Outcome of Stanford type B dissection in patients with Marfan syndrome

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Visual abstract

Key question

What is the outcome of Stanford type B aortic dissection in Marfan patients?

Key finding(s)

The risk for TBAD in MFS patients is substantial, higher than previously reported and occurs far below accepted thresholds for intervention in the vast majority of patients.

Take-home message

Lifelong follow-up is of utmost importance in MFS patients.

Abstract

Objective

To determine the outcome of Stanford type B aortic dissection in patients with Marfan syndrome and to evaluate aortic diameters at time of dissection as well as the impact of previous aortic root replacement.

Methods

Analysis of all patients with Marfan syndrome fulfilling Ghent criteria seen at this institution since 1995 until 2022.

Results

Thirty-six (19%) out of 188 patients with Marfan syndrome suffered from Stanford type B aortic dissection during the study period. Mean aortic diameter at time of dissection was 39.0mm (95% CI: 35.6-42.3). Mean pre-dissection diameter (available in 25% of patients) was 32.1mm (95% CI: 28.0-36.3) and mean expansion was 19% (95% CI: 11.9-26.2). There was no correlation between age and diameter at time of dissection (<20, 21-30, 31-40, 41-50, 51-60, <61 years; p=0.78). Freedom-from-intervention after

dissection was 53%, 44%, 33% at 1, 5 and 10 years. Aortic growth rate in those patients that had to undergo intervention within the 1st year after dissection was 10.2mm/y (95% CI: 4.4-15.9) compared to 5.8mm/y (95% CI: 3.3-8.3), p=0.109 in those thereafter. Mean time between dissection and intervention was 1.8 years (95% CI: 0.6-3.0). While type B dissection seems more frequent after previous elective aortic repair (58% vs. 42%), there was no difference between valve-sparing root replacement (VSRR) compared to Bentall procedures (HR for VSRR 0.78, 95% CI: 0.31 – 2.0, p-value=0.61). Mean age of the entire population at end of follow-up was 42 years (95% CI: 39.2 – 44.7). Mean follow-up time was 9 years (95% CI: 7.8 – 10.4).

Conclusions

Stanford type B dissection in patients with Marfan syndrome occurs far below accepted thresholds for intervention. Risk for type B dissection is present throughout lifetime and two third of patients need an intervention after dissection. There is no difference in freedom from type B dissection between a Bentall procedure and a valve-sparing root replacement.

Glossary of Abbreviations

AAD = Acute aortic dissection

CT = Computed tomography

MFS = Patients with Marfan syndrome

MRI = Magnetic resonance imaging

TAAD = Stanford type A acute aortic dissection

TAAR = Thoracoabdominal aortic aneurysm replacement

TBAD = Stanford type B acute aortic dissection

TEVAR = Thoracic endovascular aortic repair

Introduction

Marfan syndrome (MFS) is an autosomal dominant disorder caused by pathogenic variations of FBN1 gene, encoding for the extracellular matrix protein fibrillin-1 (1-3). Morbidity and mortality in MFS patients are determined by acute aortic dissection (AAD) and its sequalae (4, 5). Prophylactic aortic root replacement has fundamentally changed the prognosis of patients with MFS. Nevertheless, morbidity and mortality have shifted from the aortic root towards the more distal aorta. Analysis of the Euro Heart Survey database revealed that 31% of aortic interventions in patients with MFS have been performed on the distal aorta (6). A retrospective study on 192 MFS patients revealed that 18% of primary interventions were due to lesions on the distal aorta (7). Furthermore, AAD is the main risk factor driving the need for re-interventions in MFS (8, 9). We have previously shown that 86% of MFS patients suffering from Stanford type B aortic dissection (TBAD) had to undergo re-operation during follow-up (8). However, despite the clinical impact of TBAD on morbidity and mortality, data on incidence, etiology and outcome of TBAD in MFS patients is scarce. This report aims to narrow the gap in evidence in patients with MFS.

Aim

Aim of the current study was to evaluate the outcome of Stanford type B dissections in MFS patients and to evaluate the aortic diameters at time of dissection. Furthermore, we wanted to weigh the impact of previous aortic root replacement.

Additionally, we compared the risk of intervention at the level of the thoracoabdominal aorta between patients with TBAD in comparison to patients after proximal repair for TAAD.

Methods

Ethics statement

The study was approved by the local ethics committee (Swiss Association of Research Ethics Committees (swissethics)) (approval no. 2019-01534).

Informed consent was waived given the retrospective nature of the study.

Patient selection and data collection

All MFS patients fulfilling Ghent criteria between January 1995 and April 2022 seen at this institution were included in this observational retrospective single-center study.

An observational design was used conforming to the STROBE statement (10). All data was gathered in a standardized database using the Research-Electronic-Data-Capture (REDCap) system. Patient characteristics, procedural data and outcomes are shown in Table 1.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Diagnosis

Until the identification of the FBN1 as the causal gene for MFS and until the publication of the Ghent nosology(11) in 1996 the patients with Marfan syndrome were diagnosed using a defined set of clinical criteria (Berlin nosology)(12). The Ghent nosology was revised in 2009 (13), with the implication that every patient that was seen after 2010 was reevaluated regarding the diagnosis. Moreover, while MFS has been a clinical diagnosis in the past, nowadays all patients with a suspicion of MFS undergo genetic testing to confirm the diagnosis even if the patient already fulfills Ghent criteria. In this study only patients with the diagnosis of MFS defined by the Ghent criteria and/or a pathogenic variant in FBN1 were included.

