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## Prevalence and progression of aortic dilatation in adult patients with Turner syndrome: a cohort study

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1 Prevalence and progression of aortic dilatation in adult patients with  
2 Turner syndrome: a cohort study

3

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19

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21

22 Keywords: Turner syndrome, aortic dilatation, magnetic resonance imaging, mortality, bicuspid aortic  
23 valve.

24 Abbreviations: ASI: aortic systolic index; AD: aortic dilatation; BAV: bicuspid aortic valve; BSA: body  
25 surface area; IQR: inter-quartile range; MRI: magnetic resonance imaging; SMR: standard mortality  
26 ratio.

27

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29

## 30 ABSTRACT

31

### 32 **Objective**

33 Turner syndrome (TS) is a rare disorder affecting 1/2500 female newborn. Aortic dilatation (AD) and  
34 aortic dissection represent a major concern in TS. The aims of our study were to describe the aortic  
35 root growth, potential aortic dilatation (AD) risk factors and cardiovascular outcomes in a cohort of  
36 patients with TS.

### 37 **Methods**

38 Among 204 adult patients included, 197 were studied using a standardized 1.5 Tesla magnetic  
39 resonance imaging (MRI) protocol. AD was defined as an aortic diameter  $\geq 20$  mm/m<sup>2</sup> at the Valsalva  
40 sinuses and/or at the ascending aorta, when indexed to body surface area.

### 41 **Results**

42 At baseline, AD was present in 81/197 (41.1%) and 32/197 (16.2%) of patients, at the levels of  
43 Valsalva and ascending aorta, respectively. The aortic Valsalva diameter was larger in patients  
44 treated for thyroiditis ( $p < 0.001$ ). Potential risk factors of AD were aging ( $p < 0.001$ ) and presence of  
45 bicuspid aortic valve (BAV) ( $p = 0.002$ ). The hazard ratio (HR) of AD occurrence in the presence of BAV  
46 was 2.2 (95%CI 1.33-3.71). After a median follow-up period of 5.1 years ( $n = 143$ ), AD was present in  
47 58/143 (40.6%) and 25/143 (17.5%) of patients at the levels of Valsalva and ascending aorta,  
48 respectively. The median aortic growth of the Valsalva sinuses remained stable. At the ascending  
49 aorta, it increased by  $0.14 \pm 0.61$  mm/year. Only one aortic-related death was observed.

### 50 **Conclusion**

51 AD is common in adult patients with TS. However, our results are rather reassuring, as the median  
52 aortic diameters remained stable after 5.1 years and few aortic events were observed.

## 53 INTRODUCTION

54

55 Turner syndrome (TS) is a rare disorder (ORPHA #881) which affects 1/2500 female  
56 newborns and is characterized by the complete or partial loss of the second X chromosome.  
57 The associated clinical conditions include growth failure (95-100% of cases), primary ovarian  
58 insufficiency (95%), autoimmune disease (58%), as well as congenital or acquired  
59 cardiovascular disease (1).

60 Congenital cardiovascular malformations are present in about half of patients with TS (2).

61 The most frequent one is bicuspid aortic valve (BAV), occurring in 20% to 30% of TS (3). In  
62 the general population, its prevalence is 2-3% in males and 0.05% in females (4). It has been  
63 reported that the prevalence of BAV and other congenital cardiovascular malformations are  
64 more frequent in patients with a homogenous 45,X karyotype than in patients with  
65 45,X/46,XX mosaicism (1, 5). BAV is associated with proximal aortic dilatation (AD) and is a  
66 predisposing risk factor for subsequent aortic dissection (2). In patients with BAV or Marfan  
67 syndrome, beta-blocker or losartan treatments are recommended when AD is detected (2,  
68 6).

69 The mortality of patients with TS is increased three-fold when compared to the general  
70 population (SMR=3.0; 95%CI 2.7-3.4) (7), in association with the occurrence of  
71 cardiovascular diseases including aortic dissection. The incidence of aortic dissection  
72 diagnosed by echocardiography in a cohort of Swedish women with TS, after 23 years of  
73 follow-up, was 110 cases/100 000 patients-years (8). The risk factors of aortic dissection in  
74 this study were the presence of AD, hypertension, BAV and aortic coarctation. However, in  
75 11% of the cases reported in the literature, TS by itself was an independent risk factor of

76 aortic dissection (9). European guidelines concerning screening for AD in TS have been  
77 published in 2017 (2). They recommend measuring aortic root diameters at reference levels,  
78 such as the aortic annulus, Valsalva sinuses, sinotubular junction as well as ascending aorta  
79 and indexing the aortic diameter to the adult patient's body surface area (BSA) (2). The  
80 primary objective of our study was to describe the aortic root growth using standardized  
81 screening by magnetic resonance imaging (MRI) in a large cohort of adult patients with TS.  
82 The secondary objectives were to identify risk factors of AD and to describe the  
83 cardiovascular outcomes.

84

85

## 86 PATIENTS AND METHODS

87

### 88 *PATIENTS*

89 Adult patients with TS were recruited in our unit, labeled by the French Ministry of Health as  
90 a *Reference Center for Rare diseases of Growth Disorders and development* since 2006. This  
91 center belongs to the national endocrine rare disease network named FIREENDO ([firendo.fr](http://firendo.fr)),  
92 and to the Endo-ERN network ([endo-ern.eu](http://endo-ern.eu); id 739527).

