

1 Outcome of Stanford type B dissection in patients with Marfan syndrome

2

3

4 Murat Yildiz, MD; Maria Nucera, MD, Silvan Jungi, MD; Paul Philipp Heinisch, MD;
5 Selim Mosbahi, MD; Daniel Becker, MD; Matthias Siepe, MD; Florian Schoenhoff,
6 MD

7

8

9

10 Department of Cardiac Surgery, Inselspital Bern, University Hospital Bern, Bern,
11 Switzerland

12

13 Conflict of interest: None

14

15 Source of funding: No funding was obtained for this study.

16

17 Institutional Review Board: approval no. 2019-01534

18

19

20

21 Word count: 2736

22

23

24

25

26 Corresponding author:

27 Murat Yildiz, MD

28 Department of Cardiac Surgery

29 University Hospital Bern

30 3010 Bern, Switzerland

31 Phone: +41 31 6322111

32 Fax: +41 31 6324443

33 E-Mail: murat.yildiz@insel.ch

1

34 **Visual abstract**

35 Key question

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

37

38 Key finding(s)

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

41

42 Take-home message

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

44

45 **Abstract**

46

47 **Objective**

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

51

52 **Methods**

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

55

56 **Results**

57 Thirty-six (19%) out of 188 patients with Marfan syndrome suffered from Stanford type
58 B aortic dissection during the study period. Mean aortic diameter at time of dissection
59 was 39.0mm (95% CI: 35.6-42.3). Mean pre-dissection diameter (available in 25% of
60 patients) was 32.1mm (95% CI: 28.0-36.3) and mean expansion was 19% (95% CI:
61 11.9-26.2). There was no correlation between age and diameter at time of dissection
62 (<20, 21-30, 31-40, 41-50, 51-60, <61 years; p=0.78). Freedom-from-intervention after

63 dissection was 53%, 44%, 33% at 1, 5 and 10 years. Aortic growth rate in those
64 patients that had to undergo intervention within the 1st year after dissection was
65 10.2mm/y (95% CI: 4.4-15.9) compared to 5.8mm/y (95% CI: 3.3-8.3), p=0.109 in
66 those thereafter. Mean time between dissection and intervention was 1.8 years (95%
67 CI: 0.6-3.0). While type B dissection seems more frequent after previous elective aortic
68 repair (58% vs. 42%), there was no difference between valve-sparing root replacement
69 (VSRR) compared to Bentall procedures (HR for VSRR 0.78, 95% CI: 0.31 – 2.0, p-
70 value=0.61). Mean age of the entire population at end of follow-up was 42 years (95%
71 CI: 39.2 – 44.7). Mean follow-up time was 9 years (95% CI: 7.8 – 10.4).

72

73 **Conclusions**

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

ACCEPTED MANUSCRIPT

79 **Glossary of Abbreviations**

80 AAD = Acute aortic dissection

81 CT = Computed tomography

82 MFS = Patients with Marfan syndrome

83 MRI = Magnetic resonance imaging

84 TAAD = Stanford type A acute aortic dissection

85 TAAR = Thoracoabdominal aortic aneurysm replacement

86 TBAD = Stanford type B acute aortic dissection

87 TEVAR = Thoracic endovascular aortic repair

88

89 **Introduction**

90 Marfan syndrome (MFS) is an autosomal dominant disorder caused by pathogenic
91 variations of FBN1 gene, encoding for the extracellular matrix protein fibrillin-1 (1-3).
92 Morbidity and mortality in MFS patients are determined by acute aortic dissection
93 (AAD) and its sequelae (4, 5). Prophylactic aortic root replacement has fundamentally
94 changed the prognosis of patients with MFS. Nevertheless, morbidity and mortality
95 have shifted from the aortic root towards the more distal aorta. Analysis of the Euro
96 Heart Survey database revealed that 31% of aortic interventions in patients with MFS
97 have been performed on the distal aorta (6). A retrospective study on 192 MFS patients
98 revealed that 18% of primary interventions were due to lesions on the distal aorta (7).
99 Furthermore, AAD is the main risk factor driving the need for re-interventions in MFS
100 (8, 9). We have previously shown that 86% of MFS patients suffering from Stanford
101 type B aortic dissection (TBAD) had to undergo re-operation during follow-up (8).
102 However, despite the clinical impact of TBAD on morbidity and mortality, data on
103 incidence, etiology and outcome of TBAD in MFS patients is scarce. This report aims
104 to narrow the gap in evidence in patients with MFS.

105 **Aim**

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

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

112

113 **Methods**

114

115 **Ethics statement**

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

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

119

120 **Patient selection and data collection**

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

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

127

128 **Data availability statement**

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

131

132 **Diagnosis**

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

142 Every aortic intervention in our cohort was counted. Isolated valve replacement was
143 not counted as an aortic intervention. Patients were followed in our MFS clinic 3, 6 and
144 12 months after elective surgery and then depending on the findings. Patients
145 underwent complete imaging at least all 3 years even if the aorta was stable. Patients
146 automatically receive an invitation for imaging and consultation at pre-specified
147 intervals. Patients were evaluated using ECG-gated, CT angiography to plan surgery,
148 as a follow-up in patients with dissections and in the acute setting. In uneventful cases
149 and during follow-up, MR angiography was performed to reduce cumulative radiation
150 exposure. Consent was obtained to contact their primary care provider regarding
151 recent developments, changes in medication or imaging that has been performed
152 outside our institution.

