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ARTICLE HIGHLIGHTS

Type of research: Retrospective population-based cohort study.

Key findings: After the acute phase of aortic dissection (AD), freedom from any aortic branch-related intervention, aneurysm, rupture, malperfusion, or death, was 48% at 15 years. Type B AD (HR 3.5; P=.033), patency of the aortic false lumen (HR 6.8; P=.038) and malperfusion syndrome at presentation (HR 6.0; P=.023) were predictors of late aortic branches-related events. Dilatation of the aortic branches occurred in 29% of cases; patency of the aortic false lumen, initial branch diameter, and Marfan syndrome were significantly associated.

Take home message: In patients with AD, aortic branch involvement was responsible for a significant long-term morbidity, without any related mortality. Type B AD, patency of the aortic false lumen, or malperfusion syndrome at presentation had a higher risk of branch events during the long-term follow-up. Dilatation of the aortic branches was observed in one third of cases, in particular in case of a patent aortic false lumen or Marfan syndrome.

Table of contents summary

This retrospective population-based cohort study showed that aortic branch involvement was responsible for a significant long-term morbidity, without any related mortality. Type B AD, patency of the aortic false lumen, or malperfusion syndrome at presentation had a higher risk of branch events during the long-term follow-up. Future studies should focus on strategies to limit branch vessel growth and prevent vascular complications in patients with a previous AD.

ABSTRACT

Objective: Late morbidity and mortality related to aortic branches in patients with aortic dissection (AD) are not well described. We aimed to investigate the fate of aortic branches in a population cohort of patients with newly diagnosed AD.

Methods: We used the Rochester Epidemiology Project record linkage system to identify all Olmsted County, MN, residents diagnosed with AD from 1995 to 2015.

Only patients with >30 days of available follow-up imaging were included in the analysis. The primary outcome was freedom from any branch-related event (any intervention, aneurysm, malperfusion, rupture, or death occurring after the acute phase >14 days). Secondary outcome was the diameter change of the aortic branches. Univariate and multivariable Cox proportional hazards models were used to identify predictors of branch-related events; univariate and multivariate linear regression models were used to assess aortic branches growth rate.

Results: Of 77 total incident AD cases, 58 patients who survived with imaging follow-up were included, 28 (48%) with type A and 30 (52%) with type B AD. The presentation was acute in 39 (67%) cases; 6 (10%) had branch malperfusion. Of 177 aortic branches involved by the AD, 81 (46%) arose from the true lumen, 33 (19%) from the false lumen, 63 (36%) from both.

After the acute phase, freedom from any branch-related event at 15 years was 48% (95%CI 32-70). Thirty-one branch-related events occurred in 19 patients over 15 years: 12 interventions (76% freedom, 95%CI 63-92), 10 aneurysms (67% freedom, 95%CI 50-90), 8 malperfusions (76% freedom, 95%CI 61-94) and 1 rupture (94% freedom, 95%CI 84-100). There were no branch-related deaths. Type B AD (HR 3.5, 95%CI 1.1-10.8; P=.033), patency of the aortic false lumen (HR 6.8, 95% CI 1.1-42.2; P=.038) and malperfusion syndrome at presentation (HR 6.0, 95% CI 1.3-28.6; P=.023) were predictors of late aortic branches-related events.

Overall growth rate of aortic branches was 1.3±3.0 mm/year. Patency of the aortic false lumen, initial branch diameter, and Marfan syndrome were significantly associated with diameter increase.

Conclusions: In patients with AD, aortic branch involvement was responsible for a significant long-term morbidity, without any related mortality. Type B AD, patency of the aortic false lumen, or malperfusion syndrome at presentation had a higher risk of branch events during the long-term follow-up. Dilatation of the aortic branches was observed in one third of cases during follow-up, in particular in case of a patent aortic false lumen or Marfan syndrome.

INTRODUCTION

Acute aortic dissection (AD) may present with aortic side branches compromise, because of severe compression of the true lumen at the level of the ostium or due to progression of the dissection process into the aortic side branch. Clinical manifestations of malperfusion are present in up to 30% of patients with acute AD, and these cases are associated with an increased early mortality[1,2].

In patients with AD, the risk of aortic branches compromise may still be maintained also after the acute phase, because of progression to static or dynamic obstruction, recurrence of aortic dissection with involvement of the aortic branches, or occurrence of isolated dissection of the branch vessels. Furthermore, the progressive size increase that is typically described for the chronically dissected aorta[3] may affect also the non-aortic arterial segments.

However the long-term fate of aortic branches in terms of malperfusion, aneurysm formation, intervention, rupture, and related mortality are not well described. The objective of this study was to investigate the long-term morbidity and mortality related to aortic branches in a population cohort of patients with newly diagnosed AD.

METHODS

Patients. We used the Rochester Epidemiology Project (REP) record linkage system to identify all Olmsted County, MN, residents diagnosed with AD from 1995 to 2015. The detailed methods for the identification of the original cohort are described elsewhere[4]. In brief, the REP represents a unique collaboration of health care providers linking together medical records of virtually all residents of Olmsted County, MN. This allows the identification of incident diagnoses at a population level and allows follow-up of patients across providers. Within the REP, adult

residents (≥18 years of age) with a new diagnosis of AD from 1995-2015 were identified using International Classification of Disease codes (ICD, 9th and 10th revision) and Hospital Adaptation of the International Classification of Diseases codes (HICDA, 2nd edition). For diagnosis, patients were required to have imaging confirmation of AD (computed tomography with arterial contrast, magnetic resonance imaging, ultrasound, or conventional angiography), primary diagnosis of AD on their death certificate, or autopsy confirmation of AD. The study was approved by the Institutional Review Boards of the two major health care providers in the REP, Mayo Clinic and Olmsted Medical Center. All individuals included in the study had already provided informed consent for the use of their medical records in research as part of the REP[5].

