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

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

3
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29

30 **Glossary of abbreviations:**

31 AAS: acute aortic syndrome

32 ACS: acute coronary syndrome

33 AECVP: Association for European Cardiovascular Pathology

34 AHA: American Heart Association

35 BAV: bicuspid aortic valve

36 CAD: coronary artery disease

37 CI: confidence interval

38 CV: cardiovascular

39 EFFL: elastic fibre fragmentation/loss

40 EFT: elastic fibre thinning out

41 GFR: glomerular filtration rate

42 HR: hazard ratio

43 ICI: intralamellar collagen increase

44 I-MEMA: intralamellar mucoid extracellular matrix accumulation

45 IRAD: International Registry of Acute Aortic Dissection

46 LMC: laminar medial collapse

47 MD: medial degeneration

48 MDRD: modification of diet in renal disease

49 MFS: Marfan syndrome

50 SCVP: Society for Cardiovascular Pathology

51 SD: standard deviation

52 SHR: sub-hazard ratio

53 TCI: translamellar collagen increase

54 T-MEMA: translamellar mucoïd extracellular matrix accumulation

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79 **ABSTRACT**

80 **Objectives:** To describe the aortic histopathologic substrates in patients with type A surgically
81 treated acute aortic syndromes, to provide clinico-pathological correlations, and to identify the
82 possible prognostic role of histology.

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

87 **Results:** We identified two histopathologic patterns: 122 (77%) patients with degenerative
88 alterations and 36 (23%) with mixed degenerative-atherosclerotic lesions. Patients with mixed
89 alterations were older (mean 69.6 ± 8.7 vs. 62.2 ± 12.4 , $p=0.001$) and more hypercholesterolemic
90 (33.3% vs. 13.9%, $p=0.017$). The degenerative subgroup showed more Intralamellar-Mucoid
91 Extracellular Matrix Accumulation (86% vs. 66.7%, $p=0.017$), and a lower prevalence of
92 Translamellar Collagen Increase (9.8% vs. 50%, $p<0.001$). Patients with mixed degenerative-
93 atherosclerotic abnormalities more frequently had long-term non-aorta-related events compared to
94 those with degenerative abnormalities alone ($p=0.046$); no differences were found between the
95 groups with respect to ~~long-term~~ mortality, major aorta-related events and cardiovascular non-aorta-
96 related events.

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

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

104

105 INTRODUCTION

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

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

120

121 METHODS

122

123 Clinical setting

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

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

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

132

133 **Pathology**

134 An average of six samples were obtained from ascending aortic specimens of patients operated for
135 type A AAS and paraffin embedded (**supplementary figure 1**). The histologic sections were
136 stained with Hematoxylin-Eosin and stainings for collagen (Azan-Mallory trichrome) and elastic
137 fibres (Weigert-Van Gieson).

138 The samples were evaluated de novo, blind to clinical data, applying the AECVP/SCVP documents
139 diagnostic criteria (**7, 8**).

140 Degenerative aortic medial damage was assessed as overall medial degeneration (MD) resulting
141 from the sum of 6 individual abnormalities: mucoid extracellular matrix accumulation (MEMA),
142 both intralamellar (I-MEMA) and translamellar (T-MEMA); elastic fibre fragmentation/loss
143 (EFFL); elastic fibre thinning out (EFT); laminar medial collapse (LMC); intralamellar collagen
144 increase (ICI) and translamellar collagen increase (TCI).

145 Overall MD was graded as mild, moderate or severe, considering both severity and distribution of
146 single abnormalities.

147 Atherosclerotic plaques were described according to the American Heart Association (AHA)
148 scheme (**9, 10**). Atherosclerosis was then graded as not significant, mild, moderate or severe. Only
149 moderate to severe lesions were considered causative of significant medial damage.

150

151 **Clinical definitions**

152 Major aorta-related events were defined as re-hospitalizations for the following aortic complications
153 in some cases requiring re-intervention: organ malperfusion, increasing aortic diameter, progressive
154 false lumen dilation, aortic rupture, re-dissection, moderate/severe aortic regurgitation.