93 To be included, each patient had a standard karyotype on blood cells with at least 10% of  
94 cells displaying a total or partial loss of one X chromosome. This observational study was  
95 approved by the Paris Nord Ethics Review Committee for Biomedical Research Projects  
96 (CEERB) (N° 12-029). All the patients' files were included in the CEMARA database. This  
97 national database has been declared to the French data protection agency (Commission  
98 Nationale de l'Informatique et des Libertés (CNIL), N° 909474 in 2010). In compliance with

99 French law, consent of non-opposition to collect and use the data was obtained from each  
100 patient.

101 Data collected for the present study included the patient's date of birth, auxological data,  
102 karyotype and previous history of surgery. Congenital heart malformations, such as bicuspid  
103 aortic valve (BAV) or other valvulopathies and aortic coarctation were recorded, as well as  
104 past and present medical treatments. BSA was calculated according to Dubois' formula (10).  
105 Automated office blood pressure readings were obtained in the seated position, with an  
106 appropriate cuff size at the level of the patient's right atrium, as recommended (2).  
107 Diagnosis of thyroiditis was established by TSH level and/or the presence of anti-thyroid  
108 antibodies (anti-thyroperoxydase and anti-thyroglobulin), as recommended (2). When  
109 patients were treated with L-thyroxin at the time of inclusion, they were defined as under  
110 treatment.

111

## 112 *IMAGING*

113 All patients were scanned using the same acquisition protocol for baseline and follow-up  
114 imaging with a 1.5 Tesla MRI (Signa HDxt; GE Medical Systems; Wisconsin; USA). A standard  
115 non-contrast MRI protocol with a dedicated phased-array cardiac coil and retrospective ECG  
116 gating was performed. Gradient echo localizers were used to obtain anatomic axes of the  
117 aorta. Cine b-SSFP imaging was performed in coronal oblique view (or left ventricular  
118 outflow tract 2 – LVOT 2 view), sagittal oblique view and axial oblique view centered on the  
119 aortic valve. Aortic diameters were assessed for all aortic MRI scans by experienced  
120 cardiovascular radiologists on a dedicated workstation (Carestream Health; Rochester; NY)  
121 using the coronal oblique and sagittal oblique cine images at the Valsalva sinuses and  
122 tubular ascending aorta. Measures were obtained using the classic inner edge to inner edge

123 method in diastole (11). Aortic valve morphology and assessment for aortic regurgitation  
124 and/or stenosis were evaluated with cine axial oblique images. The intraclass correlation  
125 coefficient (ICC) and its 95% confidence intervals (CI) (estimated by bootstrap) were used to  
126 assess the concordance of measurements between 3 operators from the same radiology  
127 department for Valsalva and ascending aorta measurements in a sample of patients: the ICC  
128 are 0.83 (CI95% 0.35-0.90) and 0.84 (CI95% 0.47-0.92) for MRI measurements at the Valsalva  
129 level and at the ascending aorta level, respectively.

130

### 131 *Aortic dilatation*

132 AD was defined as an absolute aortic diameter at the Valsalva sinuses and/or at the  
133 ascending aorta larger than 32 mm and/or  $\geq 20$  mm/m<sup>2</sup>, when indexed to BSA. Aortic systolic  
134 index (ASI) was defined as the ascending aorta diameter indexed to BSA (2).

135

### 136 *Aortic root growth*

137 When at least two MRIs were available, kinetics of aortic root diameters were systematically  
138 assessed at the Valsalva sinuses and ascending aorta. The rate of progression was expressed  
139 in millimeter per year (mm/y) and was defined as: (last MRI aortic diameter – first MRI aortic  
140 diameter [mm])/ (elapsed time between the last and the first MRI [year]). As previously  
141 described, the threshold of 1 mm/year was used to define rapid aortic growth (12).

142

### 143 *STATISTICAL ANALYSIS*

144 Baseline characteristics were expressed as frequency and percentage for categorical  
145 variables and as median (interquartile range, IQR) for continuous variables. Mean baseline  
146 absolute aortic diameter at the Valsalva level was compared between patients according to

147 the presence of BAV and/or treated thyroiditis using a one-way ANOVA test. Mean baseline  
148 aortic diameter was also compared according to treated thyroiditis in patients with and  
149 without BAV by using Student's t test (Bonferroni correction, p-value <0.025).

150 AD-free survival, according to the presence of BAV, was represented using Kaplan-  
151 Meier survival curves in the population with at least one informative MRI. Risk factors of AD  
152 occurrence were evaluated using a Cox proportional hazard model. Age, interaction variable  
153 between age at diagnosis of TS and past GH treatment were forced in the model. Presence  
154 of BAV, past aortic surgery, aortic coarctation, an homogenous 45,X karyotype and treated  
155 cardiovascular risk factors were selected in univariate analysis (p-value <0.20). Proportional  
156 hazard and log-linearity hypothesis have been checked. Results were expressed as hazard  
157 ratios for Cox models with 95% confidence intervals (CIs).

158 Progression of the absolute aortic diameter at the Valsalva sinuses and the ascending  
159 aorta was studied in the population with at least 2 informative MRIs using a linear regression  
160 model. Final models were built using a backward stepwise procedure with covariates  
161 selected in the univariate analysis (p-value<0.20). Normality of the aortic diameter  
162 progression, log-linearity hypothesis, homoscedasticity and independence of residues have  
163 been checked. All analyses were performed with the SAS version 9.4 statistical software (SAS  
164 Institute Inc., Cary, NC, USA).