Only patients with a confirmed diagnosis of AD and with an available imaging follow-up >30 days were included in this analysis. Patients with a final imaging diagnosis of aortic intramural hematoma or penetrating aortic ulcer where excluded.

AD was classified using the De Bakey and the Stanford classifications. Acuity of the disease was classified as acute (<14 days from initial symptoms), subacute (2 weeks to 3 months) or chronic (>3 months)[6,7]. AD was considered subacute or chronic if the initial imaging was performed after the acute phase, but it was possible to clearly date the onset of symptoms. Acuity was categorized as "unknown" if the diagnosis of AD was made by imaging, but it was not possible to clearly date the onset of symptoms. Marfan syndrome was diagnosed by Ghent criteria and confirmed by genetic testing.

Endpoints. The primary endpoint was freedom from any branch-related event, defined by any intervention, aneurysm, malperfusion, aortic branch rupture, or death occurring after the acute phase. Any intervention performed for static or dynamic malperfusion, side branch aneurysm, or

rupture, was considered as branch-related. If the primary indication to surgery was aortic-related, the patient was considered to receive a branch-related intervention only if the surgical approach was conditioned by involvement of the aortic branch by the pathology (ie, necessity to perform fenestration of aortic intimal flap, bypass due to dissected branch vessel), as reported in the operative note.

Since the objective of the study was to evaluate the natural history of aortic branches, in order to maintain reproducibility of the results we decided to consider as endpoint the event of "aneurysm formation" basing on a pre-specified definition, and not basing on its eventual surgical treatment. For the purpose of the analysis, only aortic branches with a diameter large enough to take into consideration a surgical treatment were considered, defined by a maximum diameter >2 cm for peripheral or reno-visceral vessels[8] and 3 cm for supra-aortic trunks[9] and iliac arteries[10].

Branch vessel malperfusion was defined as any branch vessel involvement with evidence of both anatomic and clinical branch vessel compromise (e.g., static and/or dynamic branch involvement with accompanying stroke, mesenteric, visceral, renal, and/or extremity symptoms), according to most recent reporting standards[6,7]. Also the incidence of new aortic branches dissection was investigated. However, new branch dissections were not associated with malperfusion in any case, so it was not considered a clinically significant event. Therefore, new dissections of aortic branches were considered separately and not included in the primary composite endpoint.

The secondary outcome was the diameter change of the aortic branches during follow-up. The maximum branch diameter was measured at the initial and last available computed tomography angiogram (CTA). To account for minimal observer-dependent diameter changes, any diameter increase was defined as a ≥1mm increase in the maximum diameter of the aortic side branch. All the images were reviewed by a radiologist and confirmed by a vascular surgeon. The growth rate

was calculated as the difference (in millimeters) of the maximum branch diameter on the most recent study before any related intervention minus the initial maximum diameter, divided by the time in years. The growth rate was separately described for supra-aortic vessels (innominate artery, left carotid artery, left subclavian artery), reno-visceral arteries (celiac artery, superior mesenteric artery, renal arteries), and iliac arteries.

Statistical analysis. Results were reported as a number and percentage for categorical variables, mean±standard deviation or median and range for continuous variables. Time-dependent outcomes were reported using Kaplan-Meier estimates. Freedom from branch-related events was calculated *per person* and not *per artery*. In case of multiple types of complications occurring in the same patient, just the first one was considered for the estimation of freedom from any branch-related complication. For the estimation of the specific rates of freedom from intervention, aneurysm, malperfusion, aortic branch rupture, or death, just the first complication was considered, if multiple complications occurred at different time points during follow-up of the same patient. Univariable and multivariable Cox proportional hazards models were used to assess the impact of baseline characteristics on the primary outcome. Univariable and multivariable logistic regressions were used to identify factors associated with any increase in aortic branch diameter during follow-up. Univariable and multivariable linear regression models were used to identify factors associated with the aortic branches growth rate. A P-value of less than .05 was used to determine statistical significance. The R 3.5.2 software (R foundation for statistical computing, Vienna, Austria) was used for the analysis.

RESULTS

Of 77 incident AD included in the original patients cohort[4], 12 (16%) died within 30 days. In 2 of these, death was related to malperfusion of the supra-aortic vessels in patients presenting with a type A dissection. Fifty-eight patients had available imaging >30 days and met the inclusion criteria for the current analysis. Mean age was 66±14 years and most patients were males (n=40, 69%) (**Table I**).

Twenty-eight (48%) patients had type A AD and 30 (52%) had type B AD. The presentation was acute in 39 (67%) cases and twenty-five (43%) patients received open (n=23, 40%) or endovascular (n=2, 3%) aortic treatment during the acute phase. Of the 30 type B dissections, 28 were medically treated and 2 received TEVAR due to rupture (n=1) or uncontrolled hypertension/pain (n=1). Surgical treatment for type A dissections consisted in replacement of the ascending aorta in all cases, without any intervention on aortic branches. A medical conservative treatment was initially adopted in 5 cases with intimal tear at the level of the aortic arch and not involving the proximal ascending aorta. Subsequent surgical treatment was not necessary in any of these cases and there were no aortic branches events in these patients.

At presentation, 177 aortic branches were involved by the AD, 81 (46%) arising from the true lumen, 33 (19%) from the false lumen, 63 (36%) from both; concomitant clinical signs of malperfusion were present in 6 (10%) patients (1 left upper extremity ischemia, 1 paraparesis, 2 dynamic malperfusion of reno-visceral vessels, 2 isolated malperfusion of the right or left renal artery). Also 4 branch aneurysms (3 left common iliac arteries and 1celiac artery) were detected at the initial CTA.

Survival. Median follow-up was 101 months (interquartile range, 43-173 months). At 15 years, Kaplan-Meier estimated survival was 42.3% (95%CI 29-61) and freedom from aortic-related mortality was 80.3% (95%CI 65-98). Specific survival by type of dissection was 34.1% (95%CI

18-65) for type A and 50.2% (95%CI 32-77) for type B dissections (P=.800). There were no branch-related deaths.