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

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

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

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

177

178 **Statistical analysis**

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

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

186

187 **Indication for surgery and surgical techniques**

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

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

211

212 **Management of type B dissection in MFS**

213 In case of complicated TBAD, additional invasive imaging was performed when
214 necessary. Medical treatment followed established guidelines using intravenous beta-
215 blockers and nitrates followed by oral beta-blockers, ACE-inhibitors or angiotensin-
216 receptor-blockers as well as additional anti-hypertensive agents if necessary to
217 achieve a systolic target blood pressure of <120mmHg (16, 18, 21). Monitoring
218 included invasive blood-pressure monitoring and urine output. Pain control was
219 achieved by use of intravenous opiate analgesia. Further management and additional
220 imaging depended on the initial findings. Repeated CT-scans were performed at 48
221 hours after the event and 2-6 weeks thereafter. If the dissection was stable, follow-up
222 imaging was done at 3, 6, and 12 months after initial presentation. Surgical repair of
223 the aortic arch and descending aorta was considered if the diameter exceeded 55 to
224 60mm or in case of rapid enlargement or apparent organ malperfusion. The use of
225 endografts was avoided in MFS, unless a surgically created landing zone was already
226 present. In recent years, a frozen-elephant trunk procedure was performed to create a
227 stable landing-zone.

228

229 **Outcomes**

230 Four different outcomes were analysed:

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

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

236 2. In a second step we compared the aortic diameter of the MFS patients with
237 TBAD between the different age groups to see if there are any differences
238 between age and aortic diameter at time of TBAD or before. To answer this
239 question, we used the same sample size as above.

240 3. To answer the question if aortic root replacement or repair has an impact of the
241 occurrence of TBAD we searched for all patients with a Bentall procedure or
242 valve-sparing root replacement and compared these two groups against each
243 other. TBAD was defined as failure.

244 4. Lastly, we compared the intervention rate/risk of survived MFS patients after
245 TAAD with TBAD patients. All interventions were defined as failure.

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

248

249 **Results**

250

251 **Overall**

252 Overall, 188 MFS patients (mean age at last follow-up 42 years (95% CI: 39.2 – 44.7),
253 56% male patients) fulfilling Ghent criteria were identified. 139 patients underwent 284
254 aortic interventions.

255

256 **Initial presentation with AAD**

257 Out of 188 MFS patients, 39 (21%) initially presented with AAD (42 years (95% CI:
258 39.2 – 44.7) / 54% male). Of these, 29 (74%) suffered from TAAD and 10 (26%) from

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

261

262 **AAD during follow-up**

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

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

271

272 **TBAD patient characteristics**

273 Thirteen (36%) patients had an uncomplicated, fourteen (39%) a high-risk and nine
274 (25%) patients suffered from complicated TBAD.

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

277 Mean aortic diameter at time of TBAD was 39.0mm (95% CI: 35.6-42.3). Mean pre-
278 dissection diameter (available in 25% of patients) was 32.1mm (95% CI: 28.0-36.3).

279 Mean expansion at time of dissection was 19% (95% CI: 11.9-26.2). Aortic growth rate
280 in those patients that had to undergo intervention within the 1st year after TBAD was
281 10.2mm/y (95% CI: 4.4-15.9) compared to 5.8mm/y (95% CI: 3.3-8.3), p=0.109 in
282 those thereafter (Figure 3b).

283

284 **Intervention**

285

286 **Patients with TBAD**

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

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

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

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

305

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

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

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

313

314 **Follow-up and Mortality**

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

318

319 **Discussion**

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

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

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

344
345 Additionally, there were no correlations between age and aortic diameter at time of
346 TBAD. In the IRAD registry, one-fifth of (mostly non-MFS) patients did not exhibit any
347 aortic dilation at the time of dissection (aortic diameter < 3.5 cm), which suggests that
348 this phenomenon is not unique to MFS (26).

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

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

363 It has been shown that patients with TAAD have a significantly higher distal reoperation
364 rate compared with patients who underwent initial surgery for an aneurysm (28). We
365 now show that interventions at the level of the thoracoabdominal aorta in patients after
366 TBAD are more frequent than in patients after proximal repair for TAAD. A possible
367 explanation is that the primary entry in TAAD is closed, respectively resected, which is
368 not the case in patients with conservative treatment for TBAD. This finding emphasizes
369 the concept of closure of the large and/or proximal entry tears to avoid subsequent
370 aneurysmal dilatation. A Korean study has shown that MFS is a significant risk factor
371 for late aortic events after thoracic or thoracoabdominal aortic replacement for chronic
372 dissection (29). This underlines the need for close follow up of MFS patients.
373 Therefore, we recommend an initial CT at time of TBAD, and repeated CT-scans at 48
374 hours after the event and 2-6 weeks thereafter. If the dissection is stable, follow-up
375 imaging should be done at 3, 6, and 12 months after initial presentation. Thereafter we
376 recommend surveillance imaging every 2-3 years depending on risk factors and
377 situation.