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171 RESULTS:

172 **BASELINE CHARACTERISTICS**

173 Two hundred and four women were included in the cohort, between 2006 and 2019. Among  
174 them, a standardized aortic MRI scan protocol at the 2 aortic positions studied was at least  
175 performed once for 197 patients and twice for 143 patients ([Figure 1](#)). Baseline clinical  
176 characteristics, karyotypes, medical histories, past and current treatments among 197  
177 patients are reported in [Table 1](#). Other observed valvulopathies were aortic insufficiencies  
178 (4.9%) and aortic stenosis (0.5%). Cardiovascular surgery had been performed during  
179 childhood in 12/197 (6.1%), including isolated aortic coarctation repairs (n=6 patients). Sixty-  
180 five patients had thyroiditis. Among them, 43 were positive for anti-thyroid antibodies.

181

182 Median baseline aortic diameter at the Valsalva level was 18.9 mm/m<sup>2</sup> (IQR: 17.2-20.9)  
183 ([Figure 2a](#)). Median ASI was 15.9 mm/m<sup>2</sup> (IQR: 14.5-17.8) ([Figure 2b](#)). At baseline, 83/197  
184 (42.1%) patients had AD: it was observed in 81/197 (41.1%) and 32/197 (16.2%) patients at  
185 the Valsalva and at the ascending aorta level, respectively. AD was observed at the  
186 ascending aorta but not at the Valsalva level in 2 cases. The median age at patients with  
187 baseline AD was 29.4 years (IQR: 20.0-37.4) and 34.8 years (IQR: 25.9-43.0) at the Valsalva  
188 and the ascending aorta levels, respectively. Baseline aortic diameter at the Valsalva level  
189 was significantly different according to the presence of bicuspidy and/or treatment for  
190 thyroiditis (p<0.001) ([Figure 3](#)). Among patients with BAV, aortic diameters at the level of  
191 Valsalva were larger in patients treated for thyroiditis (31.8±4.5 vs 30.8±3.7; p<0.001).  
192 Among patients without BAV, a treated thyroiditis also led to larger aortic diameters  
193 (28.5±3.7 vs 27.0±3.1; p<0.001).

194

195 FOLLOW-UP

196 *Aortic dilatation (AD)-free survival*

197 AD was observed in 102/197 (51.8%) patients. The median survival time without AD was  
198 35.0 years. AD occurrence was present in 100/197 (50.8%) and 42/197 (21.3%) patients at  
199 the Valsalva and the ascending aorta level, respectively. Using multivariate Cox analysis,  
200 both aging ( $p < 0.001$ ) and the presence of BAV ( $p = 0.002$ ) were significantly associated with  
201 AD occurrence. It was not associated with past GH treatment, the presence of aortic  
202 coarctation, nor a 45,X karyotype. Adjusted hazard ratio (HR) of AD occurrence in patients  
203 with BAV was 2.2 (95% CI 1.33-3.71), as compared to those without BAV ([Figure 4](#)).

204

205 *Aortic growth*

206 Among the cohort, 143 patients had at least 2 MRIs ([Supplemental Table 1](#)). These patients  
207 were not different from the patients with one MRI (data not shown). Their median number  
208 of MRIs was 3.0 (IQR: 2.0-4.0) and their median follow-up was 5.1 years (IQR: 2.8-7.5). At the  
209 end of the follow-up period, AD was found in 58/143 (40.6%) and 25/143 (17.5%) at the level  
210 of the Valsalva sinuses and ascending aorta, respectively.

211 At the end of follow-up, mean progression of aortic diameter at the Valsalva sinuses was  $0.0$   
212  $\pm 0.80$  mm/year. Results from a multivariate linear regression analysis showed an association  
213 between baseline aortic diameter, BSA and treated hypertension and aortic growth at the  
214 Valsalva ( $p < 0.05$ ). At the end of the follow-up, mean progression of aortic diameter at the  
215 ascending aorta was  $0.14 \pm 0.61$  mm/year. According to a multivariate linear regression  
216 analysis, age, baseline aortic diameter and the presence of a valvulopathy different from  
217 uncomplicated BAV, were significantly associated ( $p < 0.05$ ) with aortic growth.

218 At the end of the study, 4 patients had a progression of their aortic diameter higher than 1  
219 mm/year at the Valsalva sinuses and 7 others at the level of ascending aorta. Ten of them  
220 had an aortic diameter above 25 mm/m<sup>2</sup> at a median age of 52 years (IQR: 36.5-65.7).

221

222 Of these 143 patients, 15 (10.5%) were treated with beta-blockers. Among them, this  
223 treatment was prescribed in the presence of AD for 8 patients. Their median age was 36.5  
224 years (IQR: 29.7-40.0). The aortic diameter growth was not significantly different between  
225 patients with beta-blockers and those without beta-blocker intake, neither at the Valsalva  
226 sinuses (p=0.18), nor at the ascending aorta (p=0.33) levels.

227

228 During the follow-up period, 11 patients became pregnant, leading to 13 births. Aortic  
229 diameters before and after pregnancy were available for 5 patients (median age: 31.0 years  
230 old [IQR: 30-35]). Their aortic growth (mm/year) was not significantly different from the rest  
231 of the cohort, both at the Valsalva (p=0.39) and the ascending aorta (p=0.22) levels. The rate  
232 of rapid progression (> 1 mm/year) was not different between pregnant and non-pregnant  
233 patients (p=0.20).