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

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

161 High CV risk included patients with history of coronary artery disease and/or stroke and/or aged
162 >40 with at least one CV risk factor (hypertension, hypercholesterolemia, diabetes, current smoking
163 habit).

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

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

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

168

169 **Statistical analysis**

170 Categorical variables are expressed as number and percentage; continuous variables as mean \pm
171 standard deviation (SD) or median and interquartile range (IQR). Categorical variables were
172 compared with Chi-square test or Fisher exact test in cases of small number of events. Shapiro-Wilk
173 W test was performed to assess normality distribution of continuous variables; then comparisons
174 were performed with Student's t-test or Mann-Whitney test accordingly. The Kaplan Meier method
175 was used to analyse the occurrence of death (Log-rank test for curves comparison); Cox regression
176 analysis was performed to identify predictors of mortality. Major aorta-related events, CV and other
177 non-aorta-related events were evaluated with cumulative incidence function with death as
178 competing risk (Pepe and Mori test for curves comparison), and competing risk regressions were
179 used to identify long-term predictors. Regarding Cox regression model, proportional-hazards
180 assumption was evaluated on the basis of Schoenfeld residuals. For other events (aorta-related, non-

181 aorta-related, CV non-aorta-related) the proportional-subhazards assumption in competing risk
182 regression was tested ensuring that coefficients were time invariant. All variables tested at the
183 univariable analysis were included in the initial multivariable model, one-by-one tested and
184 eventually excluded according to p and chi squared values of the subsequent models. All statistical
185 analyses were performed using Stata/SE 14.2 (StataCorp LP, College Station, Texas, USA). A p
186 value <0.05 was considered significant.

187

188 **RESULTS**

189 **Study population and histopathologic findings**

190 257 patients with type A AAS were considered; 218 (85%) underwent surgical treatment during the
191 index hospitalization. Surgical specimens for histology were available for 158 patients who
192 constituted our study population (**supplementary figure 2**). Baseline histopathologic characteristics
193 are reported in **Table 1**. Patients with unavailable aortic specimens (60) had similar baseline
194 characteristics to those included in the study (**supplementary table 1**). All surgical specimens
195 showed MD and this was severe in 38 patients (24%). The most frequent degenerative
196 abnormalities were EFFL (153 patients, 98.7%) and EFT (145 patients, 92.8%), and I-MEMA (129
197 patients, 81.6%), (**figure 1**). Coexisting atherosclerosis (any grade) was documented in 88 patients
198 (55.7%), and was moderate or severe in 36 (22.8%). Patients with coexisting moderate-severe
199 atherosclerosis constituted the mixed degenerative-atherosclerotic group, renamed "mixed" for
200 simplicity. The study population was therefore divided accordingly into two groups: 122 patients
201 (77.2%) with exclusively degenerative abnormalities and 36 patients (22.8%) with mixed
202 degenerative-atherosclerotic findings (**figure 2**).

203 Comparing the two groups, MEMA - especially intralamellar - was the single abnormality
204 that most characterized the degenerative group; the most frequent alteration in the mixed group was
205 TCI. LMC was found in 61 patients (50%) in the degenerative group and in 14 (38.9%) in the
206 mixed group. Among the mixed group, this abnormality was mainly (13/14) present as a dense band

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

210 **Clinical findings**

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

217

218 **Clinico-pathological correlations**

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

223 The comparison between patients with dissection (147) vs intramural haematoma (IMH, 10) did not
224 show differences in the histopathologic diagnostic category. However, patients with dissection
225 presented a higher percentage of T-MEMA (70.7% vs 36.4%, $p=0.001$) while IMH was strongly
226 associated with atherosclerotic lesions (90.9% vs 53.1%, $p=0.023$) (**supplementary table 2**).

227 Both patients with a diagnosis of MFS were included in the degenerative group with severe MD in
228 one case and moderate MD in the other. No atherosclerosis was found in these patients.

229 Of the 6 patients with bicuspid aortic valve, 5 had purely degenerative abnormalities - moderate in
230 three cases, while it was graded mild and severe in the other two patients - while mixed
231 abnormalities (with moderate MD) were found in the last patient.