Interventions. Twelve interventions in 10 patients occurred after the acute phase (**Table II**). The indication was the presence of a branch aneurysm in 4 (33%) cases (4 iliac arteries) and malperfusion in 3 (25%) (2 renal arteries, 1 iliac artery). In 2 (17%) cases an intimal flap fenestration was required for left renal artery stenting during endovascular repair of a thoracoabdominal aortic aneurysm. In 1 (8%) case with thoracoabdominal aortic aneurysm post type B dissection, a visceral artery bypass was required because of dissected branch vessels; 1 case received multiple visceral bypasses to repair a patch aneurysm after a previous type II thoracoabdominal aneurysm open repair. One patient underwent aortic arch repair for a chronic residual dissection involving also all supra-aortic vessels; proximal side branches ligation and graft replacement using a trifurcated graft was performed. The estimated freedom from branch-related interventions at 15 years was 76% (95%CI 63-92), 76% (95%CI 59-97) for type A dissections and 76.7% (95%CI 59-99) for type B (P=.500).

Aneurysm. Ten new aneurysms developed in 9 patients in a 15 years period. The affected arterial segment was the innominate artery in 1(10%) case, the subclavian artery in 1 (10%), the superior mesenteric artery in 1 (10%), and the iliac artery in 7 (70%) (**Supplementary Figure 1**). Of the 10 newly detected aneurysms, 7 were on a previously dissected artery. Freedom from any new branch aneurysm was 67% (95%CI 50-90), 74% (95%CI 50-100) for type A dissections and 59.8% (95%CI 38-94) for type B dissections (P=.300).

During follow-up, a surgical correction of the aneurysm was performed in 4 cases (1 right iliac artery, 3 left iliac artery), in 1 case due to rupture of aneurysmal right external iliac artery.

Malperfusion and new branch dissection. Eight malperfusion syndromes were detected after the acute phase, involving the superior mesenteric artery in 1 (13%) case, the renal arteries in 6 (75%) cases, and the iliac artery in 1 (13%). The resulting estimated 15-years freedom from malperfusion was 76% (95%CI 61-94) overall, 78.9% (95%CI 62-100) for type A dissections and 74.1% (95%CI 53-100) for type B (P=.590). The underlying mechanism was distal progression of the aortic dissection in 6 cases, and complete thrombosis of a branch's collapsed true lumen in 2 cases.

Twenty-five new branch dissections occurred in 13 patients (**Supplementary Figure 2**); the involved artery was the innominate artery in 4 (16%) patients, the left carotid artery in 3 (12%), the left subclavian artery in 2 (8%), the superior mesenteric artery in 2 (8%), the renal artery in 1 (4%), and the iliac arteries in 7 (28%). No one of these was associated with acute symptoms of malperfusion. One patient with a previous type B AD presented with a re-dissection involving the aortic arch, with concomitant new dissection of the innominate, left carotid and left subclavian arteries. All the remainders were incidentally detected during the follow-up imaging. One patient with a newly detected isolated innominate artery dissection developed an innominate artery aneurysm after 10.6 years.

Rupture. Only one iliac artery ruptured after 12 years from the initial presentation of a type B dissection. The patient was successfully treated in an emergent setting and survived. The estimated freedom from any non-aortic rupture was 94.4% (95%CI 84-100).

Any branch-related event. The summary of incidence and type of branch complication occurring during follow up is shown in **Table II**. Comparing the baseline characteristics of patients with any branch event vs patients without complications (**Supplementary Table I**) during follow-up, the main difference was a higher prevalence of distal aortic involvement (De

Bakey I or IIIb) in patients with any branch-related complication (89.4% vs 56.4%; P=.012). The estimated 15-years freedom from any aortic branches-related event was 48% (95%CI 32-70), 51% (95%CI 35-76) after exclusion of patients with connective tissue disorders. Specific rates by AD type were 60% (95%CI 38-94) for type A dissections and 43.2% (95%CI 24-67) for type B dissections (P=.049). Patients with extensive aortic involvement (De Bakey I or IIIb) had lower freedom from adverse events (36%, 95%CI 20-65) compared to AD with only proximal involvement (75%, 95%CI 53-100; P=.040). After adjustment using multivariable Cox proportional hazards modeling, Type B AD (HR 3.5, 95%CI 1.1-10.8; P=.033, **Figure 1A**), patency of the aortic false lumen (HR 6.8, 95% CI 1.1-42.2; P=.038, **Figure 1B**) and malperfusion syndrome at presentation (HR 6.0, 95% CI 1.3-28.6; P=.023) were predictors of aortic branches-related events after the acute phase. Other factors as initial surgical management (HR 0.83, 95%CI 0.34-2.06; P=.702) and connective tissue disease (HR 1.99, 95%CI 0.67-5.88; P=.539) were not significantly associated. Type B AD (HR 2.6, 95%CI 1.0-8.3; P=.049), patency of the aortic false lumen (HR 6.9, 95% CI 1.0-55.1; P=.046) and malperfusion syndrome at presentation (HR 6.4, 95% CI 1.1-36.6; P=.037) were confirmed to be significantly associated with aortic branch events also after exclusion of patients with connective tissue disease. In the subset of patients with distal aortic involvement, presentation with malperfusion (HR 4.7, 95%CI 1.0-23.2; P=.046) and connective tissue disorders (HR 4.2, 95%CI 1.1-15.9; P=.03) were predictors of branch-related events at the multivariate analysis.

Diameter change and growth rate. CTA imaging follow-up to assess diameter change was available for 439 aortic branches; 296 (67%) had no diameter change during follow-up, 128 (29%) had a diameter increase, and 15 (3%) had a diameter decrease. Overall growth rate was

1.3±3.0 mm/year; 1.3±3.0 mm/year for the supra-aortic vessels, 0.7±2.2 mm/year for the reno-visceral arteries, and 2.6±4.4 mm/year for the iliac arteries (P<.001).