Every aortic intervention in our cohort was counted. Isolated valve replacement was not counted as an aortic intervention. Patients were followed in our MFS clinic 3, 6 and 12 months after elective surgery and then depending on the findings. Patients underwent complete imaging at least all 3 years even if the aorta was stable. Patients automatically receive an invitation for imaging and consultation at pre-specified intervals. Patients were evaluated using ECG-gated, CT angiography to plan surgery, as a follow-up in patients with dissections and in the acute setting. In uneventful cases and during follow-up, MR angiography was performed to reduce cumulative radiation exposure. Consent was obtained to contact their primary care provider regarding recent developments, changes in medication or imaging that has been performed outside our institution.

All imaging data (CT and MRI data) was re-evaluated to assure consistent measurements throughout the follow-up period and minimize inter-observer variability (PACS IDS7 version 21.2). Standardized measurements of the aortic arch, thoracic and abdominal aorta were conducted in all available images according to Standards of

reporting in open and endovascular aortic surgery (STORAGE guidelines) (14). Aortic expansion at time of dissection was calculated with the available aortic diameter before and after TBAD.

Furthermore, TBAD was categorized into uncomplicated, high-risk and complicated, according to the 2020 SVS/STS recommendations on reporting Stanford type B aortic dissection and the STS/AATS practice guidelines on the management of type B aortic dissection (15, 16). Uncomplicated TBAD was defined as a dissection with no evidence of rupture or end-organ malperfusion. The high-risk group included patients with TBAD who have refractory pain or hypertension and those with high-risk radiographic features. Refractory was defined as persisting pain or hypertension for >12 hours despite maximal medical therapy. The high-risk radiographic features, who have been associated with late aortic complications or need for interventions were defined as follow: Hemorrhagic pleural effusions, aortic diameter >40mm, radiographic only malperfusion, entry tear located on the lesser curve, and false lumen diameter >22mm. A complicated dissection was defined as a TBAD with rupture or malperfusion. Supplementary information for these definitions are found in the SVS/STS reporting standards for type B aortic dissection and the STS/AATS practice guidelines on the management of type B aortic dissection (15, 16).

Guideline established medical treatment was initiated in all patients with MFS. All patients received therapy with a betablocker and/or angiotensin receptor antagonist.

Statistical analysis

Data are presented as mean with confidence interval (CI) or median and interquartile range (IQR) depending on data distribution. In addition to descriptive statistics, a Fine and Gray analysis was performed with death as competing risk factor for freedom from aortic dissection, freedom from intervention and survival analysis.

Analysis was performed with Stata version 16 (StataCorp, College Station, Tx). For the contingency analysis we used Fisher's exact test, t-test or ANOVA. A p-value <0.05 was considered statistically significant.

Indication for surgery and surgical techniques

Institutional surgical strategy, management of cardiopulmonary bypass and circulatory arrest, including measures for cerebral protection have already been described elsewhere (8, 17) and in general followed the 2010 AHA guidelines for the diagnosis and management of patients with thoracic aortic disease and the 2014 ESC guidelines on the diagnosis and treatment of aortic disease (18, 19). Over the course of the study period, the thresholds to recommend elective aortic root surgery were lowered from initially 50-55mm until the early 2000s, over 50mm to now 45-50mm in patients suitable for valve-sparing aortic root replacement or progressive dilation of more than 3mm per year. Prophylactic root replacements were suggested in women wishing to conceive if aortic root size exceeded 40-45mm following ESC and AHA guidelines (18, 20). Aortic root replacement according to the modified Bentall technique or valve sparing root replacement (VSRR) using the reimplantation technique in suitable candidates was the treatment of choice in the present study. If the aorta at the level of the innominate artery was 35mm or larger, repair was extended into the arch by performing partial arch replacement. In patients presenting with TAAD, the distal anastomosis was performed with an open arch by removing the concavity of the aortic arch using moderate hypothermic circulatory arrest with bilateral antegrade cerebral perfusion. If total arch replacement was necessary, separate re-implantation of the supra-aortic branches using a vascular graft with multiple side-branches was preferred. While a partial arch replacement using hypothermic circulatory arrest and bilateral selective antegrade cerebral perfusion was considered standard-of-care in patients presenting with TAAD,

primary total arch replacement using the frozen elephant trunk technique was performed if needed in order to exclude tears in the arch or proximal descending aorta.

Management of type B dissection in MFS

In case of complicated TBAD, additional invasive imaging was performed when necessary. Medical treatment followed established guidelines using intravenous beta-blockers and nitrates followed by oral beta-blockers, ACE-inhibitors or angiotensin-receptor-blockers as well as additional anti-hypertensive agents if necessary to achieve a systolic target blood pressure of <120mmHg (16, 18, 21). Monitoring included invasive blood-pressure monitoring and urine output. Pain control was achieved by use of intravenous opiate analgesia. Further management and additional imaging depended on the initial findings. Repeated CT-scans were performed at 48 hours after the event and 2-6 weeks thereafter. If the dissection was stable, follow-up imaging was done at 3, 6, and 12 months after initial presentation. Surgical repair of the aortic arch and descending aorta was considered if the diameter exceeded 55 to 60mm or in case of rapid enlargement or apparent organ malperfusion. The use of endografts was avoided in MFS, unless a surgically created landing zone was already present. In recent years, a frozen-elephant trunk procedure was performed to create a stable landing-zone.

