defined as re-hospitalizations for other CV causes (including acute coronary syndrome (ACS), congestive heart failure, arrhythmia, cerebrovascular accident, bleeding, and other CV causes) and re-hospitalization for non-CV causes, mainly neoplasms and infections.

Sudden death was considered aorta-related in cases of aortic rupture documented on post-mortem 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 and/or stroke and/or aged >40 with at least one CV risk factor (hypertension, hypercholesterolemia, diabetes, current smoking habit).

ACS-like ECG abnormalities were defined as previously described **(11-12)**.

Glomerular Filtration Rate (GFR) was estimated using the modified MDRD equation **(13)**.

Cardiac Troponin was measured with a standard assay up to 2010, and with a high-sensitivity assay thereafter.

Statistical analysis

Categorical variables are expressed as number and percentage; continuous variables as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were compared with Chi-square test or Fisher exact test in cases of small number of events. Shapiro-Wilk W test was performed to assess normality distribution of continuous variables; then comparisons were performed with Student's t-test or Mann-Whitney test accordingly. The Kaplan Meier method was used to analyse the occurrence of death (Log-rank test for curves comparison); Cox regression analysis was performed to identify predictors of mortality. Major aorta-related events, CV and other non-aorta-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, non-

aorta-related, CV non-aorta-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, one-by-one tested and eventually excluded according to p and chi squared values of the subsequent models. All statistical analyses were performed using Stata/SE 14.2 (StataCorp LP, College Station, Texas, USA). A p value <0.05 was considered significant.

RESULTS

Study population and histopathologic findings

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 **(supplementary figure 2).** Baseline histopathologic characteristics are reported in **Table 1**. Patients with unavailable aortic specimens (60) had similar baseline characteristics to those included in the study **(supplementary table 1)**. All surgical specimens showed MD and this was severe in 38 patients (24%). The most frequent degenerative abnormalities were EFFL (153 patients, 98.7%) and 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 (22.8%). Patients with coexisting moderate-severe atherosclerosis constituted the mixed degenerative-atherosclerotic group, renamed "mixed" for simplicity. The study population was therefore divided accordingly into two groups: 122 patients (77.2%) with exclusively degenerative abnormalities and 36 patients (22.8%) with mixed degenerative-atherosclerotic findings **(figure 2)**.

Comparing the two 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 (38.9%) in the mixed group. Among the mixed group, this abnormality was mainly (13/14) present as a dense band

of elastic fibre compaction bordering the lower margin of atherosclerotic plaque. In degenerative patients on the other hand, LMC was usually found in the central areas of the medial layer above or on the same level as the dissection **(supplementary figure 3)**.

Clinical findings

Baseline clinical characteristics of the study population are reported in **table 2**. 147 patients (93%) were diagnosed with acute aortic dissection, and the remaining 11 patients (7%) with intramural haematoma. Mean age was 63.9 and 68% were males. Amongst CV risk factors, hypertension was the most prevalent (114 patients, 72.2%), history of coronary artery disease (CAD) and stroke were present in 11 (7%) and in 5 patients (3.2%) respectively. Marfan syndrome (MFS) and bicuspid aortic valve coexisted in 2 (1.3%) and in 6 patients (3.8%) respectively.

Clinico-pathological correlations

Mixed group patients were older (69.6 ± 8.7 vs. 62.2 ± 12.4, p=0.001) and had a higher prevalence of hypercholesterolemia compared to those in the degenerative group (33.3% vs. 13.9%, p=0.017). Additionally, clinical presentation of patients in the mixed group was more often characterised by chest pain and ACS-like ECG abnormalities (38.9% vs. 19.7%, p=0.032) **(table 2)**.

The comparison between patients with dissection (147) vs intramural haematoma (IMH, 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=0.001) while IMH was strongly associated with atherosclerotic lesions (90.9% vs 53.1%, p=0.023) **(supplementary table 2).**

Both patients with a diagnosis of MFS were included in the degenerative group with severe MD in one case 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 - moderate in three cases, while it was graded mild and severe in the other two patients - while mixed abnormalities (with moderate MD) were found in the last patient.

Patients with ascending aorta diameter ≥55 mm at presentation had a more severe overall MD compared to patients with diameter <55 mm [51.7% (15/29) vs. 12.3% (7/57), p<0.001], showing mostly moderate/severe I-MEMA, T-MEMA and EFT **(supplementary table 3)**.

Patients over the age of 50 were more frequently found to have atherosclerotic abnormalities [59.8% (82/137) vs. 28.6% (6/21), p=0.014], I-MEMA [83,2% (114/137) vs. 71.4% (15/21), p=0.006], and moderate/severe EFFL [81.7% (112/137) vs. 23.8% (5/21), p<0.001] **(supplementary table 4)**.

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. 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 (post-operative complications in 21 cases, one patient died after reintervention for severe aortic regurgitation during follow-up), CV non-aorta-related in 8 patients (1 for ischemic strokes, 3 for haemorrhagic 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, that of non aorta-related events was 31%, 44% and 64% respectively, and that of CV non-aorta-related events was 10%, 17% and 23% respectively.

Figure 4 and **figure 5** show the 6-year clinical outcome according to histopathologic characteristics. Patients with mixed degenerative-atherosclerotic abnormalities more frequently had non-aorta-related events during follow-up compared to those with degenerative abnormalities alone (Pepe and Mori test, p=0.046, **figure 5**). No differences were found between these two subgroups with respect to mortality (34 deaths among degenerative patients and 11 among mixed patients at

the end of follow-up, log-rank test, p=0.574), 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=0.407), and CV non-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=0.202).

Table 3A and **table 3B** report the major clinical and histologic incremental risk factors for 6-year-mortality and for 6-year-non-aorta-related events. Age [HR 1.03 for each 1-year increase; 95% CI 0.99-1.06; P=0.069, borderline significance] and GFR < 60 ml/min/1.73m^2 at presentation [HR 2.33; 95% CI 1.24-4.4; P=0.009] were independent predictors of mortality (**table 3A).** Non-aorta-related events were analysed in detail**,** and no differences were found according to the patients' CV risk profile **(supplementary figure 4)**. Hypertension [SHR 1.79; 95% CI 1.01-3.21; P=0.047] and the coexistence of atherosclerotic lesions together with degenerative abnormalities [SHR 1.65; 95% CI 0.96-2.84; P=0.068, borderline significance] were found to be independent risk predictors for non-aorta-related events **(table 3B)**.

DISCUSSION

This is the first study that provides a detailed description of the histopathologic findings of aortic specimens - as well as 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: 1. Although degenerative lesions of the medial layer were present in all specimens, substantial atherosclerosis coexisted in nearly a 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 non-aorta-related events, including coronary and cerebrovascular events; 3. Histopathologic characterization could help the long-term prognostic stratification of patients following surgical treatment.