At the multiple logistic regression (**Table III**), Marfan syndrome (OR 8.18, 95%CI 2.20-32.4; P=.002) patency of the aortic false lumen (OR 2.44, 95%CI 1.19-5.28; P=.018) and dissection of the aortic branch (OR 3.0, 95%CI 1.26-7.41; P=.014) were significantly associated with any diameter increase during follow-up, while female sex (OR 0.33, 95%CI 0.15-0.70; P=.004) and β-blockers prescription at discharge (OR 0.36, 95%CI 15-0.84; P=.019) were protective factors. More specifically, Marfan syndrome (P=.044), patency of the aortic false lumen (P=.022), and initial branch diameter (P=.003), were significantly associated with the overall aortic branch growth rate (**Table IV**). After stratification by arterial segments, the use of Angiotensin-converting enzyme inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB) (P=.013) or Calcium channel blocker (P=.043) were associated with slower growth rate of supra-aortic vessels; Marfan syndrome (P=.028) and dissection of the aortic branch (P=.043) were associated with the higher growth rate of the reno-visceral arteries. Patency of the aortic false lumen (P=.026) and the initial iliac diameter (P=.039) were associated with the iliac arteries diameter increase rate.

DISCUSSION

The incidence, mechanism, and clinical impact of aortic branches complications in patients with acute AD are already well-described [1,2,6].However, only a few studies focused on the long-term behavior of non-aortic arterial segments, mainly focusing on supra-aortic arch vessels[11,12] or Marfan patients[13,14], and the general morbidity and mortality derived from aortic branches-related events during the long-term follow-up are still incompletely defined.

This study used a contemporary population cohort of patients to provide updated information on the incidence and predictors of any branch-related intervention, aneurysm, malperfusion, rupture, or death occurring after the acute phase during a 15 years follow-up period. In particular, aortic branch freedom from branch events is less than 50% 15 years after the time of diagnosis and this results in significant long-term morbidity, without any related mortality. The most frequent type of complication was aneurysm formation, occurring in 33% of patients. The most affected site was the iliac segment, which appears to be concerning since 4/7 required future intervention and one ruptured. Differently, only 1 patient developed an aneurysm of the mesenteric or renal vessels, that were more prone to late malperfusions.

Type B AD had an increased risk of branch-related events compared to survivors after a type A AD (Adjusted HR 3.5; P=.033). A possible explanation is that in this cohort of patients, an extensive aortic involvement was more common in type B AD, as 80% were classified as De Bakey IIIb; as comparison, only 53% of type A ADs had distal aortic involvement. This is consistent with the observation that 17/19 (89%) patients who had any branch-related event during follow-up originally had a type I (n=5) or IIIb (n=12) AD (P=.012).

Also after adjustment for AD type, patency of the aortic false lumen (HR 6.8; P=.038), resulted a significant risk factor for future adverse events involving the aortic branches. Residual patency of the FL has already been described as a negative prognostic factor for both type A and B ADs[3,15-18], being associated with aortic growth, aortic reinterventions, and late mortality. This study shows that persistent patency of the aortic false lumen plays a role also on branch-related complications, probably maintaining a risk of true lumen collapse or AD progression into the aortic side branch. The presence of malperfusion at presentation (HR 6.0, 95% CI 1.3-28.6;

P=.023) seems to identify another subcategory of ADs that maintains a higher risk of vascular complications also during follow-up.

Only scarce information is available regarding the diameter change of non-aortic segments in patients with AD. Yamauchi et al.[12] described an overall 1mm/year diameter increase for supra-aortic arch arteries in patients with a previous type A dissection; they also found that patency of the false lumen of a dissected branch was associated with diameter increase. Yetman et al.[14] highlighted that one third of adult patients with Marfan syndrome develop peripheral artery aneurysms, especially in case of distal aortic dissection or in patients not receiving Angiotensin-converting enzyme inhibitors.

Our study shows that diameter increase of aortic branches was detected in one third of cases. Similarly to Yetman et al.[14] , dissection of the aortic branch (OR 3.0; P=.014) favored a diameter increase; it is not unexpected that also Marfan syndrome (OR 8.18; P=.002) and patency of the aortic false lumen (OR 2.44; P=.018) were also significantly associated with any diameter increase during follow-up. Similarly to what has been described for aortic diameter[19], the use of B-blockers (OR 0.36; P=.019) provided a protective effect from increase in branch vessels size. In particular, of the four Marfan patients included in this series, the aortic false lumen was patent in 3 cases and partially thrombosed in one; a branch-related event occurred in 3 of 4 cases (75%). The high incidence of adverse branch events may be related to specific characteristics of AD in Marfan patients, compared to non-Marfan patients, or to Marfan syndrome itself, independent from the presence of AD. However, the small number of patients does not allow to fully understand the underlying mechanism.

From the clinical standpoint, it may be argued that not all diameter increases can be considered significant. Therefore, we aimed to identify baseline factors that were associated with the growth

rate of aortic branches to define those at higher risk of growth. Marfan syndrome (P=.044) and patency of the aortic false lumen (P=.022) were again confirmed to promote a faster growth rate. Additionally, the risk of growth was also higher for arteries that were already enlarged at presentation (P=.003). Interestingly, the use of ACEi/ARBs or calcium channel blockers was the only modifiable factor that could influence the growth rate, but this finding was specific only for supra-aortic arch arteries. It is also interesting to note that residual patency of the aortic false lumen was the only factor that was associated with all the primary and secondary endpoints at the multivariable analysis: any branch event, any branch diameter increase, and branch growth rate.

Our study has several limitations that are worth mentioning. This is a retrospective study where the initial code-based identification of patients with AD may have led to inherent biases. Also, the limited number of patients included in the final cohort may have limited the power of the statistical analysis. In particular, it was not possible to discriminate the effect of complete versus partial thrombosis of the aortic false lumen on branch-related complications.