378

379 **Limitations**

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

388

389 **Conclusions**

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

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

397

398 **Funding statement**

399 No funding was obtained for this study.

400

401 **Conflict of interest statement**

402 None

403

404 **Table and figure legend**

405 Table 1: Baseline characteristic of study population: Data are presented as mean with
406 95% confidence interval or n (%). TBAD, Stanford type B dissection; TAAR,
407 Thoracoabdominal aortic aneurysm repair

408

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

412

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

415

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

418

419 Figure 3: A: Box-Plot Figure showing correlation of age and aortic diameter before and
420 at the time of Stanford type B dissection. (Age group 1: 0-19years; 2: 20-29years; 3:
421 30-39years and so forth)

422 B: Box-Plot Figure showing growth rate during first year after Stanford type B dissection
423 in millimeter and need for intervention

424

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

427

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

430

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

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	39 (21%)
Stanford type A	29 (15%)
Stanford type B	10 (5%)
Dissection initially or during follow up	
Stanford type A	29 (15%)
Stanford type B	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
Supracoronary 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

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

439

440 References

441

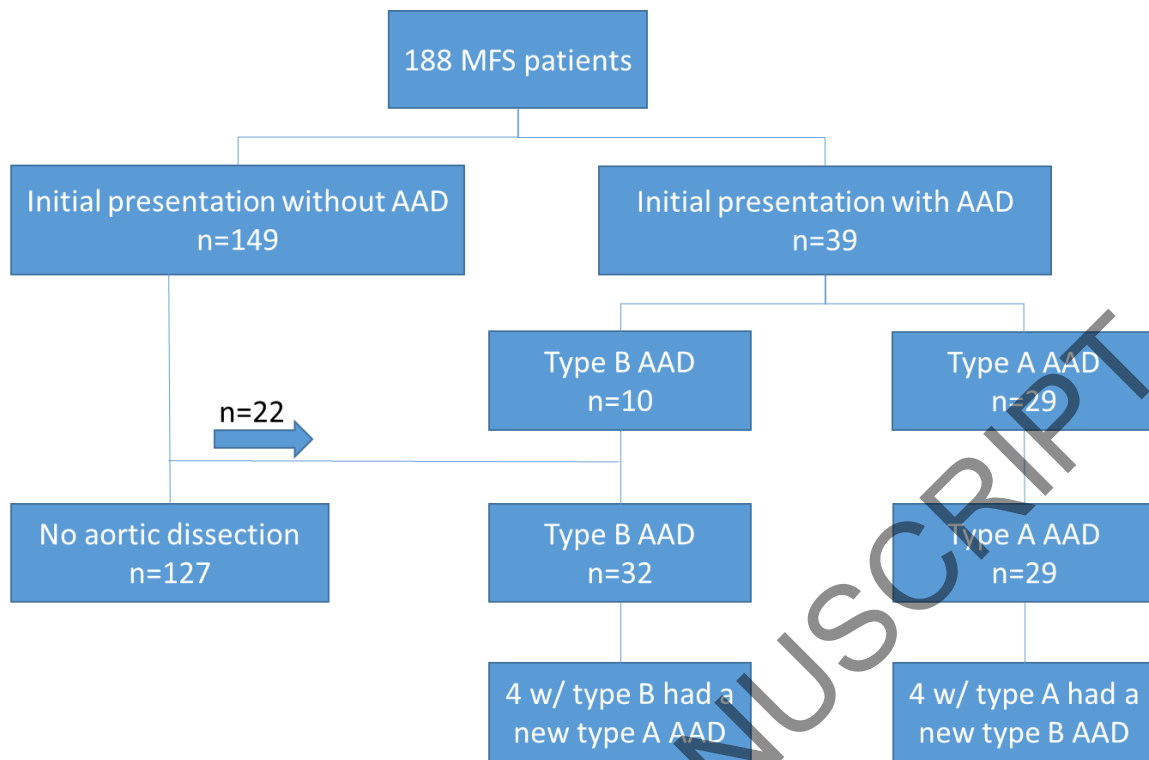
- 442 1. Judge DP, Dietz HC. Marfan's syndrome. *The Lancet*. 2005;366(9501):1965-76.
- 443 2. Faivre L, Collod-Beroud G, Loeys BL, Child A, Binquet C, Gautier E, et al. Effect of
444 Mutation Type and Location on Clinical Outcome in 1,013 Proband with Marfan Syndrome or
445 Related Phenotypes and FBN1 Mutations: An International Study. *The American Journal of*
446 *Human Genetics*. 2007;81(3):454-66.
- 447 3. Dietz HC, Cutting CR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan
448 syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*.
449 1991;352(6333):337-9.
- 450 4. Milewicz DM, Dietz HC, Miller DC. Treatment of Aortic Disease in Patients With Marfan
451 Syndrome. *Circulation*. 2005;111(11):e150-e7.
- 452 5. Cameron DE, Alejo DE, Patel ND, Nwakanma LU, Weiss ES, Vricella LA, et al. Aortic Root
453 Replacement in 372 Marfan Patients: Evolution of Operative Repair Over 30 Years. *The Annals*
454 *of Thoracic Surgery*. 2009;87(5):1344-50.
- 455 6. Engelfriet PM, Boersma E, Tijssen JGP, Bouma BJ, Mulder BJM. Beyond the root:
456 dilatation of the distal aorta in Marfan's syndrome. *Heart*. 2006;92(9):1238-43.
- 457 7. Finkbohner R, Johnston D, Crawford ES, Coselli J, Milewicz DM. Marfan Syndrome.
458 *Circulation*. 1995;91(3):728-33.
- 459 8. Schoenhoff FS, Jungi S, Czerny M, Roost E, Reineke D, Matyas G, et al. Acute Aortic
460 Dissection Determines the Fate of Initially Untreated Aortic Segments in Marfan Syndrome.
461 *Circulation*. 2013;127(15):1569-75.
- 462 9. Mimoun L, Detaint D, Hamroun D, Arnoult F, Delorme G, Gautier M, et al. Dissection in
463 Marfan syndrome: the importance of the descending aorta. *European Heart Journal*.
464 2010;32(4):443-9.
- 465 10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The
466 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement:
467 guidelines for reporting observational studies. *Journal of Clinical Epidemiology*.
468 2008;61(4):344-9.
- 469 11. De Paepe A, Devereux RB, Dietz HC, Hennekam RCM, Pyeritz RE. Revised diagnostic
470 criteria for the Marfan syndrome. *American Journal of Medical Genetics*. 1996;62(4):417-26.
- 471 12. Beighton Pd, De Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, et al.
472 International nosology of heritable disorders of connective tissue, Berlin, 1986. *American*
473 *journal of medical genetics*. 1988;29(3):581-94.
- 474 13. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The
475 revised Ghent nosology for the Marfan syndrome. *Journal of Medical Genetics*.
476 2010;47(7):476-85.