234

### 235 *Cardiovascular outcomes*

236 During the follow-up period, 2 patients had prophylactic aortic surgery for AD. ASI values at  
237 the time of surgery were 38 mm/m<sup>2</sup> and 25 mm/m<sup>2</sup> for each of these patients.

238 Three patients had died at the end of the follow-up period. One death was related to an  
239 aortic dissection in a 65-years-old patient with a major AD (44 mm at the Valsalva sinuses;  
240 30.13 mm/m<sup>2</sup>). She had previously declined aortic surgery. The second death occurred in a  
241 39-years-old patient who had cardiorespiratory arrest after surgery for a grade IV mitral

242 insufficiency. The third death occurred after a second episode of stroke in a 70-years-old  
243 hypertensive patient. Finally, a 33 year-old patient presented a spontaneous dissection of  
244 her right vertebral artery. Her aortic diameter, measured 6 months before this vascular  
245 event, was 32 mm (19.9 mm/m<sup>2</sup>) at the Valsalva sinuses. She progressively recovered from  
246 this episode and completed the study.

247

248

## 249 DISCUSSION

250

251 Our study evaluated the cardiovascular outcomes of a large cohort of adult patients  
252 with TS who had at least one 1.5 Tesla MRI, measuring aortic diameters both at the Valsalva  
253 and the ascending aorta levels. At baseline, AD was observed in 81/197 (41.1%) and 32/197  
254 (16.2%) patients, at the Valsalva and ascending aorta levels, respectively. At the end of the  
255 follow-up period, AD was present in 58/143 (40.6%) and 25/143 (17.5%) at those same  
256 levels, respectively.

257 We show that the presence of BAV was significantly associated with the occurrence of AD.  
258 Furthermore, we were able to quantify the risk of AD according to the presence of BAV, with  
259 a hazard ratio (HR) of 2.2 (95%CI 1.33-3.71). AD was found to be much more frequent at the  
260 Valsalva level than at the ascending aorta. In a cohort of 253 patients with TS, Sachdev *et al.*  
261 showed that “typical” BAV, resulting in anterior and posterior cusps, was frequent and was  
262 correlated with AD at the Valsalva level (3). Therefore, a potential explanation of the highest  
263 rate of AD at the Valsalva level might rely on this type of BAV. Unfortunately, in our study,  
264 data concerning the type of BAV were not available for all patients.

265 In our study, presence of a treated thyroiditis was associated with baseline AD. Regardless of  
266 the presence of BAV, the association remained significant ( $p < 0.001$ ). Previous studies  
267 addressing congenital aortopathies have shown that systemic auto-immunity and  
268 inflammation are present in aortic remodeling. Indeed, proliferation of smooth muscle cells  
269 of the aortic media is regulated by cytokines secreted by immune and endothelial cells,  
270 whereas muscle remodeling involves the action of metalloproteases and TGF- $\beta$ -mediated  
271 signaling (13). To our knowledge, the present study is the first one reporting a relationship  
272 between thyroiditis and AD in patients with TS.

273

274 Few studies have evaluated the progression of aortic diameters in adult patients with TS.  
275 Mortensen *et al.* (14) studied 91 patients for an average follow-up period of 8.8 years. The  
276 aortic progression was  $0.32 \pm 0.3$  mm/year and  $0.20 \pm 0.2$  mm/year at the Valsalva sinuses and  
277 the ascending aorta level, respectively. Duijnhouwer *et al.* (15) studied 171 adult patients  
278 with TS, screened either by MRI or CT-scan for AD at the tubular ascending aorta level. This  
279 study reported a median aortic progression of 0.20 mm/year (IQR: 0.0-0.4)(15). Our results  
280 based on the evaluation of aortic diameters of both the Valsalva sinuses and the ascending  
281 aorta show a median increases in size of  $0.0 \pm 0.80$  mm/year and  $0.14 \pm 0.61$  mm/year,  
282 respectively. Although AD is more frequent at baseline at the Valsalva level, the increase in  
283 aortic diameter size at this level is slower than that at the ascending aorta level. In our study,  
284 the progression of aortic diameters is lower than that reported previously. A potential  
285 explanation relies on the fact that our population has few cardiovascular risk factors and  
286 that median BMI was in the normal range ( $22.8 \text{ Kg/m}^2$ ). A past history of ischemic heart  
287 disease is present in only 1.5% of the cohort and our population is young, since the median  
288 age is 25.6 years.

289 The multivariate linear regression analysis showed that the Valsalva diameter increases with  
290 hypertension ( $p < 0.05$ ), strongly suggesting that this clinical condition enhances the  
291 development of AD. Duijnhouwer *et al.*, using a similar statistical approach, showed that GH  
292 treatment was a risk factor for aortic diameter growth (15). However, this result is not  
293 confirmed in our study since past GH treatment was related neither to baseline AD, nor to  
294 progression of aortic diameters. After multivariate analysis, we found that aortic growth at  
295 the ascending aorta was associated with other valvulopathies different from uncomplicated  
296 BAV, mainly aortic insufficiency and/or stenosis. Therefore, aortic valve diseases might be  
297 involved in aortic diameter growth.

298 At the end of the follow-up period, 10/143 (7.0%) patients experienced a progression of  
299 their aortic diameter  $> 1$  mm/year. This prevalence is higher than that (4.6%) reported in the  
300 Dutch study (15). This may be due to the fact that we measured two aortic positions, giving  
301 2.8% and 4.9% of AD at the Valsalva and the ascending aorta, respectively. However, in our  
302 cohort, the number of patients with a rapid increase of their aortic diameter was too low for  
303 identifying risk factors for a rapid progression.