Outcomes

Four different outcomes were analysed:

1. To evaluate the long-term outcome of MFS patients with TBAD we measured and evaluated all aortic diameters in all available imaging in every patient with TBAD. Furthermore, we searched for all aortic interventions as well as mortality

during follow-up time. Accordingly, the sample size for this question included all patients with TBAD from the cohort.

2. In a second step we compared the aortic diameter of the MFS patients with TBAD between the different age groups to see if there are any differences between age and aortic diameter at time of TBAD or before. To answer this question, we used the same sample size as above.
3. To answer the question if aortic root replacement or repair has an impact of the occurrence of TBAD we searched for all patients with a Bentall procedure or valve-sparing root replacement and compared these two groups against each other. TBAD was defined as failure.
4. Lastly, we compared the intervention rate/risk of survived MFS patients after TAAD with TBAD patients. All interventions were defined as failure.

Results concerning pregnancy related events have already been reported elsewhere and we did not conduct further analysis (22).

Results

Overall

Overall, 188 MFS patients (mean age at last follow-up 42 years (95% CI: 39.2 – 44.7), 56% male patients) fulfilling Ghent criteria were identified. 139 patients underwent 284 aortic interventions.

Initial presentation with AAD

Out of 188 MFS patients, 39 (21%) initially presented with AAD (42 years (95% CI: 39.2 – 44.7) / 54% male). Of these, 29 (74%) suffered from TAAD and 10 (26%) from

TBAD. Out of the 149 patients without initial AAD 22 suffered TBAD during follow-up (Figure 1). TBAD rate per 100 patient-years was 0.5.

AAD during follow-up

During follow-up, 26 patients (22 out of the 149 patients without initial AAD and four with previous TAAD) suffered from TBAD, resulting in a total number of 36 (19%) patients with TBAD in the study population. Four patients with TBAD had additionally developed unrelated TAAD whereas four patients with TAAD dissection were affected by TBAD (Figure 1).

There was no difference between mean age at time of TAAD and the mean age at time of TBAD (40years (95% CI: 35-45) vs. 41years (95% CI: 36-46), t-test p-value=0.757) (Figure 2).

TBAD patient characteristics

Thirteen (36%) patients had an uncomplicated, fourteen (39%) a high-risk and nine (25%) patients suffered from complicated TBAD.

Diameter of the descending aorta at time of presentation with TBAD showed no difference between age groups (p=0.86) (Figure 3a).

Mean aortic diameter at time of TBAD was 39.0mm (95% CI: 35.6-42.3). Mean pre-dissection diameter (available in 25% of patients) was 32.1mm (95% CI: 28.0-36.3). Mean expansion at time of dissection was 19% (95% CI: 11.9-26.2). Aortic growth rate in those patients that had to undergo intervention within the 1st year after TBAD was 10.2mm/y (95% CI: 4.4-15.9) compared to 5.8mm/y (95% CI: 3.3-8.3), p=0.109 in those thereafter (Figure 3b).

Intervention

Patients with TBAD

Fifteen (42%) of all 36 patients with TBAD initially or during follow-up had an intervention during the first year after TBAD (Figure 3b and 4). Overall, 24 (67%) of all TBAD patients needed any kind of surgical or endovascular intervention during follow-up (Figure 4 and Table 2). Mean time to intervention was 1.8years (95% CI: 0.6-3.0). Freedom-from-intervention after TBAD was 53%, 44%, 33% at 1, 5 and 10 years, respectively.

Five patients with uncomplicated TBAD and nine patients with high-risk TBAD needed an intervention due to progression in aortic diameters. One patient with initially uncomplicated TBAD after trauma developed malperfusion during follow-up and underwent operation in the same year. Eight patients with complicated and one patient with uncomplicated TBAD had an intervention due to malperfusion.

Overall, out of 36 patients with TBAD, 21 patients underwent aortic root interventions before TBAD occurred and 30 aortic root interventions in total. Furthermore 87 aortic interventions took place in 36 patients (Table 2). Four re-interventions were performed during follow-up in patients with TBAD.

Patients with TBAD had significantly more interventions during follow-up at the level of the thoracoabdominal aorta in comparison to patients after survived/operated TAAD (HR of 4.77, 95% CI: 2.29 – 9.97, p-value <0.001) (Figure 5).

In patients with TBAD, 58% had previous elective aortic root repair and 22% of all MFS patients with aortic root repair experienced TBAD.

There was no significant difference in freedom from TBAD in patients who underwent valve-sparing root replacement (VSSR) in comparison to patients who underwent a Bentall procedure (HR for VSSR = 0.78, 95% CI 0.31 – 2.0, p-value = 0.61) (Figure 6).

All TBAD patients that underwent TAAR had a Crawford type II aneurysm, except for one with Crawford type III aneurysm.

Follow-up and Mortality

Overall mean follow-up time was 9 years (95% CI: 7.8-10.4). In patients with TBAD all-cause mortality was 9%, 9%, 14%, 16% and 22% at 30 days, 1 year, 5 years, 10 years and overall, respectively.

Discussion

The current data confirms that TBAD represents a substantial source of morbidity and mortality in patients with MFS. While it has been reported in the past that TBAD represents only a small fraction of patients presenting with dissection, in this series including all MFS patients seen at a tertiary care center, 19% of patients suffered from TBAD (23). We assume the higher rate of TBAD is explained by the longer follow-up and the higher age of the population. For example in a Dutch study with 600 MFS patients 54 patients suffered TBAD, however the mean age was 36±14 years, whereas our population has a mean age of 42 years (95% CI: 39.2 – 44.7) (24). In another study from France only 6 TBAD occurred in 954 patients (25). Nevertheless, the study population is different: In the Milleron et al study, patients with previous aortic surgery were excluded. This is a bias since the patients with previous surgery are more likely to be older and have a more severe aortic phenotype. Therefore, this does not represent the true epidemiology. Secondly, patients with dissections in the descending aorta were excluded as well. Therefore, the population is much younger than our population (mean age 23 years versus 42 years).