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

235 Patients over the age of 50 were more frequently found to have atherosclerotic abnormalities
236 [59.8% (82/137) vs. 28.6% (6/21), $p = 0.014$], I-MEMA [83.2% (114/137) vs. 71.4% (15/21),
237 $p = 0.006$], and moderate/severe EFFL [81.7% (112/137) vs. 23.8% (5/21), $p < 0.001$]
238 (**supplementary table 4**).

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

241

242 **Outcome and prognostic stratification**

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

250 Cumulative incidence of major aorta-related events at 1, 3 and 6-years follow-up was 9%, 16% and
251 25% respectively, that of non aorta-related events was 31%, 44% and 64% respectively, and that of
252 CV non-aorta-related events was 10%, 17% and 23% respectively.

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

258 the end of follow-up, log-rank test, $p=0.574$), major aorta-related events (19 events among
259 degenerative patients and 10 events among mixed patients at the end of follow-up, Pepe and Mori
260 test, $p=0.407$), and CV non-aorta-related events (19 events among degenerative patients and 10
261 events among mixed patients at the end of follow-up, Pepe and Mori test, $p=0.202$).

262 **Table 3A** and **table 3B** report the major clinical and histologic incremental risk factors for
263 6-year-mortality and for 6-year-non-aorta-related events. Age [HR 1.03 for each 1-year increase;
264 95% CI 0.99-1.06; $P=0.069$, borderline significance] and GFR < 60 ml/min/1.73m² at presentation
265 [HR 2.33; 95% CI 1.24-4.4; $P=0.009$] were independent predictors of mortality (**table 3A**). Non-
266 aorta-related events were analysed in detail, and no differences were found according to the
267 patients' CV risk profile (**supplementary figure 4**). Hypertension [SHR 1.79; 95% CI 1.01-3.21;
268 $P=0.047$] and the coexistence of atherosclerotic lesions together with degenerative abnormalities
269 [SHR 1.65; 95% CI 0.96-2.84; $P=0.068$, borderline significance] were found to be independent risk
270 predictors for non-aorta-related events (**table 3B**).

271

272 DISCUSSION

273 This is the first study that provides a detailed description of the histopathologic findings of
274 aortic specimens - as well as their clinico-pathological correlation - from a large unselected cohort
275 of patients with type A AAS, applying the classification and diagnostic criteria from the recent
276 AECVP/SCVP consensus statements (**7, 8**). The main findings of the study are: 1. Although
277 degenerative lesions of the medial layer were present in all specimens, substantial atherosclerosis
278 coexisted in nearly a quarter; 2. Patients with mixed degenerative-atherosclerotic abnormalities had
279 a coherent clinical risk profile, with a more frequent presentation mimicking ACS and a long-term
280 follow-up characterized by non-aorta-related events, including coronary and cerebrovascular events;
281 3. Histopathologic characterization could help the long-term prognostic stratification of patients
282 following surgical treatment.

283 The histopathologic substrate of our cohort was heterogeneous do to the variable
284 combination – quantitatively and qualitatively - of degenerative and atherosclerotic lesions. All
285 patients showed MD abnormalities: almost all cases had elastic fibre abnormalities, including both
286 thinning out and fragmentation; MEMA was present as I-MEMA in over 80% of patients and as T-
287 MEMA (an expression of a more severe mucopolysaccharide accumulation) in 68.4%; collagen
288 increase was present with a heterogeneous distribution: intralamellar in 74% and translamellar (i.e.
289 fibrosis) in 19% of cases. It is noteworthy that more than 50% of patients had some degree of
290 atherosclerosis associated with degenerative lesions. Almost a quarter had moderate/severe
291 atherosclerosis, which the AECVP/SCVP statement (7) considers a cause of significant aortic wall
292 damage with consequent weakness.