Our findings are strengthened by the fact that this population-based approach allowed to gather detailed follow-up information of patients and to report reliable long-term follow-up results, since our patient cohort is not subject to the referral bias that is usually seen in registry or single center reports. Also we tried to include in our primary endpoint only clinically significant events, excluding sub-aneurysmal arterial dilatations and imaging findings that were not associated with any clinical or laboratory manifestation. For the same reason, any diameter change, growth rate, and aneurysm formation of aortic branches were described separately. Finally, the finding of statically significant results in a relatively small sample size suggests that these factors truly have a clinically significant impact on the population of patients affected by AD.

CONCLUSION

In patients with AD, aortic branch involvement was responsible for a significant long-term morbidity, without related mortality. Type B AD, patency of the aortic false lumen, or malperfusion syndrome at presentation had a higher risk of branch events during the long-term follow-up. Progressive dilatation of the aortic branches was observed in one third of cases; in particular a patent aortic false lumen or Marfan syndrome may have positive effects on branch vessel complications. Future studies should focus on the impact of proper medical management to limit branch vessel growth and technical advances to promote false lumen thrombosis and aortic remodeling to prevent vascular complications in patients with a previous AD.

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Table I. Baseline characteristics of the 58 patients with a newly diagnosed AD.

	Total (n=58)	Type A (n=28)	Type B (n=30)
Age, years			
Mean±SD	66.6± 14.4	64.0±15.5	69.0±13.0
Range	27 - 90	27- 86	35- 90
Female sex	18 (31.0%)	8 (28.6%)	10 (33.3%)
Race			
White	53 (91.4%)	26 (92.9%)	27 (90.0%)
Black	1 (1.7%)	0 (0.0%)	1 (3.3%)
Hawaiian/Pacific islands	1 (1.7%)	1 (3.6%)	0 (0.0%)
Unknown	3 (5.2%)	1 (3.6%)	2 (6.7%)
BMI			
Mean±SD	28.3±6.5	27.3±3.8	29.2±8.4
Range	18.1- 62.8	18.2 - 36.2	18.1 - 62.8
Previous aortic surgery	6 (11.1%)	3 (12.5%)	3 (10.0%)
Connective tissue disorder			
No	52 (89.7%)	26 (92.9%)	26 (86.7%)
Marfan	4 (6.9%)	2 (7.1%)	2 (6.7%)
Ehlers Danlos, type IV	2 (3.4%)	0 (0.0%)	2 (6.7%)
Acuity of diagnosis			
Acute	39 (67.2%)	25 (89.3%)	14 (46.7%)
Subacute	2 (3.4%)	1 (3.6%)	1 (3.3%)
Chronic	2 (3.4%)	1 (3.6%)	1 (3.3%)
Unknown	15 (25.9%)	1 (3.6%)	14 (46.7%)
De Bakey classification			
I	15 (25.9%)	15 (53.6%)	-
II	13 (22.4%)	13 (46.4%)	-
IIIa	6 (10.3%)	-	6 (20.0%)
IIIb	24 (41.4%)	-	24 (80.0%)
False lumen status			
Patent	45 (77.6%)	24 (85.7%)	21 (70.0%)
Partial thrombosis	9 (15.5%)	3 (10.7%)	6 (20.0%)
Complete thrombosis	4 (6.9%)	1 (3.6%)	3 (10.0%)
Initial management			
Medical therapy	33 (56.9%)	5 (17.9%)	28 (93.3%)
Open surgery	23 (39.7%)	23 (82.1%)	0 (0.0%)
Endovascular surgery	2 (3.4%)	0 (0.0%)	2 (6.7%)
Medications at discharge			
B-blocker	47 (81.0%)	21 (75.0%)	26 (86.7%)
ACEi/ARB	23 (39.7%)	8 (28.6%)	15 (50.0%)
Calcium blocker	20 (34.5%)	8 (28.6%)	12 (40.0%)
Aspirin	35 (60.3%)	18 (64.3%)	17 (56.7%)
Anticoagulant	11 (19.0%)	9 (32.1%)	2 (6.7%)

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II Receptor Blockers.

Table II. Aortic branches-related events occurring after the acute phase in 58 patients with AD, during a 15-years follow-up period.

	Description of events	Survival function, % (95%CI)		P
Intervention	n=12 events in 10 patients: · 4 aneurysm (1 right iliac artery, 3 left iliac artery) · 2 malperfusion (1 left renal artery, 1 right iliac artery) · 1 graft replacement/bypass during aortic open repair (1 arch repair, 2 TAAA repair) · 2 fenestration of the intimal flap for stenting during F/BEVAR (2 left renal artery) · 1 intimal flap fenestration (right renal artery)	Overall	76 (63-92)	
		Type A	76 (59-97)	.500
		Type B	77 (59-99)	
		De Bakey II/IIIa	79 (56-100)	.198
		De Bakey I/IIIb	56 (30-100)	
		No CTD	79 (66-95)	.285
		CTD	63 (32-100)	
Aneurysm	n=10 events in 9 patients: · 1 innominate artery · 1 right subclavian/vertebral artery · 1 superior mesenteric artery · 3 right iliac artery · 4 left iliac artery	Overall	67 (50-90)	
		Type A	74 (50-100)	.300
		Type B	60 (38-94)	
		De Bakey II/IIIa	82 (62-100)	.500
		De Bakey I/IIIb	61 (40-93)	
		No CTD	69 (51-95)	.356
		CTD	50 (19-100)	
Malperfusion	n=8 events in 7 patients: · 1 superior mesenteric artery · 5 left renal artery · 1 right renal artery · 1 left iliac artery	Overall	76 (61-94)	
		Type A	79 (62-100)	.590
		Type B	74 (53-100)	
		De Bakey II/IIIa	80 (57-100)	.600
		De Bakey I/IIIb	74 (55-98)	
		No CTD	77 (61-96)	.900
		CTD	75 (43-100)	
Rupture	n=1 event in 1 patient: · 1 right iliac artery	Overall	94 (84-100)	
		Type A	100 (-)	.386
		Type B	90 (73-100)	
		De Bakey II/IIIa	100 (-)	.500
		De Bakey I/IIIb	92 (77-100)	
		No CTD	94 (83-100)	.680
		CTD	100 (-)	
Death	-	Overall	100 (-)	
		Type A	100 (-)	-
		Type B	100 (-)	
		De Bakey II/IIIa	100 (-)	-
		De Bakey I/IIIb	100 (-)	
		No CTD	100 (-)	-
		CTD	100 (-)	

CTD, connective tissue disorder; F/BEVAR, fenestrated/branched endovascular aortic repair; TAAA, thoracoabdominal aortic aneurysm.