Aortic diameter has been shown to be a risk factor for AAD. However, the current data suggests, that TBAD in MFS patients occurs below threshold diameters for elective

intervention in the vast majority of patients. In the current study, mean aortic diameter at the time of TBAD was at 39.0mm (95% CI: 35.6-42.3) and the pre-dissection diameter (available in 25% of patients) was 32.1mm (95% CI: 28.0-36.3). In a large Dutch multicenter study the authors reported that a descending aortic diameter of ≥27 mm was associated with an increased risk for TBAD (24). Although we did not measure the diameter in the population without TBAD, indeed no dissection occurred below this diameter.

Additionally, there were no correlations between age and aortic diameter at time of TBAD. In the IRAD registry, one-fifth of (mostly non-MFS) patients did not exhibit any aortic dilation at the time of dissection (aortic diameter <3.5cm), which suggests that this phenomenon is not unique to MFS (26).

Furthermore, we correlated age and aortic diameter at the time of TBAD but did not find any significant differences. Therefore, patient age does not seem to influence the probability of TBAD.

We further focused on proximal aortic repair as a potential factor influencing incidence of TBAD in MFS. It is unclear whether elective aortic root replacement adds to the risk of TBAD due to increase of wall stiffness or if replacing the aneurysm will stabilize more distal segments of the aorta (27). In our population valve-sparing aortic root replacement compared to a Bentall procedure showed no significant difference in freedom from TBAD. However, 56% of all patients with TBAD had a previous aortic root replacement and 22% of all MFS with root replacement had TBAD. This is in line with findings from the Euro Heart Survey, where the rate of events in the distal aorta in MFS patients with previous elective proximal aortic surgery was increased (6). This has previously been explained by a more advanced stage of disease in patients that have already undergone aortic root surgery.

It has been shown that patients with TAAD have a significantly higher distal reoperation rate compared with patients who underwent initial surgery for an aneurysm (28). We now show that interventions at the level of the thoracoabdominal aorta in patients after TBAD are more frequent than in patients after proximal repair for TAAD. A possible explanation is that the primary entry in TAAD is closed, respectively resected, which is not the case in patients with conservative treatment for TBAD. This finding emphasizes the concept of closure of the large and/or proximal entry tears to avoid subsequent aneurysmal dilatation. A Korean study has shown that MFS is a significant risk factor for late aortic events after thoracic or thoracoabdominal aortic replacement for chronic dissection (29). This underlines the need for close follow up of MFS patients.

Therefore, we recommend an initial CT at time of TBAD, and repeated CT-scans at 48 hours after the event and 2-6 weeks thereafter. If the dissection is stable, follow-up imaging should be done at 3, 6, and 12 months after initial presentation. Thereafter we recommend surveillance imaging every 2-3 years depending on risk factors and situation.

Limitations

This study presents a retrospective observational analysis and is therefore subject to all limitations of such a study design. Although follow-up is complete, not all patients received a CT or MRI scan right before TBAD and therefore it was not possible to calculate the true absolute growth rate after dissection for each individual patient. In our interdisciplinary Marfan clinic, we see all patients with Marfan syndrome and not only those that have a history of surgery. We included all patients from the clinic database into the study. Therefore, there is no bias, which would preclude conclusions with regard to patients with Marfan syndrome in general.

Conclusions

The current data suggests a substantial and higher risk of TBAD in MFS than previously reported. Patients are at risk throughout their lifetime.

TBAD in MFS patients occurs far below accepted aortic diameter thresholds for intervention and require therefore lifelong follow-up. There is no significant difference in freedom from TBAD between patients after Bentall procedure and valve-sparing aortic root replacement. Almost 50% of MFS patients undergo intervention during the first year after TBAD.

Funding statement

No funding was obtained for this study.

Conflict of interest statement

None

Table and figure legend

Table 1: Baseline characteristic of study population: Data are presented as mean with 95% confidence interval or n (%). TBAD, Stanford type B dissection; TAAR, Thoracoabdominal aortic aneurysm repair

Table 2: Interventions in patients with TBAD. TBAD, Stanford type B dissection; TAAR, Thoracoabdominal aortic aneurysm repair; TEVAR, Thoracic endovascular aortic repair.

Figure 1: Acute aortic dissection in the study population: A flow chart showing patient distribution between groups

Figure 2: Kaplan-Meier graph depicting age at first aortic dissection in patients with Marfan syndrome

Figure 3: A: Box-Plot Figure showing correlation of age and aortic diameter before and at the time of Stanford type B dissection. (Age group 1: 0-19years; 2: 20-29years; 3: 30-39years and so forth)
B: Box-Plot Figure showing growth rate during first year after Stanford type B dissection in millimeter and need for intervention

Figure 4 (central image): All patients with Stanford type B dissection with age at dissection, indication for intervention, and/or age at time of death.

Figure 5: Kaplan-Meier graph depicting age at time of aortic intervention in patients with Marfan syndrome with either TBAD or survived/operated TAAD.