293 The comparison between exclusively degenerative or mixed subgroups reveals differences
294 in the distribution of mucoid accumulation and of fibrosis. I-MEMA was the most typical lesion in
295 purely degenerative patients, while translamellar collagen was distinctly increased in the mixed
296 group. Interestingly, 1/3 of major atherosclerotic plaques was accompanied by a thick band of
297 medial lamellar collapse, which, together with TCI, can probably be considered a final response to
298 the atherosclerotic plaque penetrating more deeply into the media. Elastic fibre alterations were
299 present in the purely degenerative and mixed groups in equal measure, probably due to the
300 heterogeneity of various causative conditions, including the aging process. Our only 2 patients with
301 Marfan syndrome and five out of six patients with bicuspid aortic valve had moderate/severe
302 degenerative lesions, in line with the findings of previous studies (14, 15).

303 Unlike previously published similar series (2-5), our study included exclusively patients
304 with AAS. The first two published series evaluating clinico-pathological features of the ascending
305 aorta described 63 (2) and 339 patients (3) who underwent surgery for aneurysm or dissection of the
306 ascending aorta. Compared to our population, the patients in these series were younger, with a
307 higher prevalence of connective tissue disorders and a lower prevalence of severe atherosclerosis.
308 MD was the most common histopathologic finding, and an inverse relationship between the severity

309 of MD and age was found **(3)**. A more recent study describing 513 patients **(4)** found that
310 connective tissue disorders were most frequently associated with MD, followed by aging and no
311 association between bicuspid aortic valve and medial degeneration was found. Severe
312 atherosclerosis was described in an exiguous number of patients. Again, it should be noted that the
313 population in this series was younger compared to ours and that both aneurysms and dissections
314 were considered. A further study on 338 surgical specimens including a few Marfan patients, found
315 that MD was a common, age-related and non-specific histological pattern in aortic aneurysms and
316 dissections **(5)**. Atherosclerosis was present only in 10% of patients, and was more frequently
317 associated with aneurysms than dissections.

318 In our study atherosclerosis was more frequent than previously described, and this is
319 probably due to the older age of our patients. On the other hand, clinical and epidemiological
320 characteristics of our study population were similar to those of the largest “real world registry”
321 IRAD (International Registry of Acute Aortic Dissection) **(16)**. In particular, mean age (63.9
322 years), prevalence of male gender (about 68.4%), hypertension (72.2%) and bicuspid aortic valve
323 (3.8%) were quite similar whereas Marfan syndrome was less frequent (1.3% vs. 4.7%) probably
324 due to the prophylactic surgery strategy adopted in our network.

325 As expected, patients with atherosclerotic lesions had a higher CV risk profile: in
326 particular, they were older, male, and hypercholesterolemic. Interestingly, atherosclerotic lesions
327 were more frequent in patients with a diameter of the ascending aorta <55 mm, and in type I AAS
328 compared with type II (borderline significance) **(figure 3)**.

329 The long-term outcome of patients with associated atherosclerosis is characterized by high
330 probability of non-aorta related events including coronary and cerebrovascular events and infectious
331 complications even if no association with overall mortality was shown. As already demonstrated by
332 other studies, renal function and age (borderline significance in our work) were found to be risk
333 factors for mortality **(17)**. Notably, along with hypertension, the presence of atherosclerotic
334 abnormalities was a probable risk factor for non-aorta-related events. Therefore, the knowledge of

335 the histopathologic substrate underlying AAS may provide additional information to the level of
336 risk derived from patients' clinical characteristics alone.

337

338 **Study limitations**

339 Due the monocentric nature of our work, the size of the study population and relative
340 events are not comparable with international registries. Twenty-seven percent of aortic specimens
341 among surgically treated patients did not reach the histology laboratory due to logistic reasons.

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

344 Whereas the description of the histopathologic spectrum - according to the current AECVP/SCVP
345 classification - in patients with type A AAS provides robust and new information, the impact of
346 clinico-pathological correlations is inevitably limited by the relatively small study population and
347 the few events during follow-up. Lastly, due to the retrospective nature of this study and the
348 emergency clinical setting, availability of laboratory data and imaging details - both at presentation
349 and during follow-up - is limited.

350

351 **Clinical implications**

352 The new AECVP/SCVP classification allows a comprehensive description of aortic wall
353 abnormalities, provides a standardised characterization of MD, and represents a useful tool for
354 nosography, clinico-pathological correlations, and prognostic information in patients with type A
355 AAS. Full knowledge of the histopathologic details of patients who underwent surgery for AAS can
356 lead to better planning of long-term follow-up, especially regarding preventive strategies for non-
357 aorta-related events.

