ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2019) **0**, 1–7
doi:10.1093/ehjci/jez065

Aortic growth rates are not increased in Turner syndrome—a prospective CMR study

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Received 17 December 2018; editorial decision 12 March 2019; accepted 15 March 2019

Background Aortic disease is a key determinant of outcomes in Turner syndrome (TS). The present study characterized aortic growth rates and outcomes over nearly a decade in adult women with TS.

Methods and results Prospective observational study assessing aortic diameters twice with cardiovascular magnetic resonance imaging in women with TS [$N = 91$; mean follow-up 8.8 ± 3.3 (range 1.6–12.6) years] and healthy age-matched female controls [$N = 37$; mean follow-up 6.7 ± 0.5 (range 5.9–8.1) years]. Follow-up also included aortic outcomes and mortality, antihypertensive treatment and ambulatory blood pressure. Aortic growth rates were similar or smaller in TS, but the variation was larger. The proximal aorta in TS grew by 0.20 ± 0.26 (mid-ascending) to 0.32 ± 0.36 (sinuses) mm/year. This compared to 0.26 ± 0.14 (mid-ascending) and 0.32 ± 0.17 (sinuses) mm/year in the controls. During 799 years at risk, 7 suffered an aortic outcome (1 aortic death, 2 aortic dissections, 2 aortic interventions, 2 surgical aortic listings) with further 2 aortic valve replacements. At baseline, two women were excluded. One died during subacute aortic surgery (severe dilatation) and one had a previously undetected type A dissection. The combined aortic outcome rate was 1126 per 100 000 observation years. The aortic and all-cause mortality rates were 1 per 799 years (125 deaths per 100 000 observation years) and 9 per 799 years (1126 deaths per 100 000 observation years). Aortic growth patterns were particularly perturbed in bicuspid aortic valves (BAV) and aortic coarctation (CoA).

Conclusion Aortic growth rates in TS are not increased. BAVs and CoA are major factors that impact aortic growth. Aortic outcomes remain a concern.

Keywords Turner syndrome • aortic dissection • aortic disease • cardiovascular magnetic resonance imaging • bicuspid aortic valve • aortic coarctation

Introduction

Aortic disease is a key determinant of outcomes in Turner syndrome (TS) but insight into aortic disease remains limited. TS is caused by a complete or partial absence of an X-chromosome.[1,2] Congenital and acquired cardiovascular disease is a major contributor to the increased risk of early death in TS.[1] Congenital heart disease is common and primarily affects the left side of the heart, including a bicuspid aortic valve (BAV) and aortic coarctation (CoA).[3]

Thoracic aortic dissection plays a major role in the increased morbidity and mortality in TS,[4,5] where dissections may involve any segment of the thoracic aorta.[6] This potentially fatal event mainly occurs when congenital risk factors are present, which include the

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common BAV and aortic arch anomalies, such as CoA and transverse aortic arch elongation (ETA).[5,7] Highly prevalent hypertension may also adversely impact aortic disease in TS.[8] However, risk stratification for aortic dissection is suboptimal because known risk factors fail to identify a considerable proportion of aortic dissections.[6]

Aortic size is the principal risk marker for aortic dissection, but the absolute aortic diameter has poor predictive value in TS due to the small stature.[9] However, the predictive capacity improves when absolute diameter is indexed for body surface area (BSAi).[2] Some aortic dissections are not predicted even when taking indexed aortic size and/or other risk factors like hypertension and BAV into account. [6] Aortic growth rates were recently included as an additional risk marker[2,10] and prospective studies have also assessed aortic growth in TS, but none with a prospective design and long-term follow-up.[5,11]

The primary aims of this study was to evaluate aortic growth rates and report aortic outcomes in a prospective study and to compare the results with healthy female age-matched controls.