- 477 14. Rylski B, Pacini D, Beyersdorf F, Quintana E, Schachner T, Tsagakakis K, et al. Standards of
478 reporting in open and endovascular aortic surgery (STORAGE guidelines). *European Journal of*
479 *Cardio-Thoracic Surgery*. 2019;56(1):10-20.
- 480 15. Lombardi JV, Hughes GC, Appoo JJ, Bavaria JE, Beck AW, Cambria RP, et al. Society for
481 Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) Reporting Standards for Type B
482 Aortic Dissections. *The Annals of Thoracic Surgery*. 2020;109(3):959-81.
- 483 16. MacGillivray TE, Gleason TG, Patel HJ, Aldea GS, Bavaria JE, Beaver TM, et al. The
484 Society of Thoracic Surgeons/American Association for Thoracic Surgery Clinical Practice
485 Guidelines on the Management of Type B Aortic Dissection. *The Annals of Thoracic Surgery*.
486 2022;113(4):1073-92.
- 487 17. Czerny M, Krähenbühl E, Reineke D, Sodeck G, Englberger L, Weber A, et al. Mortality
488 and Neurologic Injury After Surgical Repair With Hypothermic Circulatory Arrest in Acute and
489 Chronic Proximal Thoracic Aortic Pathology. *Circulation*. 2011;124(13):1407-13.
- 490 18. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010
491 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and
492 Management of Patients With Thoracic Aortic Disease. *Circulation*. 2010;121(13):e266-e369.
- 493 19. members ATF, Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, et al. 2014
494 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute
495 and chronic aortic diseases of the thoracic and abdominal aorta of the adult The Task Force for
496 the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC).
497 *European Heart Journal*. 2014;35(41):2873-926.
- 498 20. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková
499 R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases
500 during pregnancy: The Task Force for the Management of Cardiovascular Diseases during
501 Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal*.
502 2018;39(34):3165-241.
- 503 21. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of Aortic Dilatation and the
504 Benefit of Long-Term β -Adrenergic Blockade in Marfan's Syndrome. *New England Journal of*
505 *Medicine*. 1994;330(19):1335-41.
- 506 22. Nucera M, Heinisch PP, Langhammer B, Jungi S, Mihalj M, Schober P, et al. The impact
507 of sex and gender on aortic events in patients with Marfan syndrome. *European Journal of*
508 *Cardio-Thoracic Surgery*. 2022;62(5).
- 509 23. Stanger OH, Pepper JR, Svensson LG. *Surgical Management of Aortic Pathology:*
510 *Current Fundamentals for the Clinical Management of Aortic Disease*: Springer; 2019.
- 511 24. den Hartog AW, Franken R, Zwinderman AH, Timmermans J, Scholte AJ, van den Berg
512 MP, et al. The risk for type B aortic dissection in Marfan syndrome. *Journal of the American*
513 *College of Cardiology*. 2015;65(3):246-54.
- 514 25. Milleron O, Arnoult F, Delorme G, Detaint D, Pellenc Q, Raffoul R, et al. Pathogenic
515 FBN1 Genetic Variation and Aortic Dissection in Patients With Marfan Syndrome. *Journal of*
516 *the American College of Cardiology*. 2020;75(8):843-53.
- 517 26. Trimarchi S, Jonker FHW, Froehlich JB, Upchurch GR, Moll FL, Muhs BE, et al. Acute
518 type B aortic dissection in the absence of aortic dilatation. *Journal of Vascular Surgery*.
519 2012;56(2):311-6.
- 520 27. Toolan C, Oo S, Shaw M, Field M, Kuduvalli M, Harrington D, et al. Reinterventions and
521 new aortic events after aortic surgery in Marfan syndrome. *European Journal of Cardio-*
522 *Thoracic Surgery*. 2021;61(4):847-53.