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416 **FIGURE LEGENDS**

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

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

434 **Figure 3** Prevalence of atherosclerotic lesions according to age, ascending aorta diameter, gender,
435 and De Baakey subtype.

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

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

442 **TABLES**

443 **Table 1** Histopathologic findings in the overall population and in the subgroups defined by
 444 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

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

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

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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 \pm SD	63.9 \pm 12	62.2 \pm 12.4	69.6 \pm 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 \pm SD	134.5 \pm 37.3	132.6 \pm 37.3	141.1 \pm 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

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

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487 **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 Baakey 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		

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

489 AAS: Acute Aortic Syndrome; AHA: American Heart Association; BAV: Bicuspid Aortic Valve;

490 CI: Confidence Interval; GFR: Glomerular Filtration Rate; HR: Hazard Ratio.

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495 **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 Baakey 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		

496 AIC=585.9; BIC 592.1

497 AAS: Acute Aortic Syndrome; AHA: American Heart Association; BAV: Bicuspid Aortic Valve;

498 CI: Confidence Interval; GFR: Glomerular Filtration Rate; SHR: Sub-hazard Ratio.

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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 \pm SD	64.4 \pm 12.1	63.9 \pm 12	65.5 \pm 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 \pm SD	134.7 \pm 38.4	134.5 \pm 37.3	135.1 \pm 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

507 AAS: Acute Aortic Syndrome; ACS: Acute Coronary Syndrome; CT: Computed Tomography;

508 CVA: Cerebrovascular Accident; GFR: Glomerular Filtration Rate; SD: Standard Deviation; IQR:

509 interquartile range.

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Supplementary table 2 Histopathologic characteristics according to type of AAS.

VARIABLE	OVERALL	DISSECTION	INTRAMURAL HAEMATOMA	P value
	(n=158)	93% (n=147)	7% (n=11)	
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-Muroid Extracellular
526 Matrix Accumulation; T-MEMA: Translamellar- Muroid 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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593 **Supplementary figure 1** Specimens of type A aortic dissection. A: Dissection involves some 75%
594 of circumference and the false lumen contains thrombosis; atherosclerotic plaques are visible in the
595 intima (arrow). B: Aortic sample where dissection is more extensive (90% of circumference) and
596 the aortic wall is extremely thinned. C-D: Extensive dissection and irregular intimal surface due to
597 some whitish-yellow plaques (arrow).



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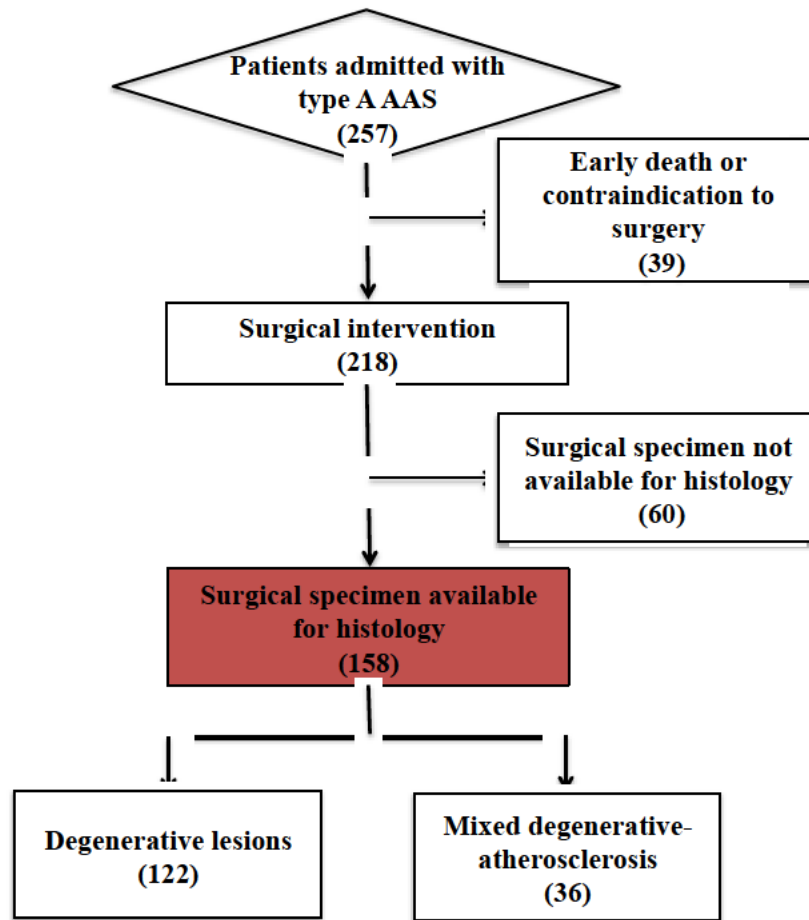
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608 **Supplementary figure 2** Study flowchart.