Methods

Study cohort

Women with TS (karyotypically proven) were recruited from an ongoing prospective study that involved four visits between 2003 and 2016. The inclusion criterion for this study was completion of cardiovascular magnetic resonance imaging (CMR) at two study visits, using the visits with the widest time-gap. Of 102 recruited women, 91 (89%) were eligible for participation. A cohort of 67 healthy age-matched women was recruited by advertisement at Aarhus University Hospital. Thirty-seven (55%) completed two visits. Only controls with no comorbidities (including ongoing medications except for contraceptives) were included at baseline. All participants had CMR, echocardiography and 24-hour ambulatory blood (ABP) pressures performed. Baseline and short-term prospective findings have been described for TS.[12] Cardiovascular outcomes were collected for all. Aortic outcomes were defined as: (1) aortic dissection, (2) prophylactic aortic surgery, (3) aortic valve surgery, and/or: (4) listing for aortic valve or prophylactic aortic surgery. Deaths were also registered. The cause of death was defined as aortic when the death was directly attributed to disease of the thoracic aorta and aortic valve or the treatment hereof.

Cardiovascular magnetic resonance imaging

All studies were performed on the same 1.5 T whole-body scanner (ACS-NT, Philips Medical Systems; maximum gradient performance 30 Tesla per meter amplitude, slew rate 150 T/m/sec), using a 5-element cardiac coil. A contrast-free, nearly isotropic (voxel size: 1.4× 1.4 × 3.0 mm), fat-saturated, three-dimensional (3D) balanced steady-state free precession and electrocardiogram-triggered (diastolic) gradient echo sequence with a respiratory navigator was used. A standardized protocol acquired a 3D data stack of the thoracic aorta. Two experienced observers—blinded to the clinical data and previous measurements—measured maximum and inner edge-to-inner edge diameters using multiplanar and double oblique reformatting. Perpendicular maximum diameters were measured for: (1) aortic sinuses (measuring cusp-to-opposing-cusp diameter); (2) sinotubular junction; (3) mid-ascending aorta; (4) distal ascending aorta; (5) proximal aortic arch (between the brachiocephalic and left common carotid arteries); (6) distal aortic arch (proximal to the left subclavian artery); (7) aortic isthmus; (8) proximal descending aorta; and (9) distal descending aorta. Structural anomalies, including CoA and ETA, were identified from the 3D datasets. Echocardiography (for aortic valve morphology, and function) and ABP were performed. Medical history, height and weight were recorded. Measurement methodology, anomaly categorisation, and observer-variability have already been described.[13]

Ethics

Informed consent was obtained from each participant, and the study protocol adhered to the 1975 Declaration of Helsinki as reflected in a priori approval by Aarhus County Ethical Scientific Committee (Denmark) (# 20010248). Clinicaltrials.gov (NCT01678274).

Statistical methods

Mathematical computations were performed using SPSS 24.0. Data was compared using independent and paired *t*-tests following evaluation for normal distribution by normal probability plots. Continuous variables are expressed as means ± standard deviations. A hypothesis-generating *post hoc* explorative correlation analysis was performed using Pearson's coefficient of correlation. A mixed model on the annual growth rate of the aortic diameter, with or without adjustment for BSA was used to study both the differences between the nine aortic measurement locations in the two groups and the influence of BAVs and/or coarctation. In this model, interaction between group and locations corresponding to heterogeneous annual growth rates in the two groups for each location was studied. Similarly, interaction between location and the presence of BAV and/or CoA corresponding to additional location-dependent heterogeneity caused by one or both covariates were also studied. The model was fitted with SAS/STAT 9.4 PROC MIXED using an unstructured covariance matrix for each group. $P < 0.05$ was considered significant. A Kaplan-Meier plot was generated using Prism 7.0 which utilized the entire recruited cohort censoring participants once an event occurred or at loss to follow-up.

Results

Study cohort demographics and loss to follow-up

The mean follow-up time was 8.8 ± 3.3 (1.6–12.6) years in TS ($N = 91$; 45, X in 64% [58/91] vs. other karyotypes in 36%). The mean follow-up time was 6.7 ± 0.5 (5.9–8.1) years in the female controls ($N = 37$). Women with TS and controls had similar ages [38.0 ± 10.5 (18–62)] years in TS vs. 39.0 ± 12.6 (19–61) years in controls, ($P = 0.6$). Two women exited at baseline. One died during prophylactic aortic root replacement due to an unseen coronary anomaly. The other had a chronic aortic dissection (Type A) at the first visit (*Table 1*). Detailed demographics have previously been presented.[12]

The aortic valve was bicuspid in 29% (26/91) in TS. In BAV, the right and left coronary cusps were fused in 81% (21/26) with the remaining having fusion of the right and non-coronary cusps. The aortic valve was stenotic in 12% (11/91) (1 severe, 3 moderate, 7 mild) with 81% (9/11) of these being BAV. Regurgitation was found in 23% (21/91) (1 moderate, 20 mild) with 52% (11/21) being BAV. Aortic valve dysfunction was mixed in 15% (6/41). Significant aortic valve dysfunction only occurred in BAV. All controls had normally functioning tricuspid aortic valves. During follow-up, two aortic valve prostheses were surgically inserted for severe BAV dysfunction (see above). CoA was present in 12% (11/91), co-segregating with BAV in 55% (6/11). All patients were surgically treated in early childhood.