Figure 6: Kaplan-Meier graph depicting Stanford type B dissection in years after aortic root replacement

433 **Tables**

Baseline characteristics	n=188
Age in years	42 years (95% CI: 39.2 – 44.7)
Male sex	56%
FBN1 confirmed in genetic testing	65%
Initially presenting with dissection Stanford type A Stanford type B	39 (21%) 29 (15%) 10 (5%)
Dissection initially or during follow up Stanford type A Stanford type B	 29 (15%) 32 (17%)
All aortic interventions	284
Mean diameter before TBAD in mm	32.1 (95% CI: 28.0-36.3)
Mean time to intervention after TBAD in years	1.8 (95% CI: 0.6-3.0)

434 Table 1: Baseline characteristic of study population: Data are presented as mean with

435 95% confidence interval or n (%). TBAD, Stanford type B dissection

Number of interventions in patients with TBAD	First intervention caused by TBAD	At end of follow-up
TAAR	11	15
Abdominal aortic replacement	3	10
Fenestrations with or without stent implantation	5	7
Descending aortic replacement	2	2
Aortic arch replacement		7
TEVAR	3	11
Supracroronary aortic replacement	-	7
Aortic root repair or replacement (Bentall procedure)	-	29
Re-operation	-	4

Aortic root intervention in TBAD	Interventions before TBAD	Total number of interventions
Bentall procedure	13	22
Valve sparing aortic root replacements	7	7
Homograft	1	1

Table 2: Interventions in patients with TBAD. TBAD, Stanford type B dissection; TAAR, Thoracoabdominal aortic aneurysm repair; TEVAR, Thoracic endovascular aortic repair.