The histopathologic substrate of our cohort was heterogeneous do to the variable combination – quantitatively and qualitatily - of degenerative and atherosclerotic lesions. All patients showed MD abnormalities: almost all cases had elastic fibre abnormalities, including both thinning out and fragmentation; MEMA was present as I-MEMA in over 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 (i.e. fibrosis) in 19% of cases. It is noteworthy that more than 50% of patients had some degree of atherosclerosis associated with degenerative lesions. Almost a quarter 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 of fibrosis. I-MEMA was the most typical lesion in purely degenerative patients, while translamellar collagen was distinctly increased in the mixed group. Interestingly, 1/3 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 fibre 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 five out of six 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 two 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 to 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 medial degeneration 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 to ours and that both aneurysms and dissections were considered. A further study on 338 surgical specimens including a few Marfan patients, found that MD was a common, age-related and non-specific histological pattern in aortic aneurysms and dissections **(5).** Atherosclerosis was present only in 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 epidemiological characteristics of our study population were similar to those of the largest "real world registry" IRAD (International Registry of Acute Aortic Dissection) **(16).** In particular, mean age (63.9 years), prevalence of male gender (about 68.4%), hypertension (72.2%) and bicuspid aortic valve (3.8%) were quite similar whereas Marfan syndrome was less frequent (1.3% vs. 4.7%) probably due to 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. Interestingly, atherosclerotic lesions were more frequent in patients with a diameter of the ascending aorta <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 non-aorta related events including coronary and cerebrovascular events and infectious complications even if no association with overall mortality was shown**.** As already 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 hypertension, the presence of atherosclerotic abnormalities was a probable risk factor for non-aorta-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

Due 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 due to logistic reasons. Marfan syndrome was less frequent in our study than in other series probably due to the prophylactic surgery strategy adopted in our network.

Whereas 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. Lastly, due to 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.

Clinical implications

The new AECVP/SCVP classification allows a comprehensive description of aortic wall abnormalities, provides a standardised characterization of MD, and represents a 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 non-aorta-related events.

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FIGURE LEGENDS

Figure 1 Microscopic images illustrating the most frequently found degenerative lesions. A-B: Aortic dissection in a Marfan patient showing severe elastic fibre fragmentation/loss around the false lumen (arrows) (A, Weigert Van Gieson, original magnification x25); detail of elastic fibre fragmentation (arrows) (B, Weigert Van Gieson, original magnification x100). C-D: Full thickness aortic specimen with an area of elastic fibre rarefaction in the outer medial layer (C, arrow: Weigert Van Gieson, original magnification x25); the detail shows thinning out of elastic fibres and enlarged spaces between them (D: Weigert Van Gieson, original magnification x400). E-F: Examples of intralamellar-mucoid extracellular matrix accumulation: there is mild (E, x100) to moderate (B, x200) enlargement of intralamellar spaces containing bluish-pink mucoid material (Haematoxylin-Eosin stain).

Figure 2 A-B: Aortic dissection samples from pure degenerative patients. A: 45 year-old male with mild medial degeneration (Haematoxylin-Eosin, original magnification x25); B: 25 year-old male with bicuspid aortic valve and severe medial degeneration (B, Weigert Van Gieson stain, original magnification x25). C-D: Aortic specimens from the mixed group. The dissection is above the atherosclerotic lesions and the underlying media shows multifocal elastic fibre fragmentation (C arrows) and translamellar (D, arrow) collagen increase (Azan Mallory trichrome, original magnification x25).

Figure 3 Prevalence of atherosclerotic lesions according to age, ascending aorta diameter, gender, and De Bakey subtype.

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

Figure 5 Non-aorta-related events (left) and cardiovascular non-aorta-related events (right) of type A AAS patients with degenerative (122 patients, green line) versus mixed (36 patients, blue line) histological abnormalities.

TABLES

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%)	0.017
Moderate/severe I-MEMA	93 (58.9%)	80 (65.6%)	13 (36.1%)	0.002
T-MEMA	108 (68.4%)	88 (72.1%)	20 (55.6%)	0.094
Moderate/severe T-MEMA	108 (68.4%)	88 (72.1%)	20 (55.6%)	0.094
Laminar medial collapse	75 (47.5%)	61 (50%)	14 (38.9%)	0.325
Dense laminar medial collapse	59 (37.3%)	46 (37.7%)	13 (36.1%)	0.982
Elastic fibre thinning out	145 (92.8%)	115 (94.3%)	30 (83.3%)	0.08
Moderate/severe elastic fibre thinning out	108 (68.4%)	87 (71.3%)	21 (58.3%)	0.205
Elastic fibre fragmentation	153 (98.7%)	117 (95.9%)	36 (100%)	0.489
Moderate/severe elastic fibre fragmentation	117 (74%)	91 (74.6%)	26 (72.2%)	0.945
Intralamellar collagen increase	117 (74%)	93 (76.2%)	24 (66.7%)	0.35
Moderate/severe intralamellar	23 (14.6%)	17 (13.9%)	6 (16.7%)	0.788

collagen increase				
Translamellar collagen increase	30 (19%)	12 (9.8%)	18 (50%)	< 0.001
Moderate/severe translamellar collagen increase	18 (11.4%)	5 (4%)	13 (36.1%)	< 0.001
Overall severe degenerative	38 (24%)	32 (26.2%)	6 (16.7%)	0.274

AAS: Acute Aortic Syndrome; I-MEMA: Intralamellar-Mucoid Extracellular Matrix Accumulation; NA: Not Applicable; T-MEMA: Translamellar- Mucoid Extracellular Matrix Accumulation.

466 **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%)	0.459
Intramural haematoma	11 (7%)	7 (5.7%)	4 (11.1%)	0.273
Plaque rupture-ulceration	0 (0%)	0 (0%)	0 (0%)	1
De Bakey type I	111 (70.3%)	89 (73%)	22 (61.1%)	0.247
Patients' characteristics				
Age (years), mean ± SD	63.9 ± 12	62.2 ± 12.4	69.6 ± 8.7	0.001
Male gender	108 (68.4%)	80 (65.6%)	28 (77.8%)	0.238
Hypertension (history)	114 (72.2%)	84 (68.9%)	30 (83.3%)	0.136
Hypercholesterolemia	29 (18.4%)	17 (13.9%)	12 (33.3%)	0.017
Diabetes	6 (3.8%)	6 (4.9%)	0 (0%)	0.337
Current smoke	31 (19.6%)	23 (18.9%)	8 (22.2%)	0.639
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%)	0.174
Previous AAS	2 (1.3%)	1 (0.8%)	1 (2.8%)	0.404
Previous stroke	5 (3.2%)	4 (3.3%)	1 (2.8%)	1
Coronary artery disease (history)	11 (7%)	6 (4.9%)	5 (13.9%)	0.127
Clinical features at presentation				
Systolic blood pressure (mmHg), mean ± SD	134.5 ± 37.3	132.6 ± 37.3	141.1 ± 37.1	0.231

Back pain	56 (35.4%)	42 (34.4%)	14 (38.9%)	0.769
Chest pain	117 (74.1%)	88 (72.1%)	29 (80.6%)	0.426
Migratory pain	16 (10.1%)	10 (8.2%)	6 (16.7%)	0.203
Abdominal pain	35 (22.2%)	27 (22.1%)	8 (22.2%)	1
CVA at presentation	5 (3.2%)	5 (4.1%)	0 (0%)	0.589
Peripheral pulse deficit	36 (22.3%)	25 (20.5%)	11 (30.6%)	0.257
Shock within 12h of admission	28 (14.3%)	24 (19.7%)	4 (11.1%)	0.322
ACS-like ECG+chest pain	38 (24.1%)	24 (19.7%)	14 (38.9%)	0.032
ACS-like ECG	48 (30.4%)	32 (26.2%)	16 (44.4%)	0.06
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)	0.955
Ascending aorta, median (IQR)	51 (46-56) (86/158)	50 (45-56) (62/122)	52 (47-56) (24/36)	0.794
Aortic arch, median (IQR)	32 (31-39) (27/158)	33 (30-34) (18/122)	31 (31-41) (9/36)	0.661
Descending aorta, median (IQR)	32 (27-38) (29/158)	33 (27-38) (21/122)	31 (28-39) (8/36)	0.961
Laboratory findings				
GFR (ml/min/1.73m^2), median (IQR)	67(53-82) (141/158)	67 (54-85) (108/122)	60 (51-77) (33/36)	0.371
Troponin positivity	33.3% (35/105)	38.8% (31/80)	16% (4/25)	0.05
Disease complications				
Pleural effusion	25 (15.8%)	20 (16.4%)	5 (13.9%)	0.801