304 To our knowledge, the impact of beta-blocker treatments in patients with TS has not been  
305 previously reported. In patients with Marfan syndrome, beta-blockers slow the rate of AD  
306 (16). Among the patients treated with beta-blockers in the present study, aortic diameter  
307 growth did not significantly differ from that in patients without a beta-blocker therapy.  
308 However, our study is not powerful enough for demonstrating the protective role of beta  
309 blockers in the development of AD.

310 Finally, during our follow-up period, the number of cardiovascular events was low (1.96%)  
311 and only one death was related to an aortic dissection. In the Dutch cohort study with a 6.8  
312 year follow-up (15), two deaths related to aortic dissection were recorded, both at the age

313 of 44 years. An American study, including 317 women with a very long follow-up (mean 11  
314 years), reported that cardio-vascular diseases were the main cause of death in TS (17).  
315 Therefore, our median follow-up period of 5.1 years in a rather young population probably  
316 underestimated the rate of cardiovascular events.

317

318 Our study has some weaknesses. It could be argued that among our initial cohort, only 143  
319 patients had performed several MRIs. However, their clinical characteristics were not  
320 different from these in the other patients included in the study. Furthermore, patients had  
321 up to 8 scans with a maximum follow-up of 11.6 years. During follow-up, some patients had  
322 a decrease of the absolute aortic diameter. This could be due to the measurement accuracy  
323 of MRI. Concerning pregnant women, although their aortic diameter growth was not  
324 significantly different from that in the rest of the cohort, their number was too low for  
325 reassuring pregnant patients concerning AD.

326 In the near future, 4D MRI imaging and measurement of stiffness/distensibility of the  
327 proximal aorta should be available (18). Further genetic studies are needed to decipher the  
328 molecular mechanisms involved in BAV and AD (19) and, therefore, to improve  
329 cardiovascular care in patients with TS.

330

331

332 **CONCLUSION**

333

334 Aortic MRI in a population of adult patients with TS demonstrated a high rate of AD,  
335 especially at the Valsalva sinuses. The rate of progression of aortic diameters during the  
336 follow up period of five years was low. Few deaths related to cardiovascular events were  
337 observed. Although our data are reassuring, a long term screening is required to identify the  
338 few patients with a pejorative aortic outcome.

339

340

341 **DECLARATION OF INTEREST:**

342 All authors declare that there is no conflict of interest that could be perceived as prejudicing  
343 the impartiality of the research reported.

344

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352 TABLES and FIGURES:

353 **FIGURE 1:**

354 Flow chart of patients included in the study.

355

356 **TABLE 1:** Baseline clinical characteristics of the cohort (n= 197 patients with TS) in the aortic  
357 dilatation (AD)-free survival analysis. Results are expressed as number of patients and  
358 percentages, or median value and inter-quartile range (IQR). Missing values (a) n=1; (b) n=2;  
359 (c) n=3.

360

361 **FIGURE 2:** Scatterplot showing the baseline values of the aortic diameter (mm) related to  
362 the patient's age (X axis). Each dot represents a patient: a) at the Valsalva sinuses (n=197); b)  
363 at the tubular ascending aorta (n= 197). The central line represents the regression line and  
364 the dotted lines represent the 95% confidence interval.

365

366 **FIGURE 3:** Baseline boxplot of aortic diameter at the Valsalva sinuses, according to the  
367 presence (+) or absence (-) of a bicuspid aortic valve (BAV) or a history of treated thyroiditis  
368 (T) (n=197). The length of the box represents the interquartile range (distance between 25th  
369 and 75th percentiles); the symbol inside the box represents the mean; the horizontal line  
370 inside the box represents the median; and the vertical lines issuing from the box extend to  
371 the minimum and maximum values.

372

373 **FIGURE 4:** Kaplan-Meier survival estimator without aortic dilatation (AD) of the Valsalva  
374 sinuses according to age (X axis), in the presence (black line) or the absence (dotted line) of  
375 aortic bicuspid valve (BAV) (n=197).

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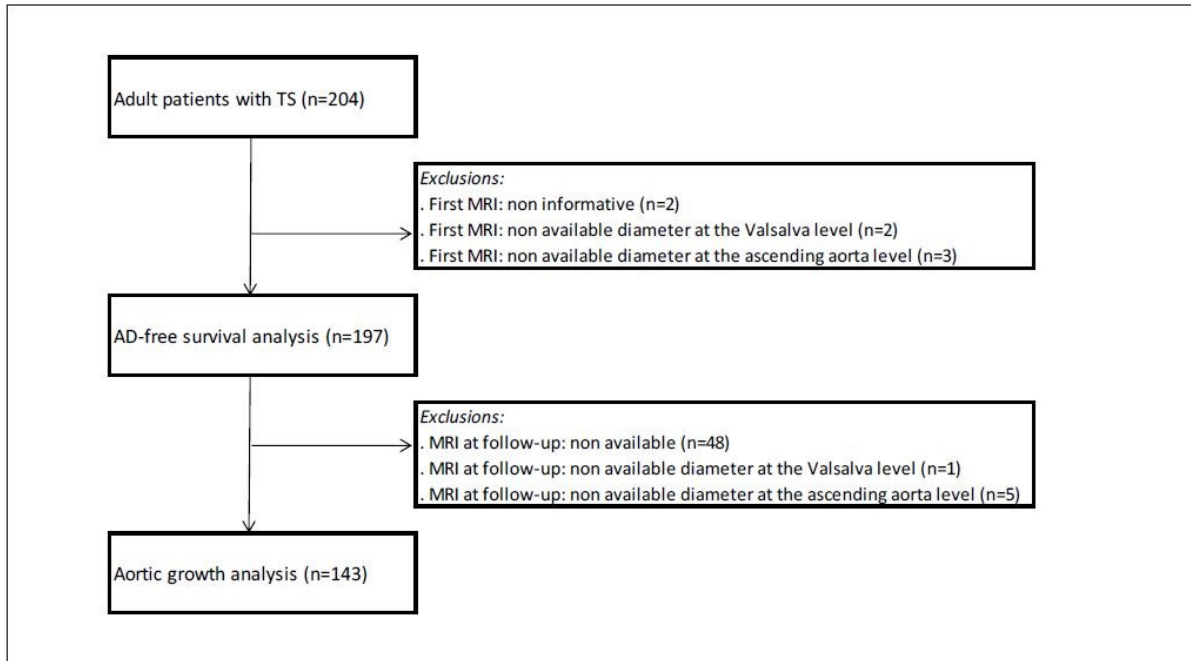
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**FIGURE 1**