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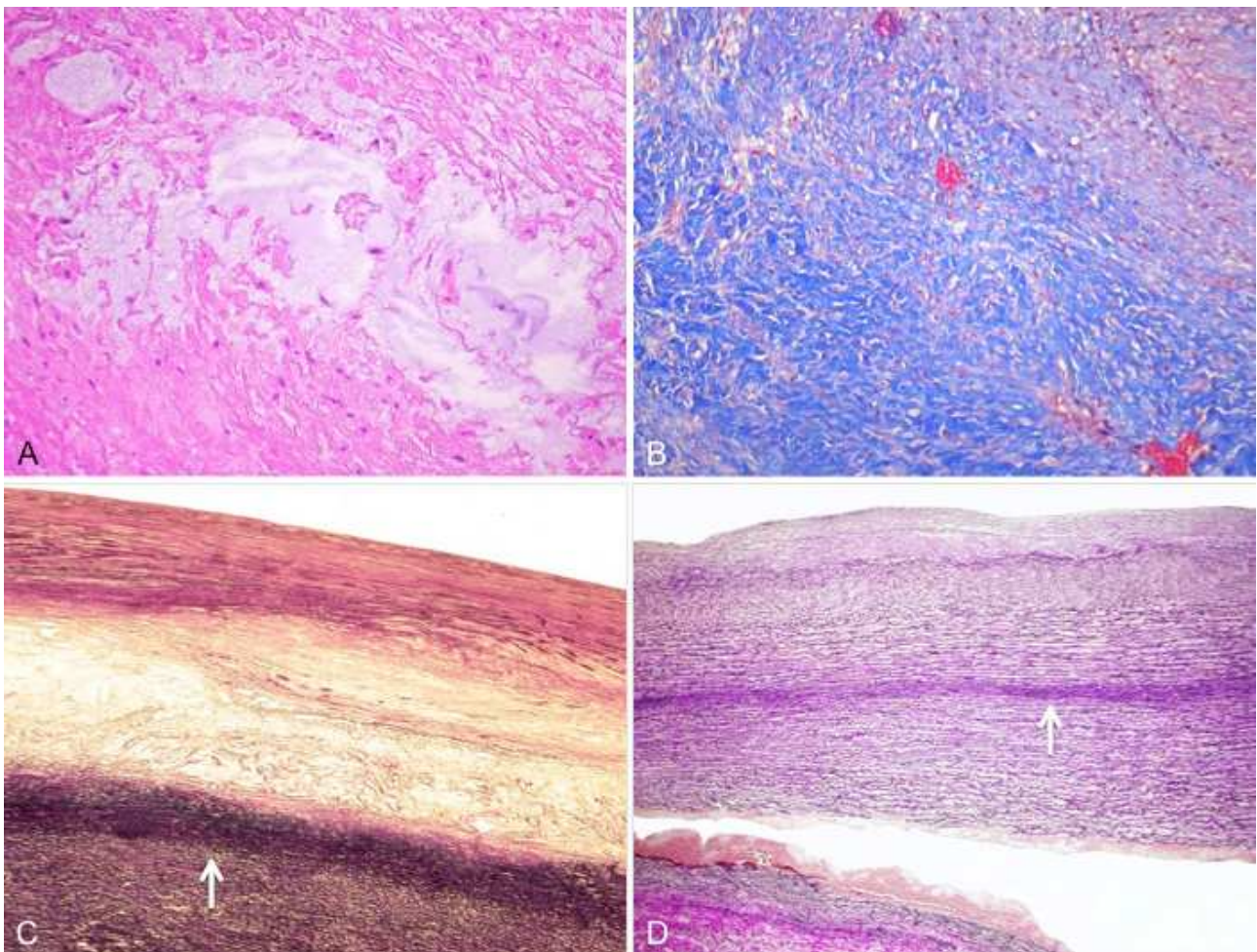
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621 **Supplementary figure 3** A: a severe focus of translamellar mucoid extracellular matrix
622 accumulation in a degenerative group patient (Haematoxylin-Eosin stain, original magnification
623 x200); B: medial fibrosis (i.e. translamellar collagen increase), a distinctive lesion of the mixed
624 group (Azan Mallory trichrome, original magnification x200). C-D: Laminar medial collapse. In
625 mixed group this lesion was frequently found as a dense band of elastic fibre compaction bordering
626 the lower margin of atherosclerotic plaques (C: arrow; Weigert Van Gieson, original magnification
627 x100); in degenerative patients the lesion was frequently seen in the central areas of the medial
628 layer above or on the same plane of the dissection (arrow) (Weigert Van Gieson, original
629 magnification x100).