Pericardial effusion	64 (40.5%)	49 (40.2%)	15 (41.7%)	0.975
Periaortic effusion	13 (8.2%)	8 (6.6%)	5 (13.9%)	0.174
Moderate/severe aortic regurgitation	61 (38.6%)	44 (36.1%)	17 (47.2%)	0.311
Cardiac tamponade	19 (12%)	15 (12.3%)	4 (11.1%)	1
Coronary ostia involvement	16 (10.1%)	12 (9.8%)	4 (11.1%)	0.761

AAS: Acute Aortic Syndrome; ACS: Acute Coronary Syndrome; CT: Computed Tomography; CVA: Cerebrovascular Accident; GFR: Glomerular Filtration Rate; SD: Standard Deviation; IQR: interquartile range.

Table 3A Risk factors for 6-year mortality of type A surgically treated AAS patients.

VARIABLE	**UNIVARIABLE ANALYSIS**		**MULTIVARIABLE ANALYSIS**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age (for each 1-year increase)	1.03 (1.01-1.06)	0.019	1.03 (0.99-1.06)	0.069
Male gender	0.95 (0.51-1.78)	0.897		
Hypertension (history)	1.16 (0.59-2.31)	0.653		
Hypercholesterolemia	1.22 (0.58-2.54)	0.587		
Diabetes	2.03 (0.62-6.59)	0.237		
Current smoke	0.67 (0.28-1.58)	0.365		
Marfan-BAV	0.33 (0.04-2.46)	0.285		
De Bakey type I	1.9 (0.47-1.71)	0.75		
GFR < 60 ml/min/1.73m^2 at presentation	2.66 (1.43-4.95)	0.002	2.33 (1.24-4.40)	0.009
Degenerative-atherosclerotic lesions	1.07 (0.54-2.11)	0.839		
Atherosclerosis (for each 1-point increase according to AHA classification)	1.12 (0.98-1.29)	0.083		

Harrell's C=0.65; Goodness of fit test (score test)=0.553; AIC=382; BIC=388

AAS: Acute Aortic Syndrome; AHA: American Heart Association; BAV: Bicuspid Aortic Valve; CI: Confidence Interval; GFR: Glomerular Filtration Rate; HR: Hazard Ratio.

Table 3B Risk factors for 6-year non-aorta-related events of type A surgically treated AAS patients.

VARIABLE	**UNIVARIABLE ANALYSIS**		**MULTIVARIABLE ANALYSIS**	
	SHR (95% CI)	**P value**	**SHR (95% CI)**	**P value**
Age (for each 1-year increase)	1.01 (0.98-1.03)	0.426		
Male gender	0.87 (0.54-1.44)	0.611		
Hypertension (history)	1.94 (1.09-3.46)	0.023	1.79 (1.01-3.21)	0.047
Hypercholesterolemia	0.97 (0.49-1.94)	0.954		
Diabetes	0.32 (0.03-2.82)	0.309		
Current smoke	0.86 (0.45-1.64)	0.651		
Marfan-BAV	0.69 (0.25-1.88)	0.472		
De Bakey type I	0.84 (0.51-1.42)	0.534		
GFR < 60 ml/min/1.73m^2 at presentation	0.67 (0.39-1.15)	0.151		
Degenerative-atherosclerotic lesions	1.83 (1.09-3.07)	0.022	1.65 (0.96-2.84)	0.068
Atherosclerosis (for each 1-point increase according to AHA classification)	1.06 (0.95-1.18)	0.245		

AIC=585.9; BIC 592.1

AAS: Acute Aortic Syndrome; AHA: American Heart Association; BAV: Bicuspid Aortic Valve; CI: Confidence Interval; GFR: Glomerular Filtration Rate; SHR: Sub-hazard Ratio.

503 **SUPPLEMENTARY FILES**

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505 **Supplementary table 1** Type A AAS surgically treated patients with available versus unavailable
506 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%)	0.116
Intramural haematoma	18 (8.3%)	11 (7%)	7 (11.7%)	0.276
Plaque rupture-ulceration	2 (0.9%)	0 (0%)	2 (3.3%)	0.074
De Bakey type I	147 (67.4%)	111 (70.3%)	36 (60%)	0.2
Patients' characteristics				
Age (years), mean ± SD	64.4 ± 12.1	63.9 ± 12	65.5 ± 12.4	0.385
Men	148 (67.9%)	108 (68.4%)	40 (66.7%)	0.939
Hypertension (history)	157 (72%)	114 (72.2%)	43 (71.7%)	0.922
Hypercholesterolemia	43 (19.7%)	29 (18.4%)	14 (23.3%)	0.526
Diabetes	9 (4.1%)	6 (3.8%)	3 (5%)	0.709
Current smoke	37 (17%)	31 (19.6%)	6 (10%)	0.107
Marfan syndrome	3 (1.4%)	2 (1.3%)	1 (1.7%)	1
Bicuspid aortic valve	7 (3.2%)	6 (3.8%)	1 (1.7%)	0.676
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%)	0.788
Previous AAS	3 (1.4%)	2 (1.3%)	1 (1.7%)	1
Previous stroke	9 (4.1%)	5 (3.2%)	4 (6.7%)	0.263

Coronary artery disease (history)	15 (6.9%)	11 (7%)	4 (6.7%)	01
Clinical features at presentation				
Systolic blood pressure (mmHg), mean ± SD	134.7 ± 38.4	134.5 ± 37.3	135.1 ± 41.9	0.932
Back pain	81 (37.2%)	56 (35.4%)	25 (41.7%)	0.489
Chest pain	161 (73.9%)	117 (74.1%)	44 (73.3%)	0.948
Migratory pain	24 (11%)	16 (10.1%)	8 (13.3%)	0.477
Abdominal pain	48 (22%)	35 (22.2%)	13 (21.7%)	0.916
CVA at presentation	9 (4.1%)	5 (3.2%)	4 (6.7%)	0.263
Peripheral pulse deficit	48 (22%)	36 (22.3%)	12 (20%)	0.975
Shock within 12 of admission	39 (17.9%)	28 (14.3%)	11 (18.3%)	0.926
ACS-like ECG+chest pain	50 (22.9%)	38 (24.1%)	12 (20%)	0.649
ACS-like electrocardiogram	62 (28.4%)	48 (30.4%)	14 (23.3%)	0.389
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)	0.019
Ascending aorta, median (IQR)	50 (46-55) (123/218)	51 (46-56) (86/158)	50 (46-54) (37/60)	0.454
Aortic arch, median (IQR)	34 (31-40) (42/218)	32 (31-39) (27/158)	37 (34-41) (15/60)	0.253
Descending aorta, median (IQR)	35 (29-41) (49/218)	32 (27-38) (29/158)	40 (31-50) (20/60)	0.059
Laboratory findings				
GFR (ml/min/1.73m^2), median (IQR)	67 (54-81) (195/218)	66 (53-82) (141/158)	70 (57) (54/60)	0.65

Troponin positivity	32% (41/128)	33.3% (35/105)	26.1% (6/23)	0.625
Disease complications				
Pleural effusion	37 (17%)	25 (15.8%)	12 (20%)	0.595
Pericardial effusion	89 (40.8%)	64 (40.5%)	25 (41.7%)	0.999
Periaortic effusion	26 (11.9%)	13 (8.2%)	13 (21.7%)	0.012
Moderate/severe aortic regurgitation	86 (39.4%)	61 (38.6%)	25 (41.7%)	0.797
Cardiac tamponade	28 (12.8%)	19 (12%)	9 (15%)	0.651
Coronary ostia involvement	21 (9.6%)	16 (10.1%)	5 (8.3%)	0.801

AAS: Acute Aortic Syndrome; ACS: Acute Coronary Syndrome; CT: Computed Tomography; CVA: Cerebrovascular Accident; GFR: Glomerular Filtration Rate; SD: Standard Deviation; IQR: interquartile range.