Table III. Univariable and multivariable logistic regression for any diameter increase of aortic side branches during a 15 years follow-up period.

	Univariable		Multivariable	
	OR (95%CI)	**P**	**OR (95%CI)**	**P**
Age	0.99 (0.97-1.00)	0.257	1.02 (0.99-1.05)	.063
Female sex	0.52 (.30-0.87)	0.016[a]	0.33 (0.15-0.70)	.004[a]
BMI	1.01 (0.98-1.04)	0.480	-	-
B-blocker	1.04 (0.60-1.83)	0.883	0.36 (0.15-0.84)	.019[a]
ACEi/ARB	1.04 (0.67-1.62)	0.851	-	-
CCB	0.95 (0.59-1.49)	0.813	-	-
Type B AD	1.15 (0.74-1.78)	0.539	1.24 (0.69-2.25)	.467
Marfan syndrome	1.53 (0.75-3.08)	0.240	8.18 (2.20-32.4)	.002[a]
Patency of the FL	2.31 (1.33-4.13)	0.004[a]	2.44 (1.19-5.28)	.018[a]
Malperfusion	0.59 (0.21-1.46)	0.283	-	-
Branch dissection	2.75 (1.44-5.34)	0.002[a]	3.00 (1.26-7.41)	.014[a]
Branch FL thrombosis	1.28 (0.48-3.24)	0.609	-	-
Acute presentation	0.92 (0.58-1.46)	0.715	-	-
Initial branch diameter	1.02 (0.98-1.08)	0.297	-	-

AD, aortic dissection; ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II Receptor Blockers BMI, body mass index; CCB, calcium channel blocker; FL, false lumen.

Table IV. Results of the multivariate linear regression for aortic branches diameter change during follow-up.

	Coefficient (95%CI)	**P value**
Overall	mean, 1.3±3.0 mm/year	
Type B AD	0.6 (-0.2;1.4)	.145
Marfan syndrome	1.7 (0.0;3.4)	.044[a]
Patent aortic false lumen	1.0 (0.1;1.9)	.022[a]
Dissected branch vessel	1.0 (-0.2;2.2)	.131
Initial artery diameter	0.2 (0.1;0.3)	.003[a]
Supra-aortic vessels	mean, 1.3±3.0 mm/year	
ACEi/ARB	-1.7 (-3.0;-0.37)	.013[a]
Calcium channel blocker	-1.5 (-2.9;-0.12)	.033[a]
Patent aortic false lumen	1.2 (-0.2;2.7)	.098
Dissected branch vessel	-1.4 (-3.5-0.59)	.160
Reno-visceral arteries	mean, 0.7±2.2 mm/year	
Marfan syndrome	1.7 (0.2;3.2)	.028[a]
Dissected branch vessel	1.4 (0.0; 2.9)	.043[a]
Acute presentation	-0.4 (-1.1;0.4)	.304
Iliac arteries	mean, 2.6±4.4 mm/year	
Marfan syndrome	2.5 (-1.6;6.6)	.226
Patent aortic false lumen	2.3 (0.0;4.6)	.047[a]
Initial iliac diameter	0.3 (0.0;0.6)	.039[a]

AD, aortic dissection; ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II Receptor Blockers.
[a]Statistically significant.

Supplementary table I. Comparison of baseline characteristics of patients with any branch-related complications vs without complications after the acute phase of AD.

	Any branch-related event (n=19)	No branch-related events (n=39)	P
Age, years			.319
Mean±SD	63.8±14.4	67.9±14.4	
Range	27-85	27-90	
Female sex	6 (31.6%)	12 (30.8%)	.950
Race			.234
White	0 (0%)	1 (2.6%)	
Black	1 (5.3%)	0 (0%)	
Hawaiian/Pacific islands	16 (84.2%)	37 (94.9%)	
Unknown	2 (10.5%)	1 (2.6%)	
BMI			.870
Mean±SD	28±5.2	28.3±7.1	
Range	18-41	18-62	
Previous aortic surgery	1 (5.3%)	5 (14.3%)	.314
Connective tissue disorder			.082
No	15 (78.9%)	37 (94.9%)	
Marfan	2 (10.5%)	2 (5.1%)	
Elhers Danlos	2 (10.5%)	0 (0%)	
Acuity of diagnosis			.894
Acute	12 (63.2%)	27 (69.2%)	
Subacute	1 (5.3%)	1 (2.6%)	
Chronic	1 (5.3%)	1 (2.6%)	
Unknown	5 (26.3%)	10 (25.6%)	
De Bakey classification			.226
I	5 (26.3%)	10 (25.6%)	
II	2 (10.5%)	11 (28.2%)	
IIIa	0 (0%)	6 (15.4%)	
IIIb	12 (63.2%)	12 (30.7%)	
Distal aortic involvement (I/IIIb)	17 (89.4%)	22 (56.4%)	.012[a]
Stanford classification			.224
Type A	7 (36.8%)	21 (53.8%)	
Type B	12 (63.2%)	18 (46.1%)	
False lumen status			.233
Patent	17 (89.4%)	28 (71.8%)	
Partial thrombosis	2 (10.5%)	7 (17.9%)	
Complete thrombosis	0 (0%)	4 (6.9%)	
Initial management			.847
Medical therapy	11 (57.9%)	22 (56.4%)	
Open surgery	7 (36.8%)	16 (41.0%)	
Endovascular surgery	1 (5.3%)	1 (2.6%)	

[a]Statistically significant.