Table 1 Aortic outcomes in Turner syndrome

Outcome	Follow-up	Aortic size, aortic growth and other aortic risk factors							Comment
		Maximum diameter[a]	Growth	BAV[b]	CoA	ETA	HTN	Pregnancy	
Death									
24-year old	None	48 mm [35 mm/m^2]	–	Yes [2A]	Yes	Yes	No	No	Death during aortic root surgery relating to injury to an anomalous LCx
Dissection									
50-year old	None	40 mm [26 m/m^2]	–	Yes	No	No	No	No	Type A dissection: Urgent ascending inter-position graft surgery and surviving after 12 years.
36-year old	5 years	28 mm [15 mm/m^2] [1A]	None	Yes	No	Yes	Yes	No	Type B dissection: treated conservatively
Prophylactic graft									
39-year old	11 years	39 mm [29 mm/m^2]	2 mm	Yes	Yes	No	Yes	No	Listed for surgery at final visit
48-year old	5 years	51 mm [35 mm/m^2] [1B]	11 mm	Yes [2B]	No	Yes	Yes	No	Composite graft with no complications
49-year old	4 years	35 mm [26 mm/m^2]	1 mm	Yes	No	No	Yes	No	Composite graft with no complications
65-year old	5 years	38 mm [31 mm/m^2]	3 mm	Yes	No	No	Yes	No	Listed for surgery but died of stroke on waiting list
Valve replacement									
48-year old	11 years	26 mm [16 mm/m^2]	2 mm	Yes [2C]	No	Yes	Yes	No	Uncomplicated mechanical valve replacement
53-year old	8 years	31 mm [20 mm/m^2]	2 mm	Yes [2D]	No	Yes	Yes	No	Uncomplicated mechanical valve replacement

BAV, bicuspid aortic valve; CoA, aortic coarctation; ETA, elongated transverse arch; HTN, hypertension; LCx, Circumflex artery.
[a]Maximum diameters are given for the mid-ascending aorta except for: **1A**) The proximal descending aorta at the later dissection site with the ascending diameter increasing from 38 to 39 mm [21 mm/m^2] during the follow-up, and: **1B**) The aortic sinuses with the mid-ascending increasing from 33 to 36 mm [24 mm/m^2].
[b]*No significant aortic valve dysfunction was present except for:* ***2A****) moderate aortic valve stenosis,* ***2B****) mild aortic valve regurgitation progressing to severe,* ***2C****) progressive severe mixed dysfunction, and:* ***2D****) severe aortic valve stenosis.*

One woman had a jump graft at arch level for childhood relief for an interrupted transverse arch. In TS, the ETA arch was seen in 54% (49/91). All controls had unobstructed thoracic aortas with conventional arch morphology.

All baseline ABPs and heart rates were elevated in TS compared to controls (*Table 2*). The proportion on antihypertensive medication in TS increased from 31% (28/91) to 59% (54/91) during the follow-up. No control took antihypertensive medication at baseline but 14% (5/37) did at follow-up. In TS, systolic (day) ABP, diastolic (day, 24-hour) ABP, and heart rates (day, night, 24-hour) decreased during the follow-up (*Table 3*). Women with TS taking antihypertensive medication at follow-up had reductions in systolic ABP, diastolic ABP, and heart rate (all 24-hour) from baseline to follow-up (Supplementary data online, *Table S1*). In TS, heart rate and blood pressures were comparable at baseline for those on antihypertensives and the treatment naïve (Supplementary data online, *Table S1*). Systolic (day, night, 24-hour) and diastolic (day, 24-hour) ABPs were comparable for TS and controls at follow-up with only diastolic (night) ABP remaining elevated in TS (*Table 3*). Women with TS were shorter [1.47 ± 0.07 (TS) vs. 1.69 ± 0.06 m (controls), $P < 0.001$] with lower body weight [57.4 ± 12.4 (TS) vs. 69.0 ± 12.8 (controls) kg, $P < 0.001$] and BSA [1.49 ± 0.16 (TS) vs. 1.78 ± 0.15 (controls) m^2, $P < 0.001$], but higher Body mass index [26.6 ± 5.6 (TS) vs. 24.1 (controls) kg/m^2, $P = 0.02$]. Increases in body weight drove a BSA increase during follow-up (all $P < 0.02$) for both TS (1.51 ± 0.18 m^2) and controls (1.81 ± 0.16 m^2).