524 **Supplementary table 2** Histopathologic characteristics according to type of AAS.

VARIABLE	OVERALL (n=158)	DISSECTION 93% (n=147)	INTRAMURAL HAEMATOMA 7% (n=11)	P value
Atherosclerosis	**88 (55.7%)**	**78 (53.1%)**	**10 (90.9%)**	0.023
Severe	8 (5.1%)	6 (4.1%)	2 (18.2%)	0.098
Moderate	28 (17.7%)	26 (17.7%)	2 (18.2%)	1
Mild	52 (32.9%)	46 (31.3%)	6 (54.5%)	0.179
Not significant	70 (44.3%)	69 (46.9%)	1 (9.1%)	0.023
Degenerative lesions	**158 (100%)**	**147 (100%)**	**11 (100%)**	NA
I-MEMA	129 (81.6%)	121 (82.3%)	8 (72.7%)	0.425
Moderate/severe I-MEMA	93 (58.9%)	90 (61.2%)	3 (27.3%)	0.051
T-MEMA	108 (68.4%)	104 (70.7%)	4 (36.4%)	0.001
Moderate/severe T-MEMA	108 (68.4%)	104 (70.7%)	4 (36.4%)	0.001
Laminar collapse	75 (47.5%)	69 (46.9%)	6 (54.5%)	0.757
Dense laminar collapse	59 (37.3%)	54 (36.7%)	5 (45.4%)	0.747
Elastic fibre thinning out	145 (92.8%)	134 (91.2%)	11 (100%)	0.601
Moderate/severe elastic fibre thinning out	108 (68.4%)	102 (69.4%)	6 (54.5%)	0.326
Elastic fibre fragmentation	153 (98.7%)	143 (97.3%)	10 (90.9%)	0.306
Moderate/severe elastic fibre fragmentation	117 (74%)	110 (74.8%)	7 (63.6%)	0.477
Intralamellar collagen increase	117 (74%)	107 (72.8%)	10 (90.9%)	0.291
Moderate/severe intralamellar collagen increase	23 (14.6%)	19 (12.9%)	4 (36.4%)	0.056
Translamellar collagen increase	30 (19%)	27 (18.4%)	3 (27.3%)	0.438
Moderate/severe translamellar collagen increase	18 (11.4%)	16 (10.9%)	2 (18.2%)	0.363
Degenerative group	122 (77.2%)	115 (78.2%)	7 (63.6%)	0.274
Mixed group	36 (22.8%)	32 (21.8%)	4 (36.4%)	0.274
Overall severe degenerative	38 (24%)	36 (24.5%)	2 (18.2%)	1

525 AAS: Acute Aortic Syndrome; NA: Not Applicable; I-MEMA: Intralamellar-Mucoid Extracellular
526 Matrix Accumulation; T-MEMA: Translamellar- Mucoid Extracellular Matrix Accumulation.
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551 **Supplementary table 3** Histopathologic findings according to aortic diameter at presentation.

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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%)**	**0.882**
Severe	6 (7%)	2 (6.9%)	4 (7%)	1
Moderate	18 (20.9%)	5 (17.2%)	13 (22.8%)	0.779
Mild	21 (24.4%)	8 (27.6%)	13 (22.8%)	0.791
Not significant	41 (47.7%)	14 (48.3%)	27 (47.4%)	0.882
Degenerative lesions	**86 (100%)**	**29 (100%)**	**57 (100%)**	1
I-MEMA	62 (72.1%)	24 (82.8%)	38 (66.7%)	0.187
Moderate/severe I-MEMA	40 (46.5%)	19 (65.5%)	21 (36.8%)	0.022
T-MEMA	51 (59.3%)	23 (79.3%)	28 (49.1%)	0.014
Moderate/severe T-MEMA	51 (59.3%)	23 (79.3%)	28 (49.1%)	0.014
Laminar medial collapse	29 (33.7%)	12 (41.4%)	17 (29.8%)	0.406
Dense laminar medial collapse	25 (29.1%)	11 (37.9%)	14 (24.6%)	0.298
Elastic fibre thinning out	77 (89.5%)	26 (89.7%)	51 (89.5%)	0.729
Moderate/severe elastic fibre thinning out	26 (30.2%)	22 (75.9%)	4 (7%)	<0.001
Elastic fibre fragmentation	82 (95.3%)	29 (100%)	53 (93%)	0.358
Moderate/severe elastic fibre fragmentation	57 (66.3%)	23 (79.3%)	34 (59.6%)	0.114
Intralamellar collagen increase	62 (72.1%)	23 (79.3%)	39 (68.4%)	0.418
Moderate-severe intralamellar	13 (15.1%)	5 (17.2%)	8 (14%)	0.754

collagen increase				
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%)	0.763
Mixed group	24 (27.9%)	7 (24.1%)	17 (29.8%)	0.622
Overall severe degenerative	21 (24.4%)	15 (51.7%)	7 (12.3%)	<0.001

553 AAS: Acute Aortic Syndrome; I-MEMA: Intralamellar-Mucoid Extracellular Matrix Accumulation;

554 NA: Not Applicable; T-MEMA: Translamellar- Mucoid Extracellular Matrix Accumulation.

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571 **Supplementary table 4** Histopathologic findings in patients aged > 50 years versus patients aged ≤

572 50 years.

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VARIABLE	OVERALL (n=158)	AGE > 50 YEARS (n=137, 86.7%)	AGE ≤ 50 YEARS (n=21, 13.3%)	P value
Atherosclerosis				
Severe	8 (5.1%)	8 (5.8%)	0 (0%)	0.598
Moderate	28 (17.7%)	27 (19.7%)	1 (4.8%)	0.127
Mild	52 (32.9%)	47 (34.3%)	5 (23.8%)	0.457
Not significant	70 (44.3%)	55 (40.1%)	15 (71.4%)	0.014
- Degenerative lesions				
I-MEMA	129 (81.6%)	114 (83.2%)	15 (71.4%)	0.006
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%)	0.184
Moderate/severe T-MEMA	108 (68.4%)	91 (66.4%)	17 (80.9%)	0.216
Laminar medial collapse	75 (47.5%)	68 (49.6%)	7 (33.3%)	0.240
Dense laminar medial collapse	59 (37.3%)	53 (38.7%)	6 (28.6%)	0.471
Elastic fibre thinning out	145 (92.8%)	129 (94.2%)	16 (76.2%)	0.787
Moderate/severe elastic fibre thinning out	108 (68.4%)	96 (70.1%)	12 (57.1%)	0.313
Elastic fibre fragmentation	153 (98.7%)	132 (96.3%)	21 (100%)	0.374
Moderate/severe elastic fibre fragmentation	117 (74%)	112 (81.7%)	5 (23.8%)	< 0.001
Intralamellar collagen increase	117 (74%)	104 (75.9%)	13 (61.9%)	0.187
Moderate-severe intralamellar	23 (14.6%)	19 (13.9%)	4 (19%)	0.513

collagen increase				
Translamellar collagen increase	30 (19%)	28 (20.4%)	2 (9.5%)	0.371
Moderate-severe translamellar collagen increase	18 (11.4%)	17 (12.4%)	1 (4.8%)	0.471
Degenerative group	122 (77.2%)	102 (74.5%)	20 (95.2%)	0.047
Mixed group	36 (22.8%)	35 (25.5%)	1 (4.8%)	0.047
Overall severe degenerative	38 (24%)	31 (22.6%)	7 (33.3%)	0.284