LEGENDS

Table I. Baseline characteristics of the 58 patients with a newly diagnosed AD.

Table II. Aortic branches-related events occurring after the acute phase in 58 patients with AD, during a 15-years follow-up period.

Table III. Univariable and multivariable logistic regression for any diameter increase (≥1 mm) of aortic side branches during a 15 years follow-up period.

Table IV. Results of the multivariate linear regression for aortic branches diameter change during follow-up.

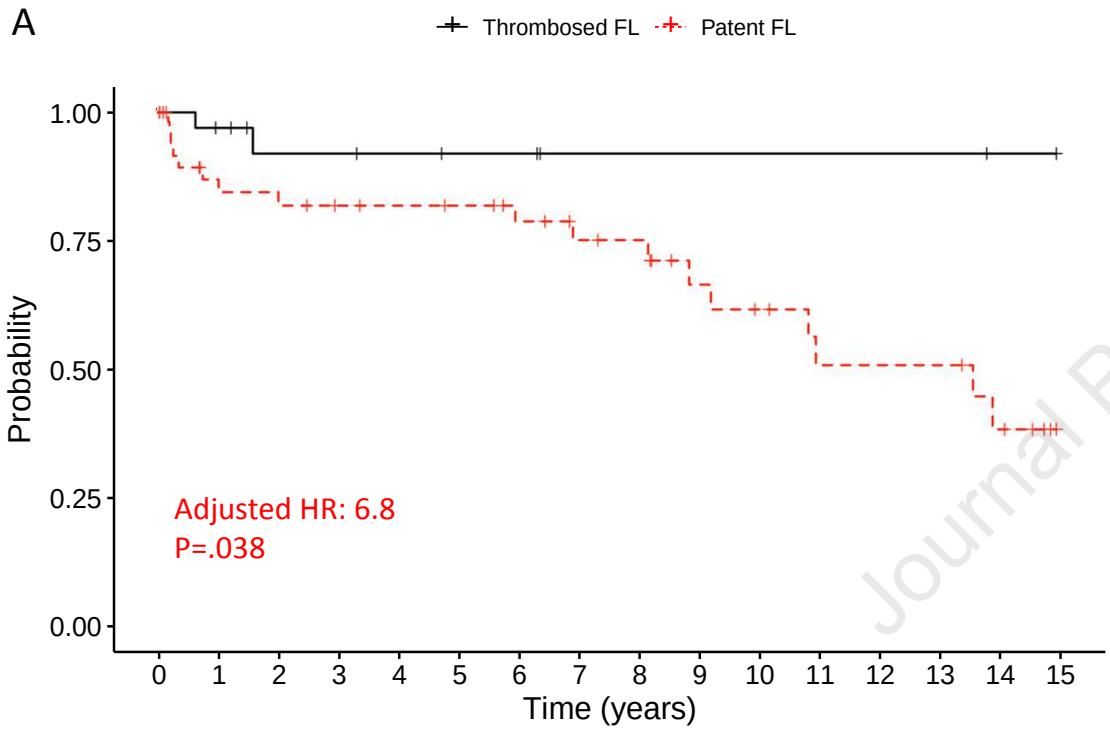
Figure 1. A) Adjusted freedom from any branch intervention, aneurysm, malperfusion, rupture or death at 15 years, stratified by Stanford classification. The curves are adjusted for false lumen status and presence of malperfusion at presentation using Cox proportional hazards. The * indicates Standard Error >10%. **B)** Adjusted freedom from any branch intervention, aneurysm, malperfusion, rupture or death at 15 years, stratified by aortic false lumen status. The curves are adjusted for Stanford classification and presence of malperfusion at presentation using Cox proportional hazards. The * indicates Standard Error >10%.

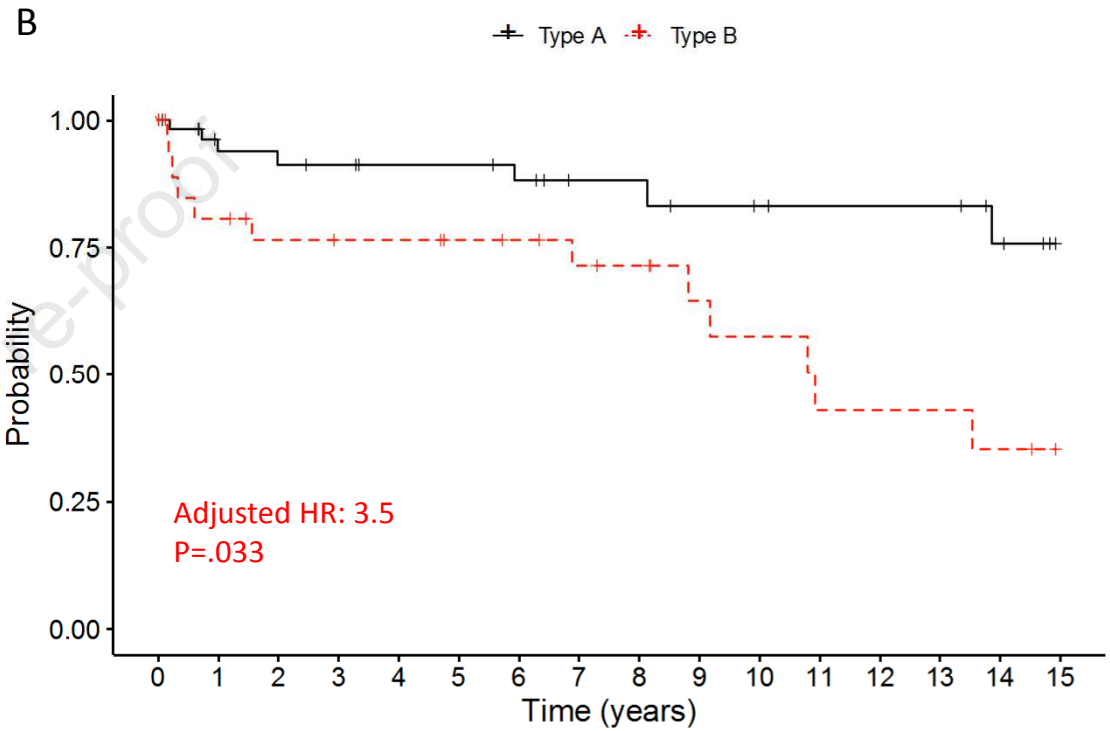
Supplementary Figure 1. Aneurysmatic evolution of the right common iliac artery in a patient with chronic type B aortic dissection. **A)** Baseline CTA. **B)** Follow-up CTA at 3 years. **C)** Follow-up CTA at 8 years.