Aortic diameter

Absolute aortic diameters were smaller at baseline in TS than in controls at all locations except the mid-arch and aortic isthmus (*Table 3*). During follow-up, the absolute aortic diameters increased at all locations in TS (except for the proximal arch) and in controls (*Table 2*). The BSAi aortic diameters were also all larger in TS than controls (Supplementary data online, *Table S2*).

Aortic growth rates

Aortic growth rates were comparable between TS and controls at the aortic sinus, sinotubular junction, and mid-ascending aorta. Conversely, growth rates were smaller in TS in the distal ascending aorta, transverse arch, aortic isthmus, and descending aorta (*Table 3*). The BSAi aortic diameters increased in the aortic sinuses, sinotubular junction, mid-ascending aorta, distal ascending aorta, and proximal descending aorta in TS and at all locations in the controls. When taking BSA into account, the aortic growth rates were comparable between TS and their controls at all locations except the distal ascending aorta, transverse arch and descending aorta (Supplementary data online, *Table S2*). Aortic growth rates had larger standard deviations in TS than controls signifying a larger variation at

Table 2 Blood pressure and antihypertensive treatment in Turner syndrome (*N* = 91) and their controls (*N* = 37)

	Turner syndrome		Controls		*P**		*P***	
	Baseline	*Follow-up*	*Baseline*	*Follow-up*	*Baseline*	*Follow-up*	*TS*	*C*
Blood pressure (mmHg)								
Systolic (day)	128 ± 15	124 + 15	118 ± 12	121 + 11	<0.001	0.33	0.04	0.10
Systolic (night)	111 ± 14	108 ± 15	100 ± 10	102 ± 11	<0.001	0.09	0.19	0.15
Systolic (24-hour)	122 ± 14	119 + 14	112 ± 10	114 + 11	0.001	0.15	0.10	0.42
Diastolic (day)	82 ± 11	78 ± 11	76 ± 8	77 ± 7	0.002	0.49	0.003	0.65
Diastolic (night)	69 ± 12	67 ± 10	60 ± 7	61 ± 7	<0.001	0.04	0.24	0.19
Diastolic (24-hour)	77 + 11	74 ± 10	71 ± 7	71 ± 7	0.003	0.11	0.04	0.75
Heart rate (min^{-1})								
Day	82 ± 10	75 ± 11	73 ± 8	71 ± 7	<0.001	0.02	<0.001	0.05
Night	70 ± 9	67 ± 10	61 ± 7	59 ± 7	<0.001	<0.001	0.003	0.03
24-hour	77 ± 9	72 ± 11	70 + 7	66 ± 6	<0.001	0.002	<0.001	0.001
Antihypertensive	28 (31%)	54 (69%)	0	5 (14%)	–	–	–	–

*Student's independent t-test comparing Turner syndrome (TS) to controls (C) at baseline and follow-up, respectively.
**Paired t-test comparing baseline and follow-up for Turner syndrome (TS) and controls (C).