574 AAS: Acute Aortic Syndrome; I-MEMA: Intralamellar-Mucoid Extracellular Matrix Accumulation;

575 NA: Not Applicable; T-MEMA: Translamellar- Mucoid Extracellular Matrix Accumulation.

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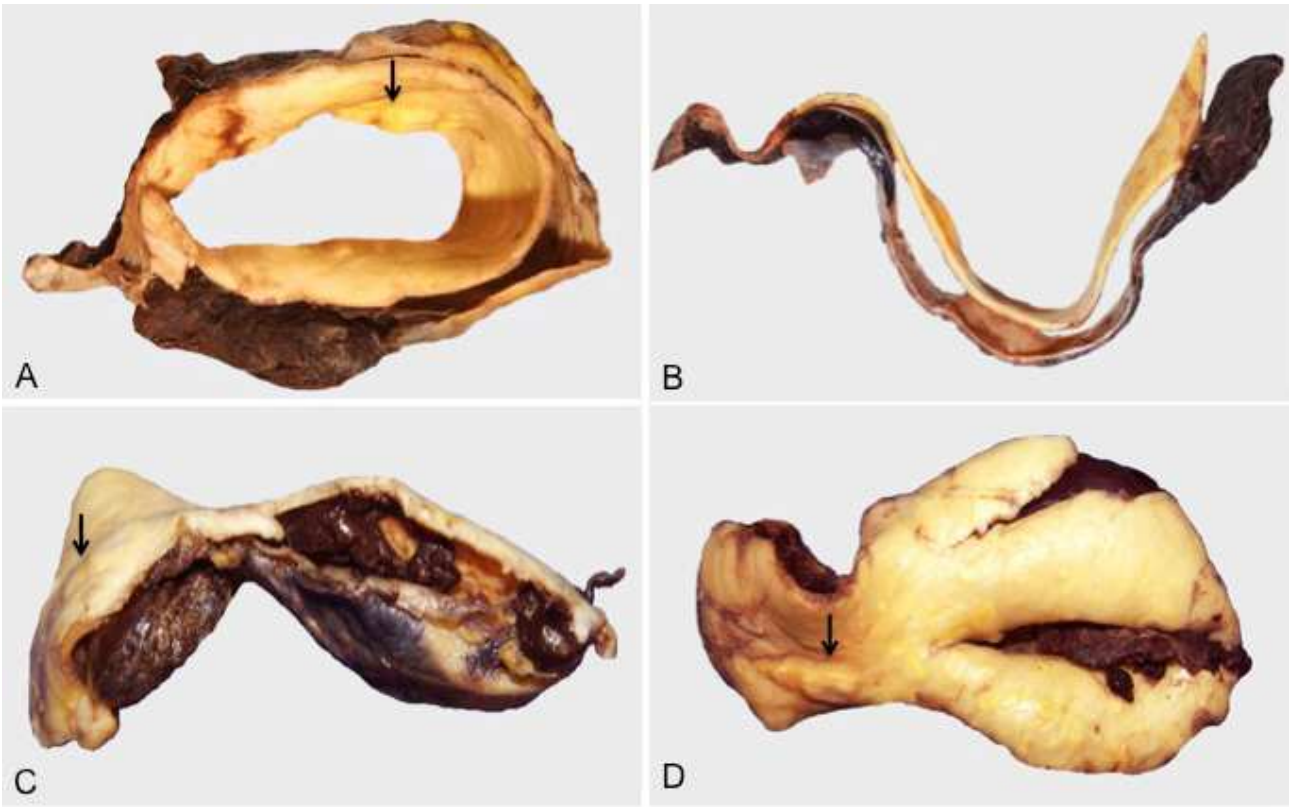
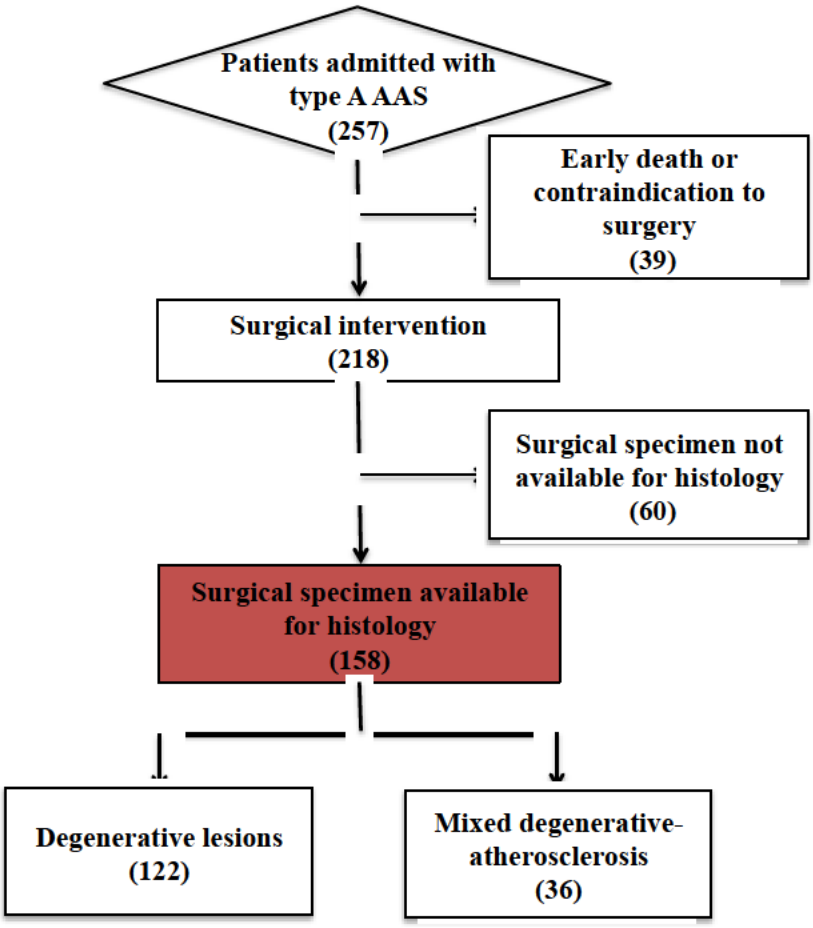
Supplementary figure 1 Specimens of type A aortic dissection. A: Dissection involves some 75% of circumference and the false lumen contains thrombosis; atherosclerotic plaques are visible in the intima (arrow). B: Aortic sample where dissection is more extensive (90% of circumference) and the aortic wall is extremely thinned. C-D: Extensive dissection and irregular intimal surface due to some whitish-yellow plaques (arrow).



608 **Supplementary figure 2** Study flowchart.