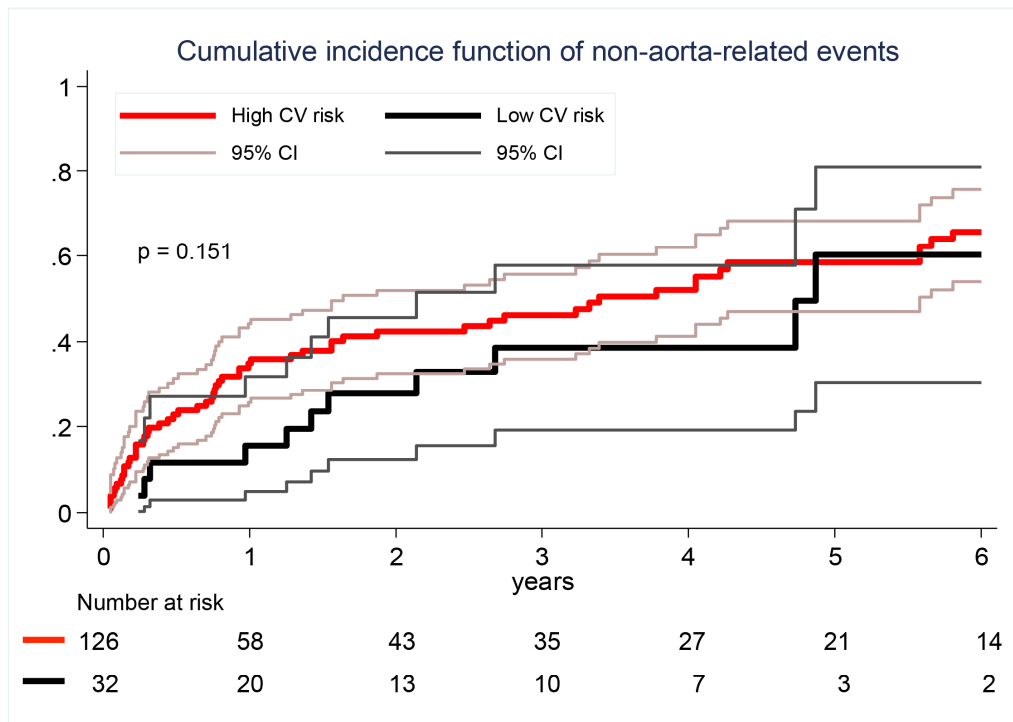
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634 **Supplementary figure 4** 6-year non-aorta-related events of type A AAS according to patients' CV
 635 risk profile. High CV risk means patients with history of coronary artery disease and/or history of
 636 stroke and/or aged 40 or older with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



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