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Figure 1

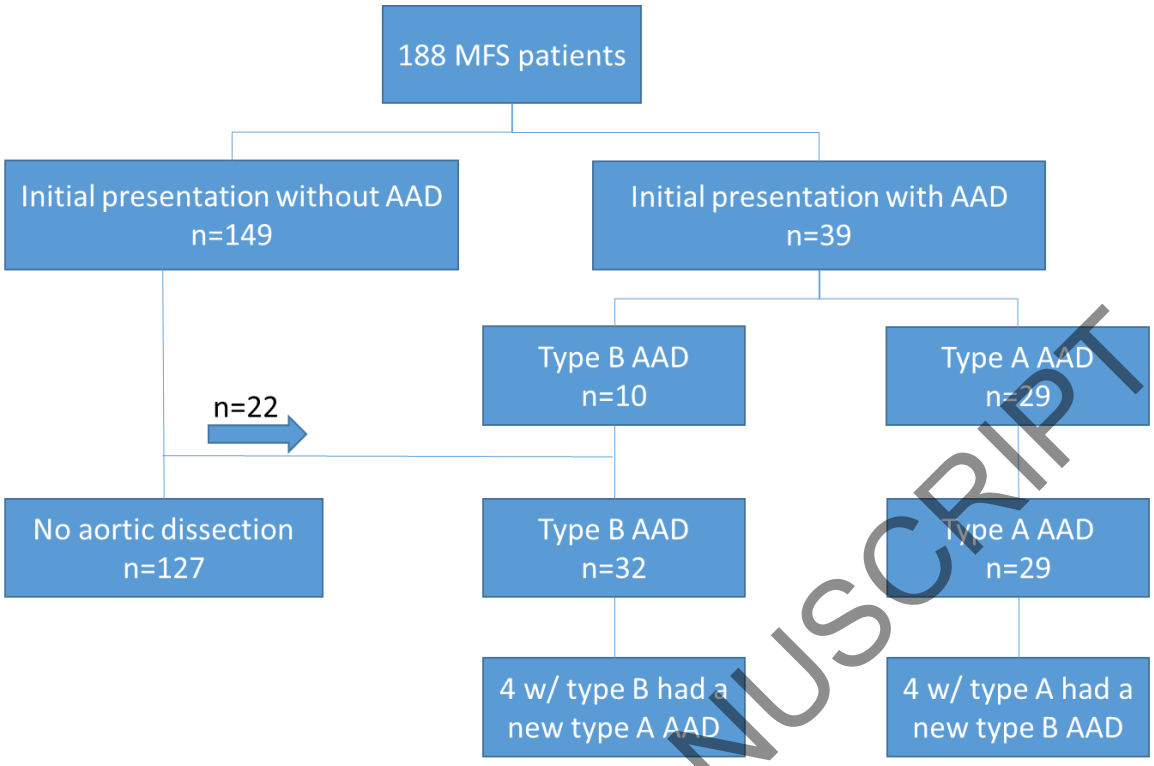


Figure 2

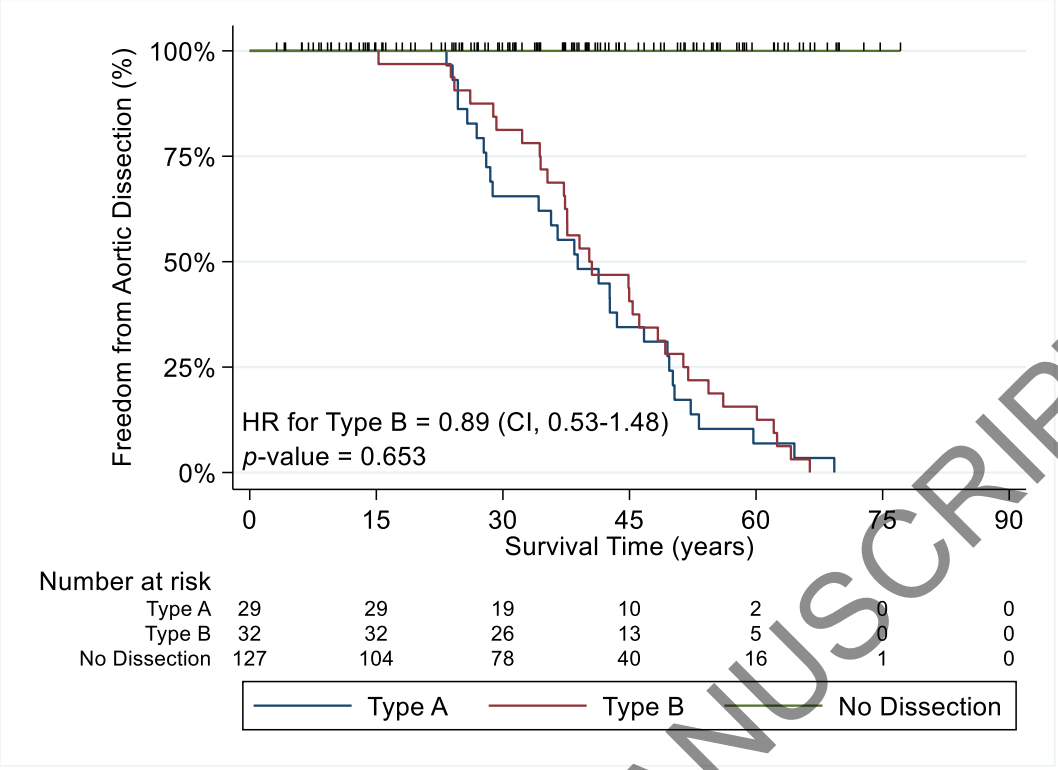
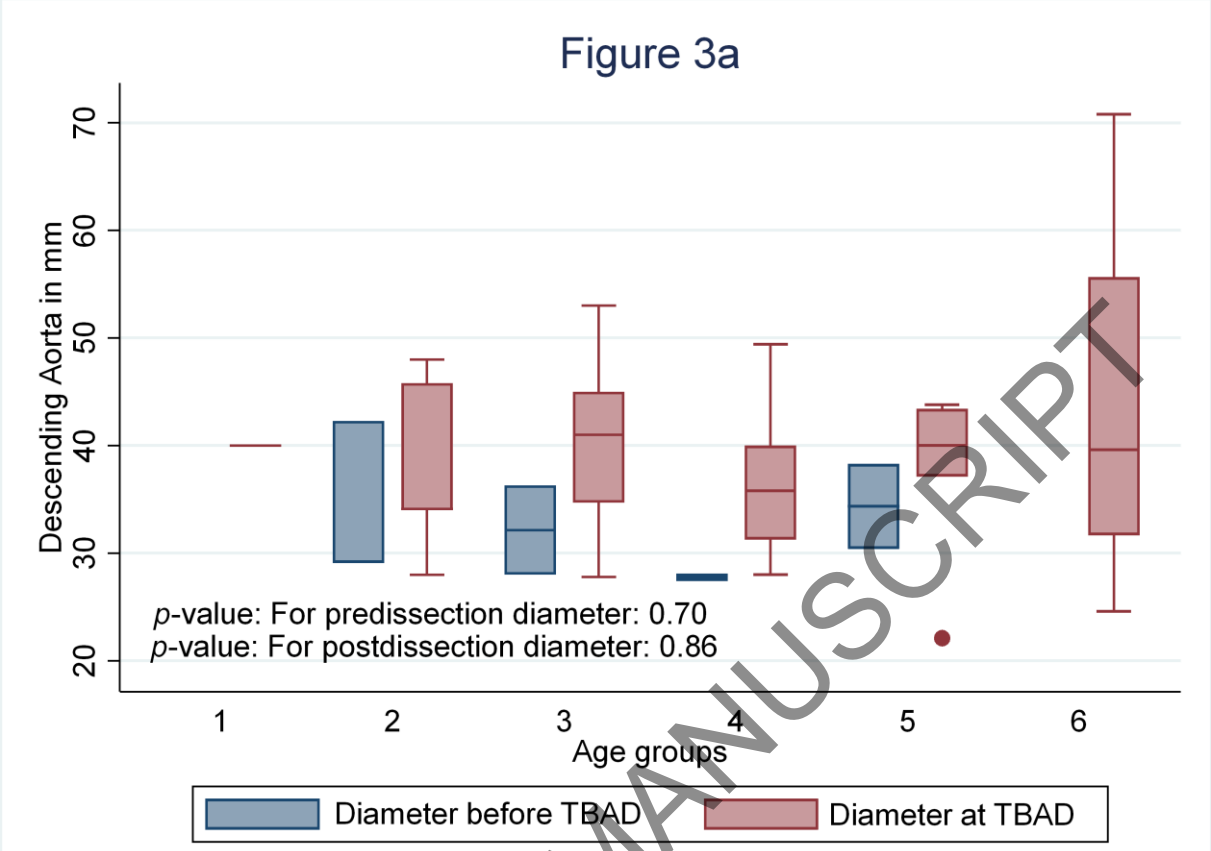
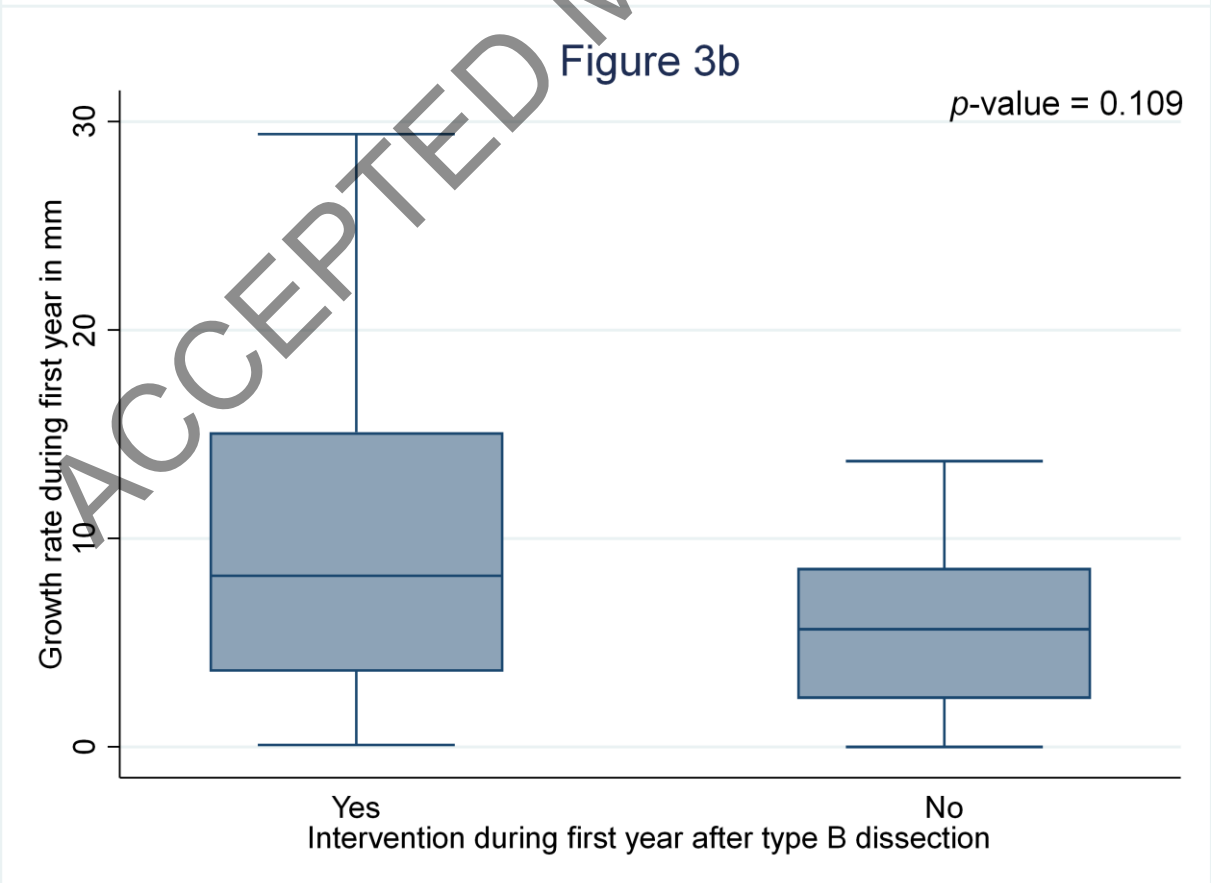