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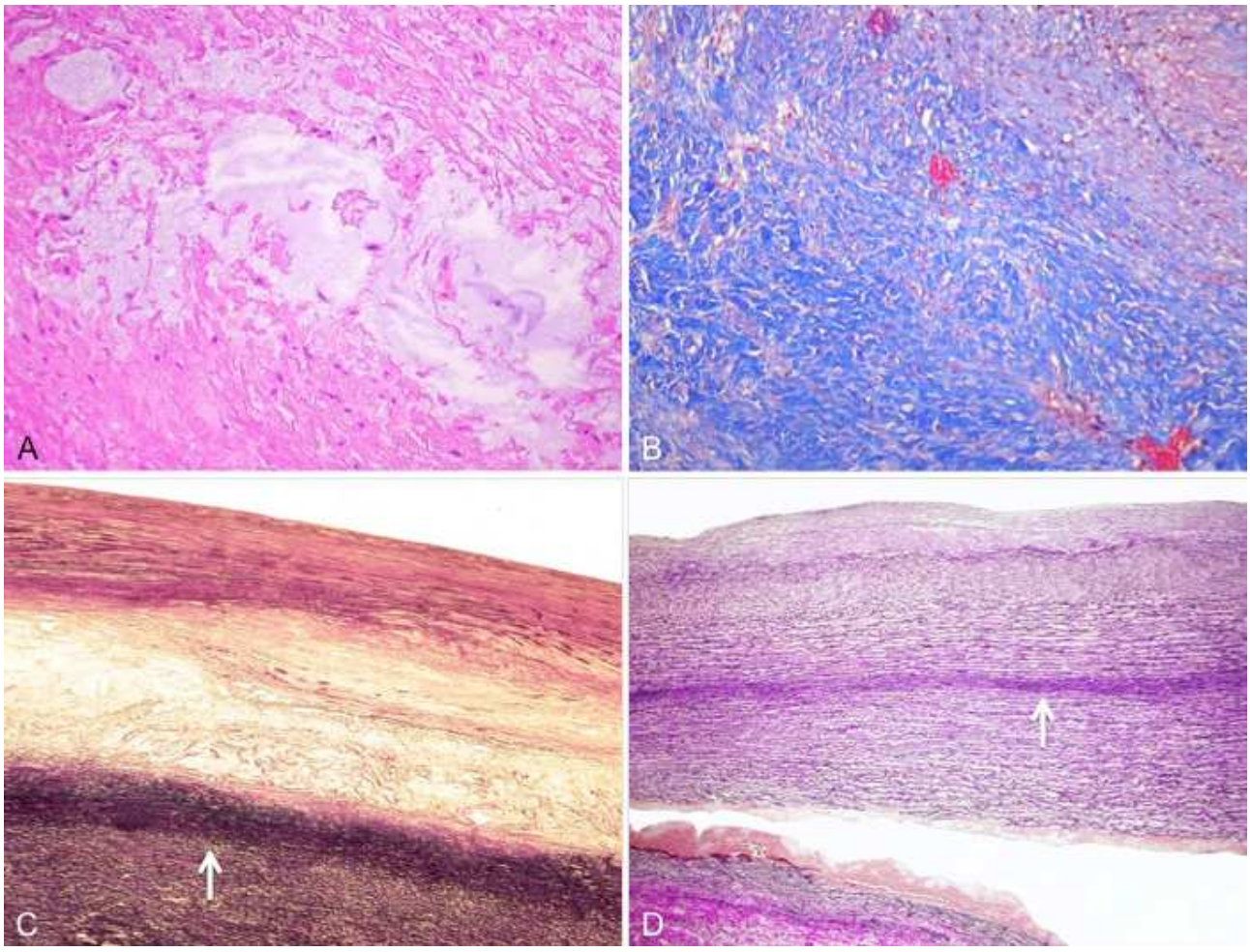
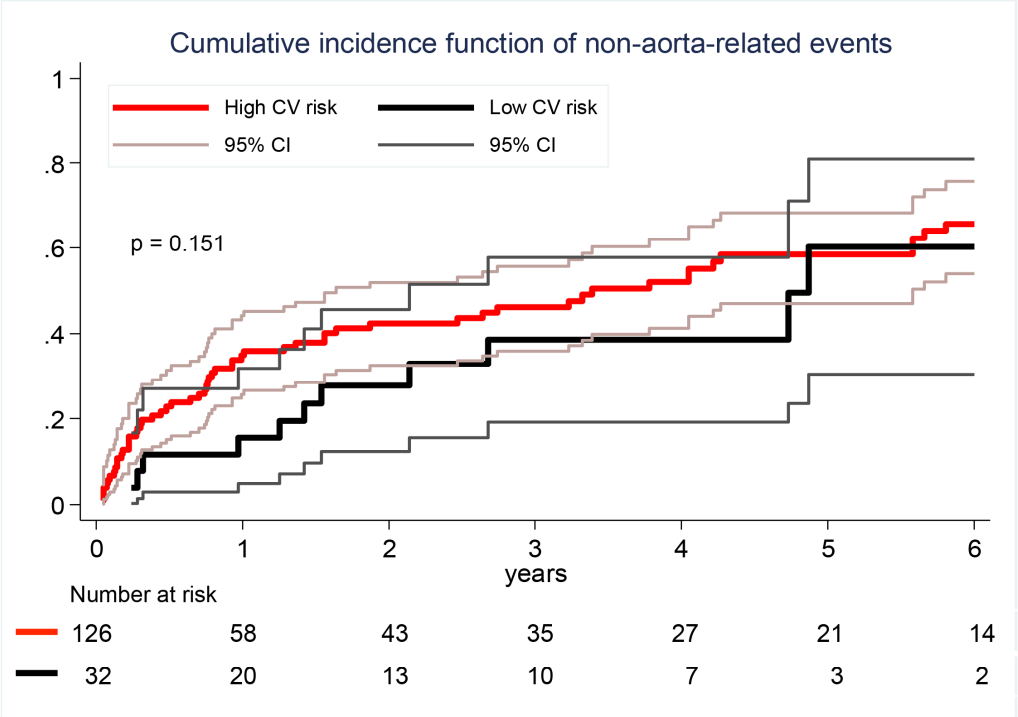
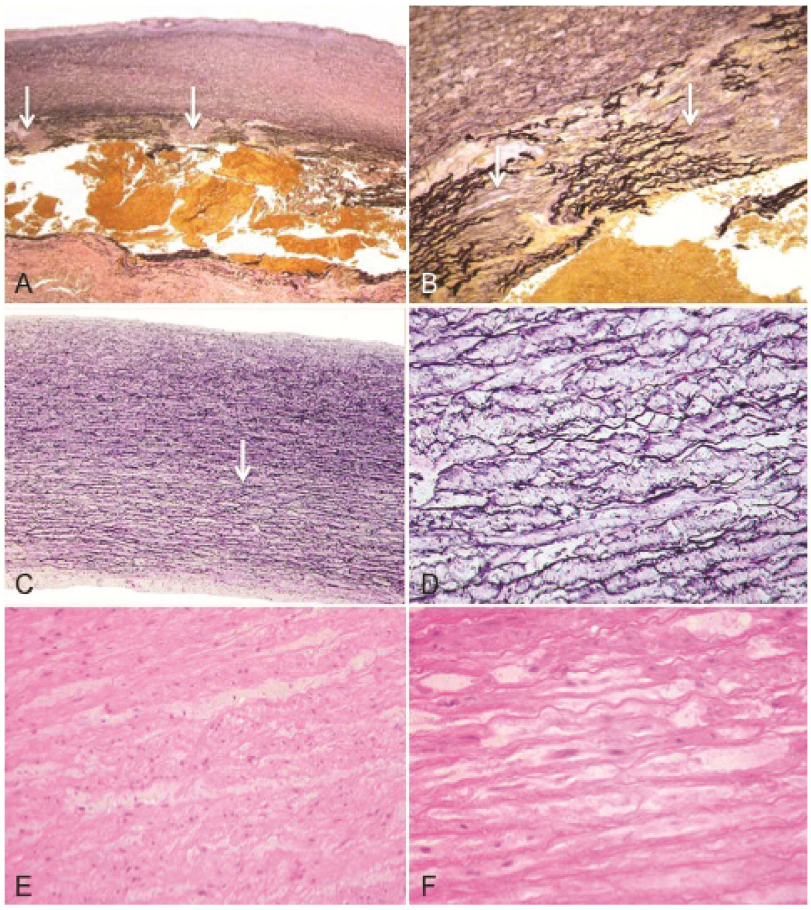
Supplementary figure 3 A: a severe focus of translamellar mucoid extracellular matrix accumulation in a degenerative group patient (Haematoxylin-Eosin stain, original magnification x200); B: medial fibrosis (i.e. translamellar collagen increase), a distinctive lesion of the mixed group (Azan Mallory tricrhome, original magnification x200). C-D: Laminar medial collapse. In mixed group this lesion was frequently found as a dense band of elastic fibre compaction bordering the lower margin of atherosclerotic plaques (C: arrow; Weigert Van Gieson, original magnification x100); 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 x100).