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AD-free survival analysis Population (n=197)	
	n (%) or median [IQR]
Age (yrs)	25.6 [19.6 ; 34.2]
Years since diagnosis	18.0 [10.0 ; 24.0]
<b>Karyotype</b>	
45,X	79 (40.1)
45,X/i(Xq)+	32 (16.2)
45,X/46,XX	21 (10.7)
45,X/46,Xr(X)	20 (10.2)
45,X/Y+	10 (5.1)
45,X/47,XXX	7 (3.6)
Others	28 (14.2)
<b>Anthropometric values</b>	
Height (cm)	152.0 [147.0 ; 157.0]
Weight (Kg)	52.0 [46.0 ; 60.0]
BMI (Kg/m <sup>2</sup> )	22.8 [20.3 ; 25.7]
BSA (m <sup>2</sup> )	1.5 [1.4 ; 1.6]
Median blood pressure level (mmHg)	110/70 [102/63;120/77]
<b>Medical history</b>	
Tabagism	23 (11.9) <sup>(c)</sup>
Diabetes (antidiabetic drug)	12 (6.1) <sup>(a)</sup>
Dyslipidemia (lipid-lowering drug)	10 (5.1) <sup>(a)</sup>
Coronaropathy (medical treatment)	3 (1.5)
Hypertension (antihypertensive drug)	9 (4.6)
Past treatment with GH	147 (75.0) <sup>(a)</sup>
Thyroidal supplementation	65 (33.2) <sup>(a)</sup>
Sexual hormonal replacement therapy	177 (90.8) <sup>(b)</sup>
Aortic coarctation	16 (8.1)
Bicuspid aortic valve (BAV)	45 (22.8)
Valvulopathies different from BAV	24 (12.2)
<b>Basal aortic diameters</b>	
<b>Valsalva level</b>	
(mm/m <sup>2</sup> )	18.9 [17.2 ; 20.9]
Dilatation	81 (41.1)
<b>Ascending aorta level</b>	
(mm/m <sup>2</sup> )	15.9 [14.5 ; 17.7]
Dilatation	32 (16.2)

**TABLE 1**

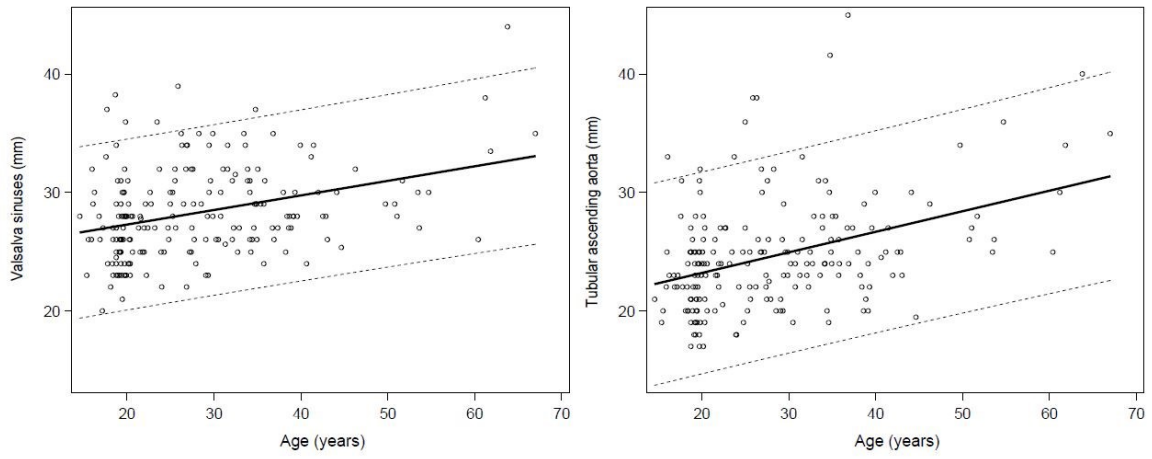
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**FIGURE 2**