- 523 28. Kari FA, Russe MF, Peter P, Blanke P, Rylski B, Euringer W, et al. Late complications and
524 distal growth rates of Marfan aortas after proximal aortic repair†. *European Journal of Cardio-*
525 *Thoracic Surgery*. 2013;44(1):163-71.
- 526 29. Jung JC, Chang HW, Lee JH, Park K-H. Fate of remaining dissected aorta after
527 descending thoracic or thoracoabdominal aorta replacement for chronic dissection. *European*
528 *Journal of Cardio-Thoracic Surgery*. 2022;61(6):1328-35.
- 529

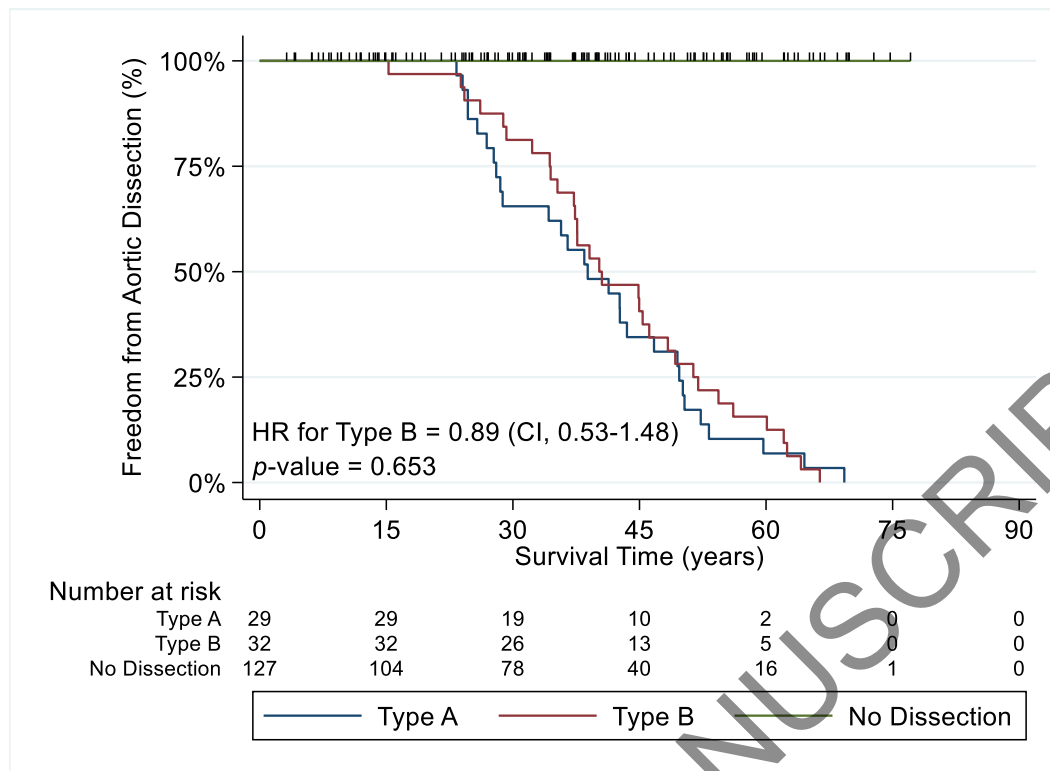
ACCEPTED MANUSCRIPT

Figure 1



ACCEPTED MANUSCRIPT

Figure 2



ACCEPTED MANUSCRIPT

Figure 3

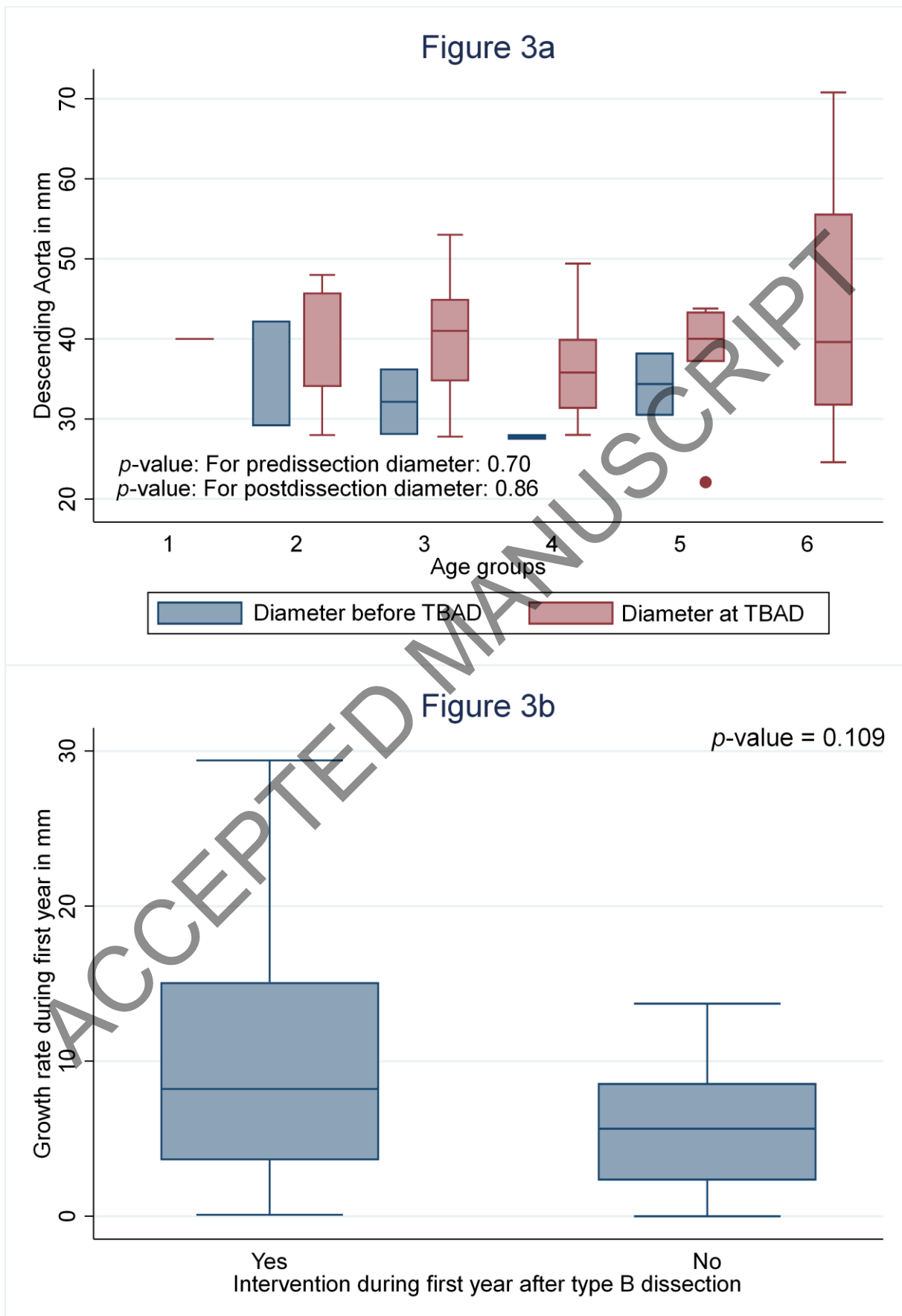
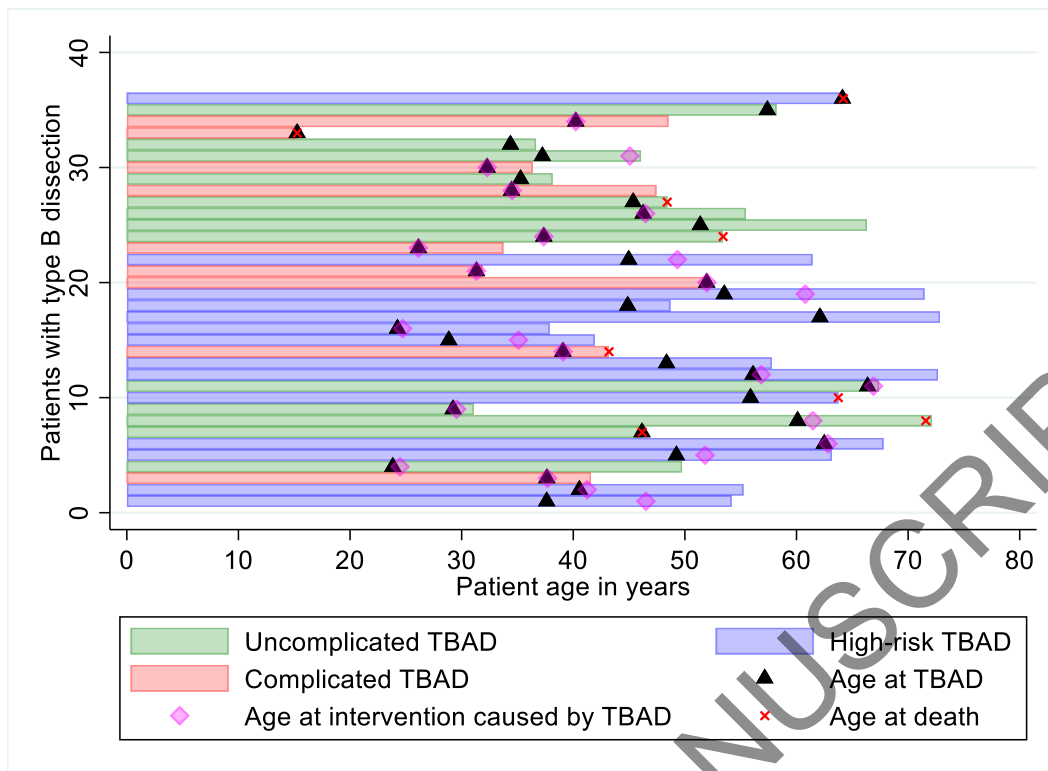
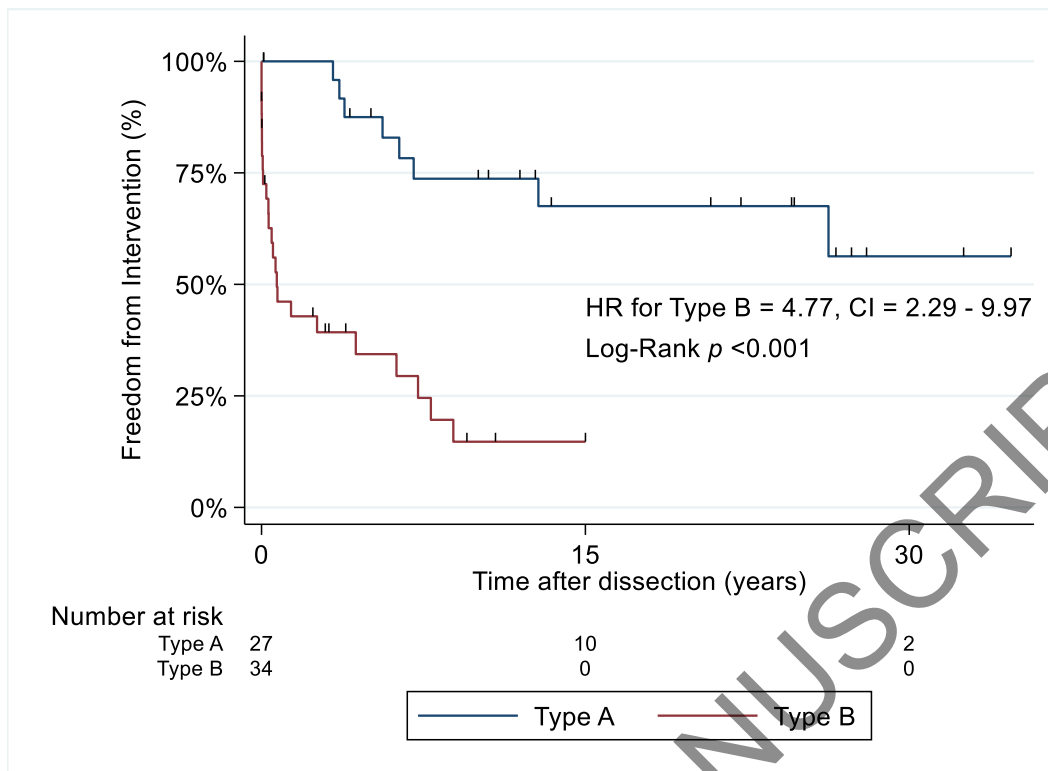