Figure 3





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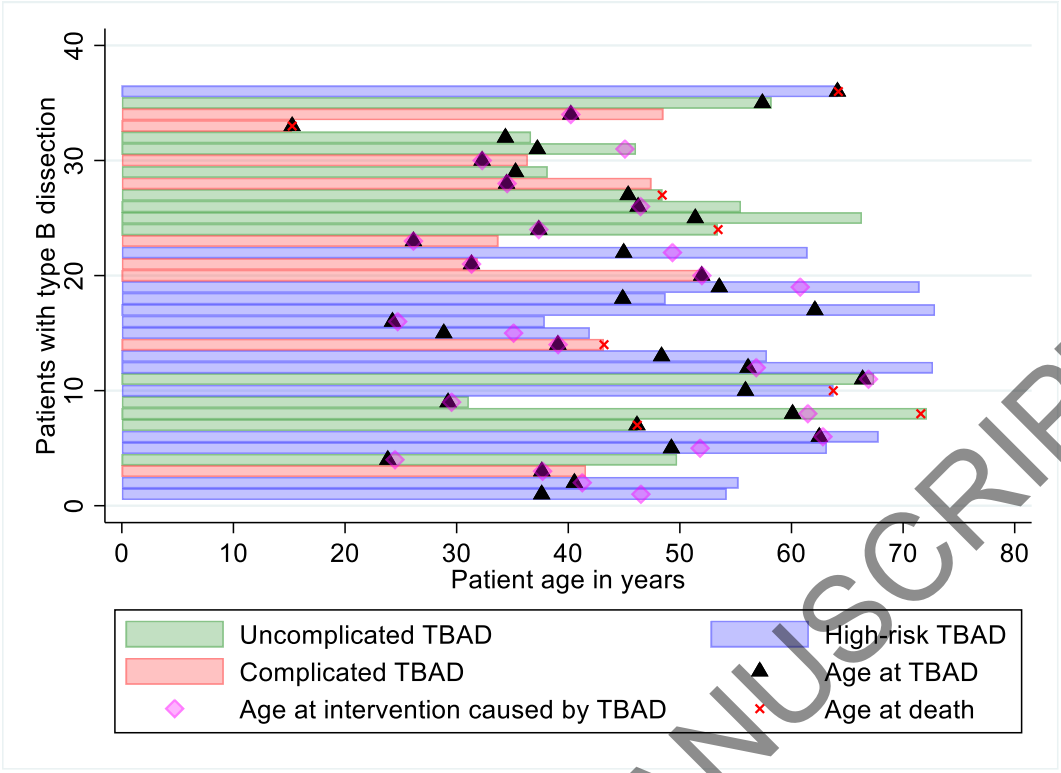