Table 3 Aortic diameters and aortic growth rates in Turner syndrome (*N* = 91) and controls (*N* = 37)

	Turner syndrome		Controls		Turner syndrome	Controls	
	Baseline[a] mm	Follow-up[b] mm	Baseline[a] mm	Follow-up[c] mm	Growth rate mm/year	Growth rate mm/year	*P**
Aortic sinus	29.1 ± 3.8	31.9 ± 4.7	30.0 ± 3.2	32.3 ± 3.3	0.32 ± 0.36	0.32 ± 0.17	0.99
Sinotubular junction	25.2 ± 4.1	26.5 ± 4.7	25.3 ± 2.9	26.4 ± 3.0	0.14 ± 0.26	0.16 ± 0.10	0.54
Mid-ascending	27.2 ± 4.9	29.2 ± 5.5	26.3 ± 3.6	28.1 ± 3.9	0.20 ± 0.26	0.26 ± 0.14	0.15
Distal Ascending	25.2 ± 3.6	25.8 ± 3.7	25.0 ± 3.4	26.5 ± 3.6	0.06 ± 0.17	0.22 ± 0.11	<0.001
Proximal arch	23.5 ± 3.6	23.8 ± 3.8	23.9 ± 3.3	25.2 ± 3.7	-0.01 ± 0.26	0.19 ± 0.12	<0.001
Mid-arch	20.3 ± 2.6	20.6 ± 2.5	22.5 ± 2.8	23.5 ± 2.9	0.03 ± 0.18	0.16 ± 0.08	<0.001
Isthmus	19.1 ± 2.3	19.6 ± 2.3	21.1 ± 2.6	22.0 ± 2.6	0.06 ± 0.22	0.14 ± 0.09	0.04
Proximal descending	19.5 ± 3.1	20.4 ± 3.4	19.6 ± 2.5	21.1 ± 2.7	0.07 ± 0.17	0.22 ± 0.10	<0.001
Distal descending	18.2 ± 2.3	18.5 ± 2.3	18.2 ± 2.4	19.3 ± 2.3	0.01 ± 0.13	0.16 ± 0.08	<0.001

[a]Baseline aortic diameters were comparable at all locations of the thoracic aorta when comparing Turner syndrome to their controls except for the mid-arch and isthmus where they were smaller in Turner syndrome (Student' independent t-test, P < 0.001).
[b]Aortic diameters increased from baseline to follow-up in Turner syndrome at all **locations** except the proximal arch (Student's paired t-test, P < 0.004).
[c]Aortic diameters increased from baseline from follow-up in the controls at all **locations** (Students paired t-test, P < 0.001).
*Student's independent t-test comparing aortic growth rates for Turner syndrome to controls.

all locations (*Table 3*). At the most proximal aortic locations where the mean aortic growth rates were largest overall, the highest individual annual growth rates in TS were 2.2 (sinuses), 1.2 (sinotubular junction), and 1.2 (mid-ascending) mm/year. This compared to 0.85, 0.58, and 0.65 mm/year for the controls in the same locations. The highest growth rates for the sinuses and sinotubular junction were in a woman with a progressively regurgitant BAV who went for a composite aortic graft after 5.1 years of follow-up.

Determinants of aortic growth rates

An explorative bivariate analysis was performed (Supplementary data online, *Text T1*) that indicated an impact of BAV, aortic valve regurgitation, ABP, and heart rate on the proximal aorta. There was no impact of karyotype. In the subsequent mixed models, a strong interaction was present between group (TS vs. controls) and location for both absolute and BSAi growth rates ($P = 0.0008$). In other words, any differences in absolute growth rate between the TS and the control group appeared to depend on the aortic location. When BAV and CoA both were added as covariates to the mixed model, the above-mentioned interaction between group and location was no longer significant ($P = 0.07$). Conversely, interactions between location and both BAV ($P = 0.006$) and CoA were significant ($P = 0.0009$) indicating that BAV and CoA have a location-dependent influence on aortic growth rates. No other variable showed similar interactions, including ETA, ABP, heart rate, antihypertensives, age, and body size.