Figure 4



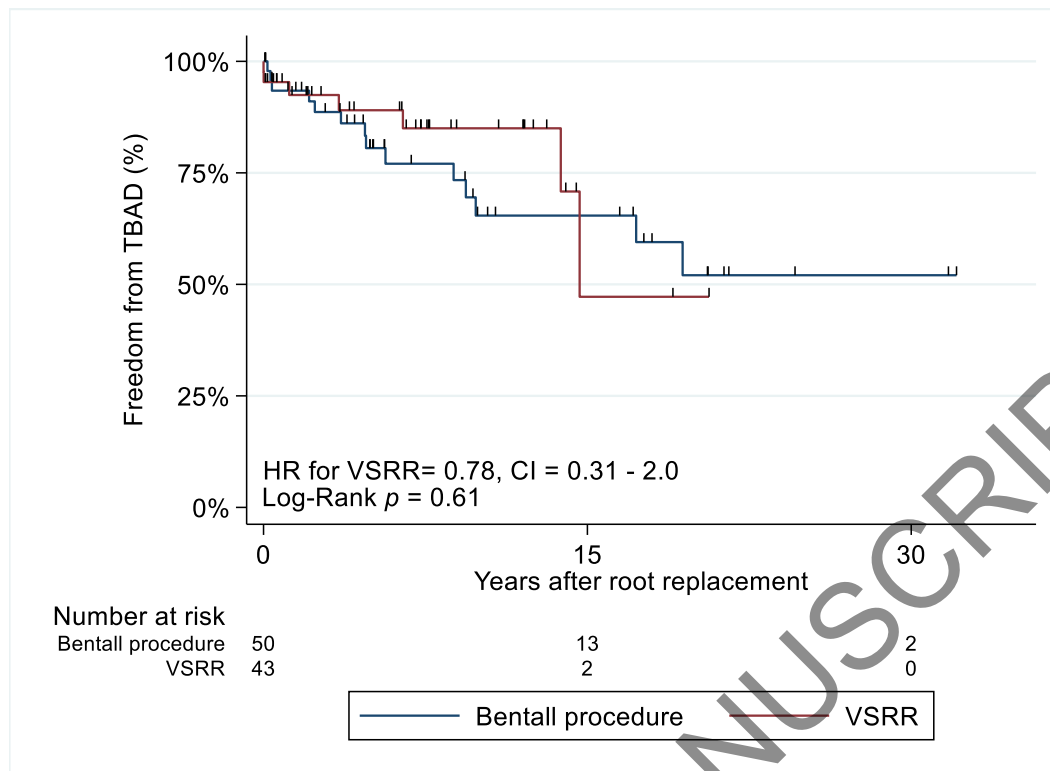
ACCEPTED MANUSCRIPT

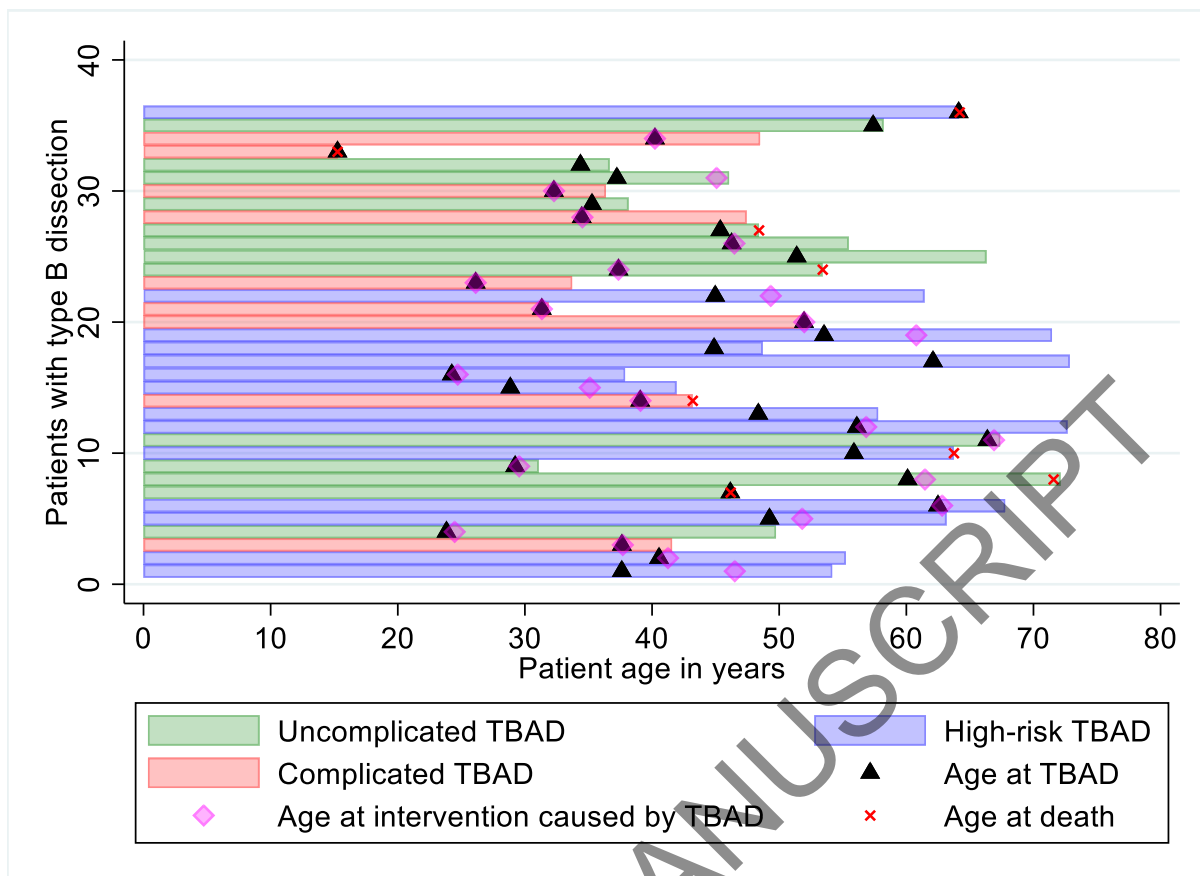
Figure 5



ACCEPTED MANUSCRIPT

Figure 6





ACCEPTED MANUSCRIPT