Supplementary figure 4 6-year non-aorta-related events of type A AAS according to patients' CV risk profile. High CV risk means patients with history of coronary artery disease and/or history of stroke and/or aged 40 or older with at least one CV risk factor (hypertension, hypercholesterolemia, diabetes, current smoke).

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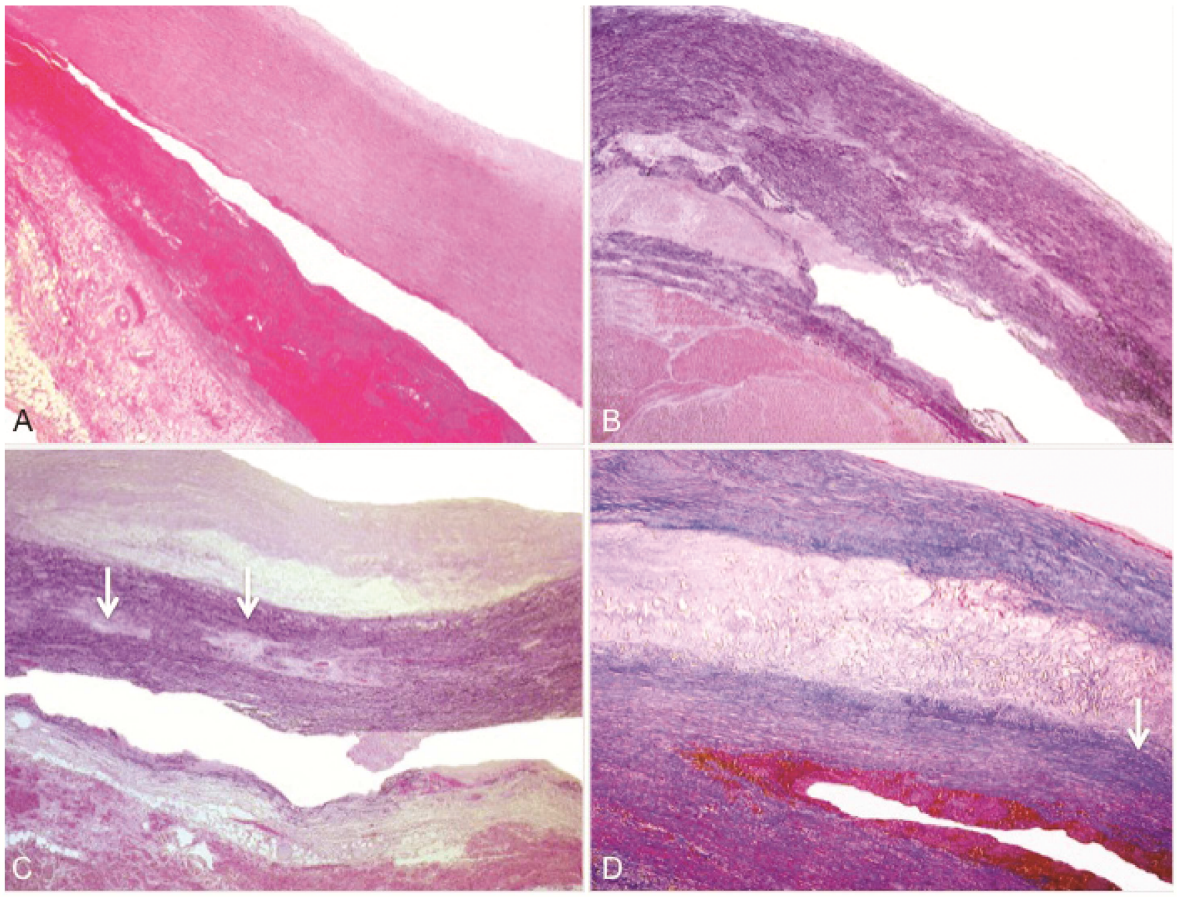
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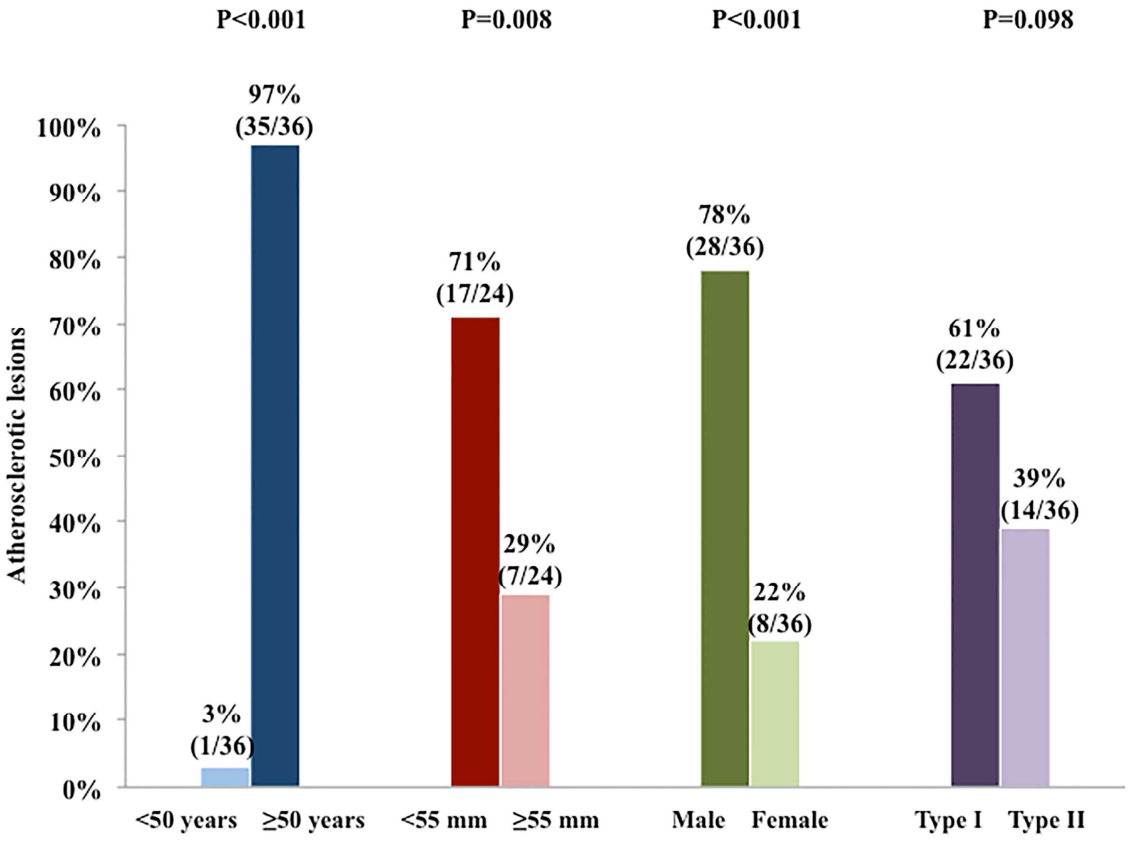
P<0.001
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Atherosclerotic lesions
100%
90%