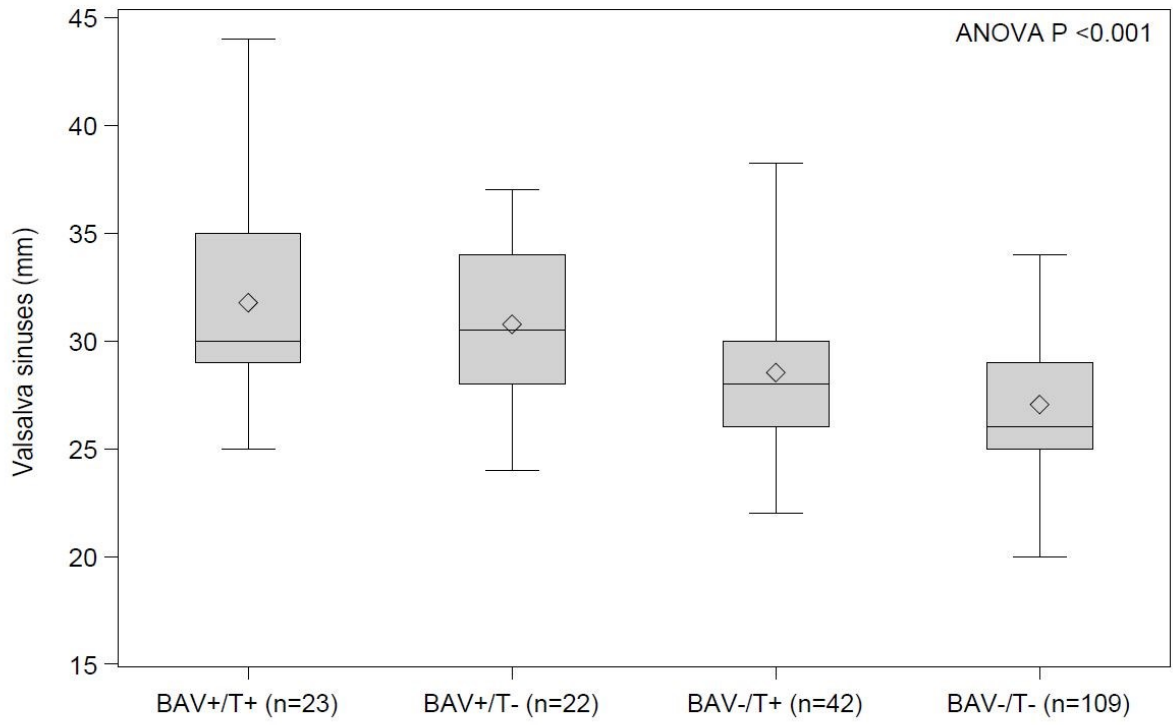
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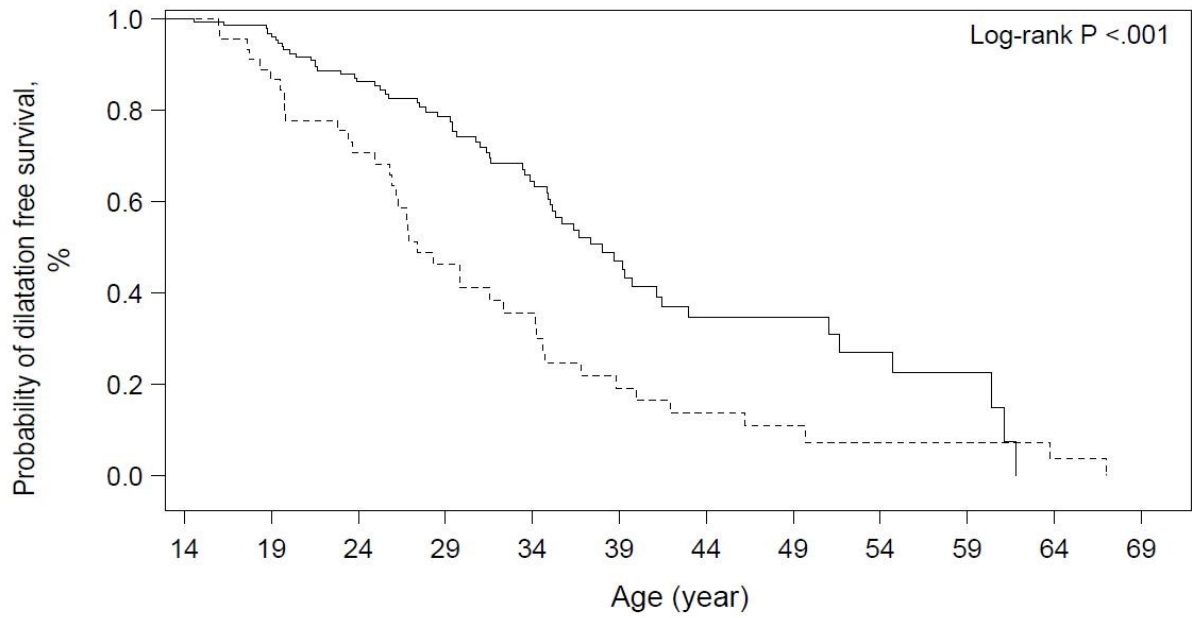
**FIGURE 3**

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		stratum											
		BAV-					BAV+						
N à risque		14	19	24	29	34	39	44	49	54	59	64	69
Non	152	141	102	74	51	25	15	9	6	3	0		
Oui	45	39	29	18	13	7	5	3	2	2	1	0	