Supplementary Figure 2. Evolution of a new isolated dissection of the left carotid artery in a patient with a chronic dissection of the aortic arch. **A)** Baseline CTA. **B)** The follow-up CTA at 6 months shows the presence of a new dissection of the left carotid artery (arrow). The patient was

completely asymptomatic **C)** Follow-up CTA at 3 years, showing remodeling with complete thrombosis of the false lumen (arrow). No related clinical events were observed during the follow-up.

Supplementary Table I. Comparison of baseline characteristics of patients with any branch-related complications vs without complications after the acute phase of AD.





N. at risk	13	12	8	8	7	6	6	4	4	4	4	4	4	4	3	3
SE	.00	.07	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09
N. at risk	45	33	32	29	28	27	25	24	20	15	13	11	10	10	7	3
SE	.00	.05	.06	.06	.06	.06	.07	.07	.07	.08	.08	.09	.09	.09	.10*	.10*

N. at risk	28	23	21	19	17	17	16	12	12	10	9	8	8	8	5	2
SE	.00	.05	.06	.07	.07	.07	.08	.08	.08	.09	.09	.09	.09	.09	.13*	.13*
N. at risk	30	23	20	19	19	17	16	14	13	10	9	8	7	7	6	5
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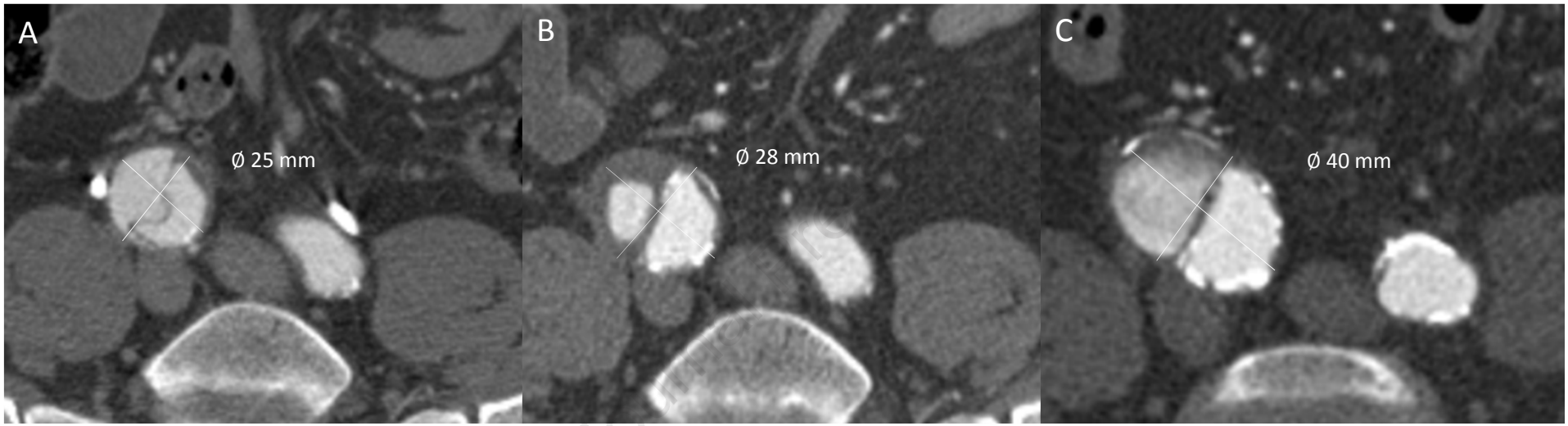
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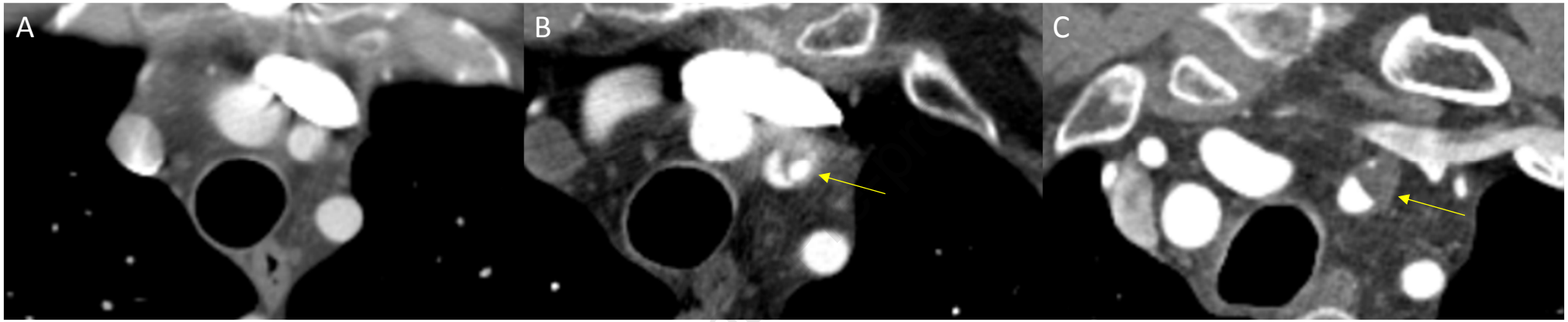

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