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0%
97% (35/36)
3% (1/36)
71% (17/24)
29% (7/24)
78% (28/36)
22% (8/36)
61% (22/36)
39% (14/36)
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≥55 mm
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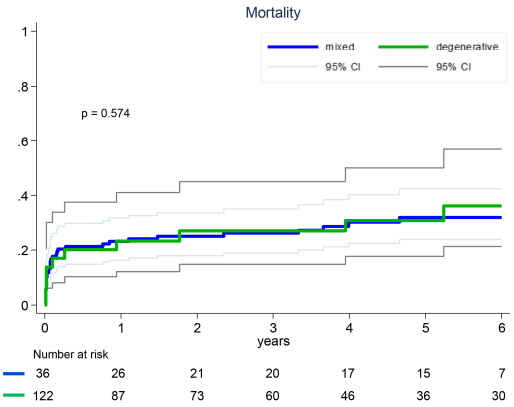
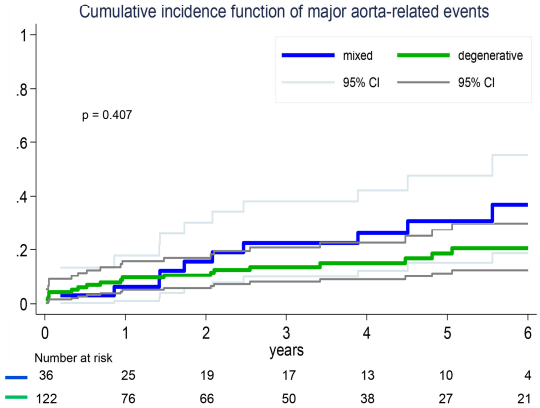
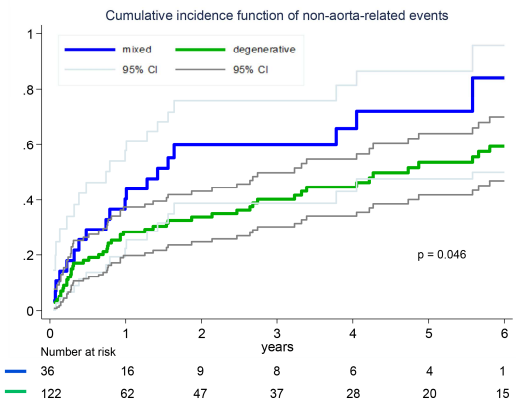
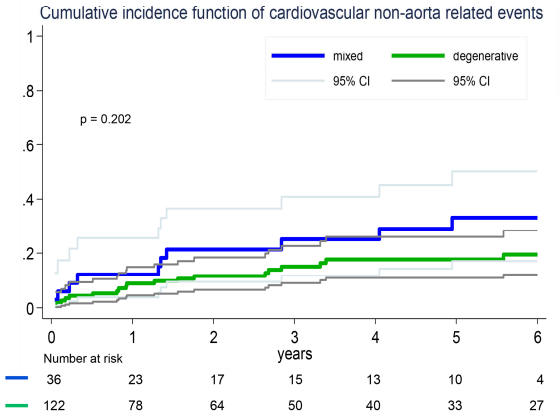
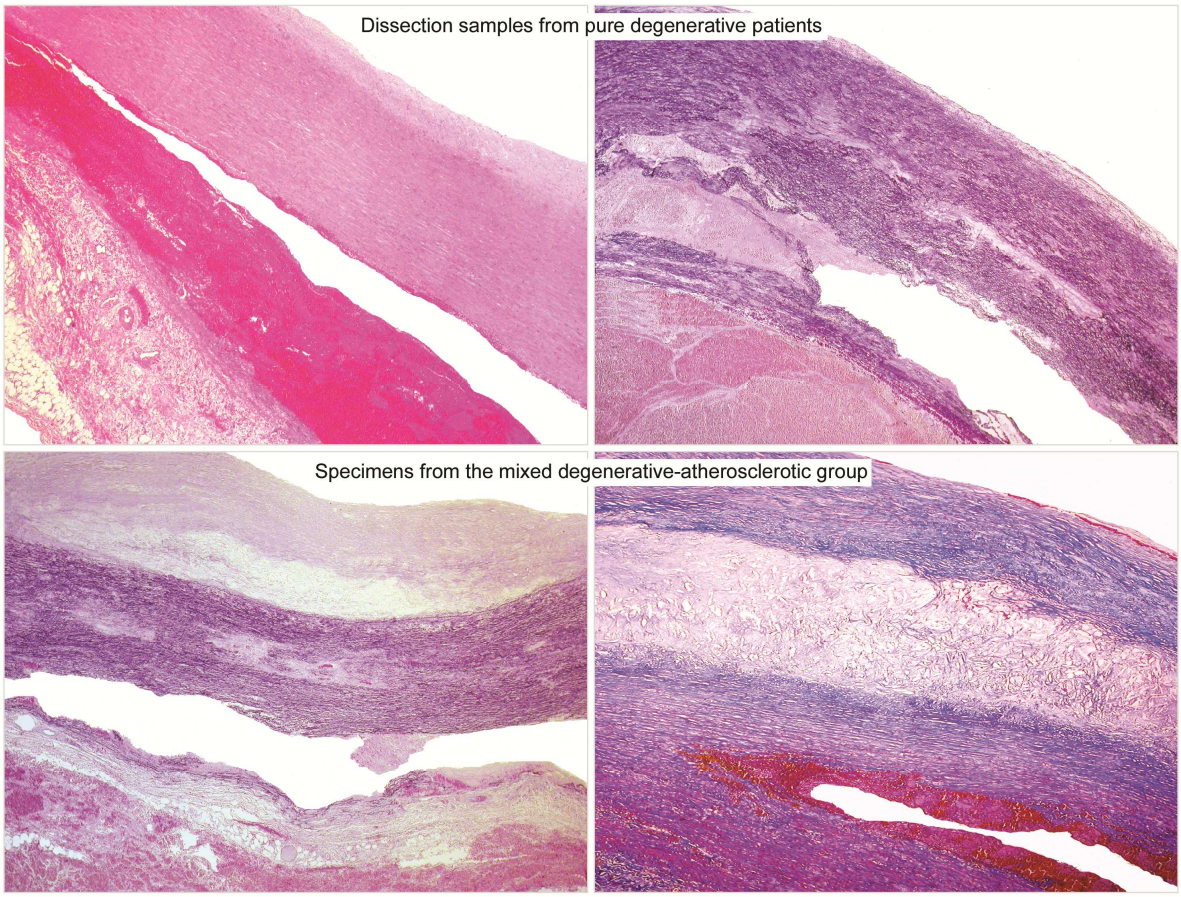
Female
Type I
Type II










Dissection samples from pure degenerative patients
Specimens from the mixed degenerative-atherosclerotic group