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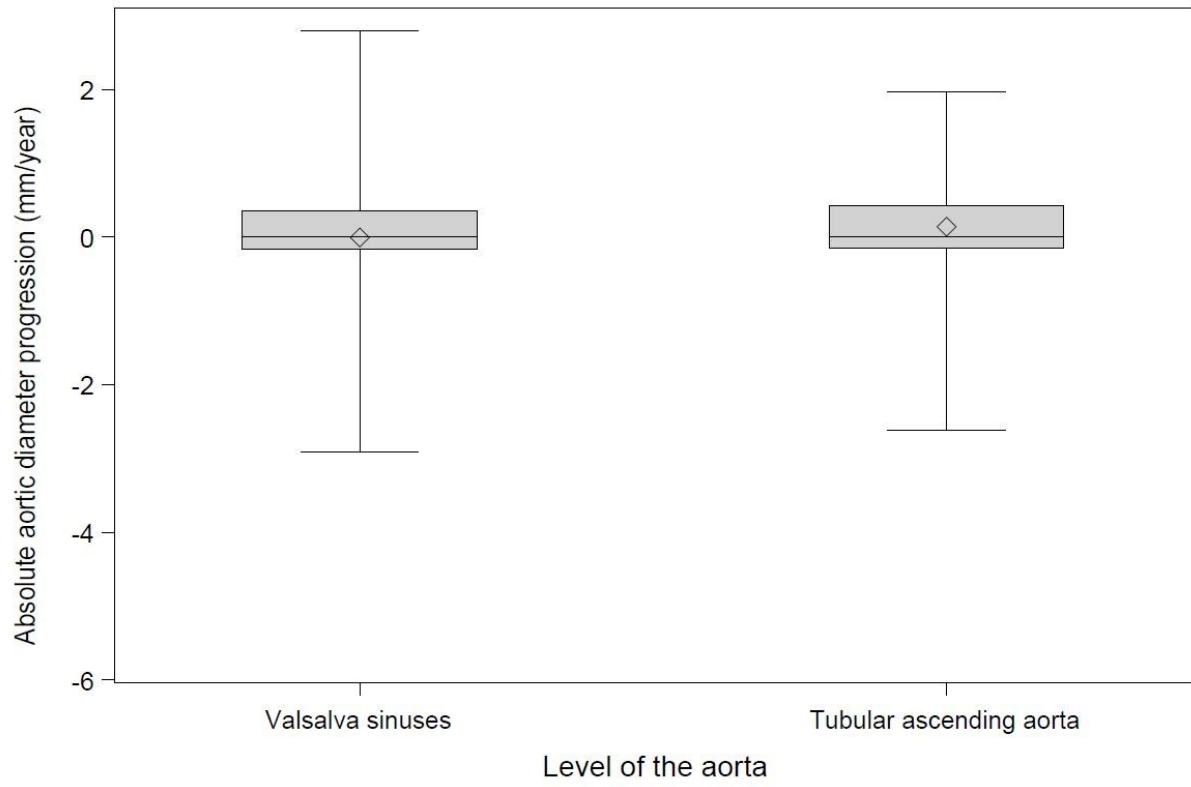
**FIGURE 4**

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**FIGURE 5**

487 **Supplemental TABLE 1:** Baseline clinical characteristics of the patient in the aortic growth analysis (n=143 with TS and MRIs  
 488 at least performed twice). Results are expressed as number of patients and percentages, or median value and inter-quartile  
 489 range (IQR). Missing values: (a) n=1 ; (b) n=2 ; (c) n=3.  
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<b>Aortic growth analysis population</b>	
	<b>n (%) or median [IQR]</b>
<b>Age (yrs)</b>	25.6 [19.5; 34.2]
Years since diagnosis	18.0 [11.0; 25.0]
<b>Karyotype</b>	
45,X	61 (42.7)
45,X/i(Xq)+	24 (16.8)
45,X/46,XX	15 (10.5)
45,X/46,Xr(X)	11 (7.7)
45,X/Y+	5 (3.5)
45,X/47,XXX	6 (4.2)
Others	21 (14.7)
<b>Anthropometric values</b>	
Height (cm)	153.0 [146.0; 157.0]
Weight (Kg)	51.0 [46.0; 58.0]
BMI (Kg/m <sup>2</sup> )	22.6 [20.2; 25.2]
BSA (m <sup>2</sup> )	1.5 [1.4; 1.6]
Median blood pressure level (mmHg)	116/74 [106/66;126/80]
<b>Medical history</b>	
Tabagism	13 (9.3) <sup>(c)</sup>
Diabetes (antidiabetic drug)	5 (3.5) <sup>(a)</sup>
Dyslipidemia (lipid-lowering drug)	6 (4.2) <sup>(a)</sup>
Coronaropathy (medical treatment)	2 (1.4)
Hypertension (antihypertensive drug)	6 (4.2)
Past treatment with GH	109 (76.8) <sup>(b)</sup>
Thyroidal supplementation	51 (35.9) <sup>(b)</sup>
Hormonal replacement therapy	129 (90.8) <sup>(b)</sup>
Aortic coarctation	13 (9.1)
Bicuspid aortic valve (BAV)	37 (25.9)
Valvulopathies different from BAV	17 (11.9)
<b>Basal aortic diameters</b>	
<b>Valsalva level</b>	
(mm/m <sup>2</sup> )	19.0 [17.4; 21.1]
Dilatation	59 (41.3)
<b>Ascending aorta level</b>	
(mm/m <sup>2</sup> )	16.3 [14.5; 18.3]
Dilatation	24 (16.8)

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**Supplemental TABLE 1**