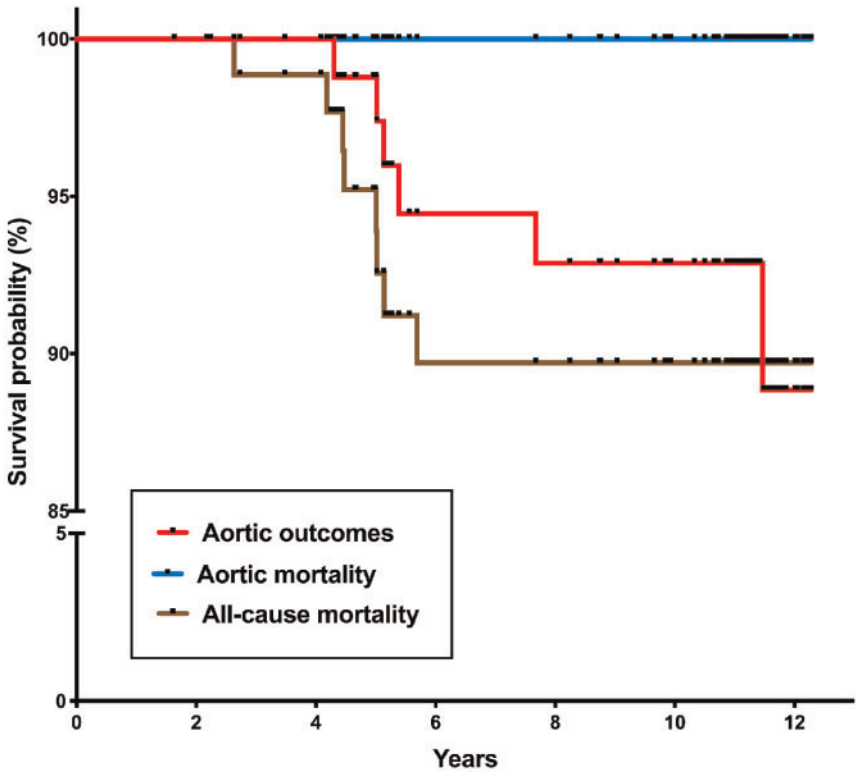

Figure 1 Kaplan-Meier plot of survival free years from aortic outcomes, aortic death and all-cause mortality in Turner syndrome.
The y-axis has been truncated for illustration purposes.

Aortic outcomes

Over 799 prospectively registered years in TS, one woman suffered aortic dissection (Type B), two women had elective uncomplicated composite aortic grafts, two women were electively listed for aortic interposition grafts, and two women with normal aortic size had elective aortic valve placements (*Table 1*). Thus, the incidence of the combined aortic and aortic valve-related outcome was 9 (1126 events per 100 000 observation years) (*Figure 1*). Cardiovascular, but non-aortic, mortalities included two deaths from ischemic stroke of which one woman was on the waiting list for prophylactic aortic surgery. No women with an ascending aorta above the current surgical threshold suffered an acute aortic event (Supplementary data online, *Table S3*). Further fatalities included: two from unknown cause (no autopsy) and four from confirmed non-cardiovascular causes (disseminated malignancies, sepsis, and during hip surgery). The aortic mortality was 1 per 799 years (125 deaths per 100 000 observation years). The combined all-cause mortality rate was 9 per 799 years (1126 deaths per 100 000 observation years). There were no fatalities in the control group. The remaining loss to follow-up [9% (9/102)] was caused by: implantation of cochlear implants (non-CMR compatible), emigration, withdrawal for non-health-related reasons, and technically inadequate CMR (repeat imaging declined). Among the healthy female controls, no cardiovascular events led to loss to follow-up or occurred during follow-up in the 37 participating women with 249 prospectively registered years at risk.

Discussion

This prospective study of aortic disease in TS unveiled comparable or smaller aortic growth rates compared with age- and gender-matched controls during pragmatic treatment for clinical hypertension. Aortic growth in TS differed from healthy controls with larger standard deviations, but also in a location dependent fashion with comparable growth rates in the root and mid-ascending aorta but smaller for most of the remaining locations. This means that dilatation of the aorta in a woman with TS does not evolve in the same manner as that of a normal woman. This perturbation was, at least, partly driven by the presence of BAV and CoA. Speculatively, this TS specific aortic growth perturbation has a genetic origin with lack of X-chromosome material playing an important role.[14] The study also showed that aortic disease continues to have an impact on morbidity and mortality in TS.

Aortic growth rates have been included as a risk marker for aortic dissection because of an intuitive link between rapid growth and more aggressive aortic disease.[5,15] The observed aortic growth rates did not unequivocally identify this cohort of women with TS as different from their female peers even though some exhibited comparatively more rapid growth and the range of growth was larger in TS. This was not owed to a different physical stature. This is an intriguing finding because aortic outcomes in TS were inferior to controls with around 6% of the TS patients suffering from a form of aortic disease.