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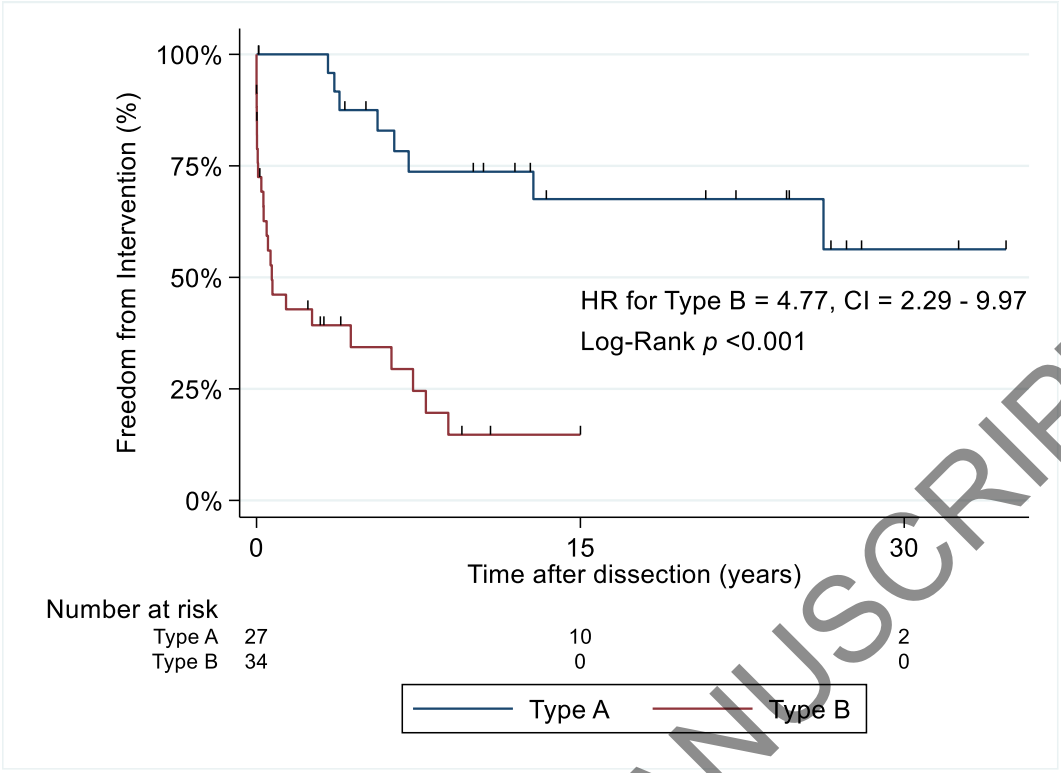

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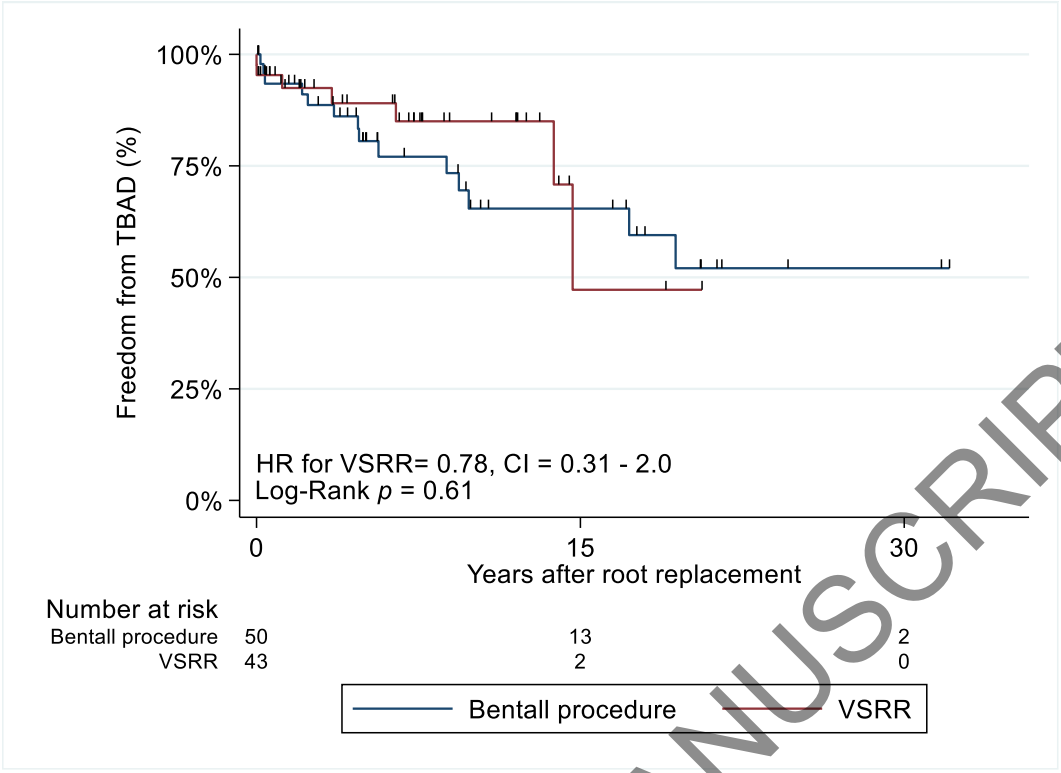

Central image