Other studies have investigated growth rates in both aortic diseases and the background population, and they have arrived at very varied levels of growth over time.[5,16,17] Selection towards a more severe phenotype is an important consideration. This was attempted minimized by recruiting from an endocrine outpatient clinic and the national TS society rather than from a cardiology setting that might have biased findings towards worse aortic phenotypes. With the longest follow-up for aortic diameter in TS using a standardized technique, the reported diameters may thus serve as reference for expected growth rates in TS using gold-standard, non-contrast, radiation-free 3D imaging with electrocardiogram-triggering for optimal measurement variability.[3,18]

The presence of BAV and/or CoA did, at least to some extent, explain the perturbed aortic growth in TS. However, the standard deviations remained larger in TS compared with controls. This suggests the presence of further potential differentiators that may relate either to having TS *per se* or unidentified factors within TS. Aortic valve function and morphology appeared to be important determinants of aortic growth rates, confirming shorter-term observations in TS.[12] These findings mirror outcome studies in non-syndromic BAV where aortic valve regurgitation marks inferior outcomes.[15,19] This study therefore indicates that caution may be warranted not just in BAV but also in aortic valve regurgitation. The range of aortic growth rates was higher in TS, and the highest ascending growth rates did occur in a woman who finally had prophylactic surgery. Due to the small effect size and relatively low event rate it is difficult to establish a link between aortic growth rates and events. Emerging surrogate markers of aortic disease may be of help to assess the significance of growth, and structural and functional risk markers may come to play a role to disease assessment in TS and other aortic disease states.[20,21]

Considerable aortic disease caused exclusion at baseline or early exit from the prospective study due to aortic dissections (type A and B) or elective surgery. This was evident with aortic and aortic valve-related outcomes occurring in 1001 per 100 000 observation years. No cases of confirmed death from aortic dissection occurred but one death did occur during prophylactic aortic surgery. Practices for screening for and treatment of aortic disease in TS have changed considerably over the course the study.[2,10] This coincided with knowledge of the adverse impact of aortic disease on morbidity and mortality in TS becoming well-established,[6,22,23] and a threshold has been proposed above which the risk of aortic dissection seems particularly increased.[2,4,24] Current consensuses suggest surgery at mid-ascending aortic diameters (BSAi) $\geq$25 mm/m^2 with a stronger recommendation when other risk factors for aortic dissection are present.[2,10,24] This change in knowledge and recommended management strategies has likely impacted surgical referral patterns towards increasingly proactive management as the study progressed. This was, perhaps, most evident by a woman being listed for surgery after her follow-up despite minimal aortic growth and exceeding the surgical threshold already at baseline. The best practice today is based on relatively few incident cases and further evidence is needed to better understand the association of aortic diameters with dissection in TS. No death occurred due to diseases of the native thoracic aorta or aortic valve in our cohort and the increased all-cause mortality is in keeping with prior epidemiological studies.[22,23] This reflects the heavy burden of morbidity and mortality from a range of associated features, and further study is needed to assess how this impacts the risk of cardiovascular surgeries.

A striking finding was the large proportion in TS who received or commenced antihypertensive treatment during follow-up. Hypertension is known to be very prevalent in TS, and negatively impacts aortic disease in TS.[8,12] However, correlations were limited between aortic growth rates and blood pressure in this study, and the same applied to any potential impact of antihypertensive treatment that was indicated to beneficially impact aortic growth rates in our shorter-term study.[13] The ABP findings from the study were fed back to the clinicians outside the study in the outpatient clinic, where treatment would be initiated according to existing guidelines and patient preference.[25] The findings relating to blood pressure and antihypertensive treatment do thus not compare to strict observational or controlled interventional settings; any impact of blood pressure or antihypertensive drugs may be masked by different practices.

Study limitations

The study cannot be compared to an interventional trial where specific drugs, doses, and targets are assessed. Therefore, antihypertensive treatment was registered as a dichotomous variable rather than class-specific parameter and drug effectiveness cannot be further assessed beyond ABP. Since guidelines for surgical interventions changed over the study period fewer dissections should speculatively occur with later outcomes impacted more by surgical outcomes than 'true' native disease. Moreover, changes in guidelines and different local practices will also have impacted the surgical referral patterns across the different centres to whom the study findings were fed back to. It is a major strength that outcome parameters were evaluated over nearly a decade in the heterogeneous outpatient clinic. This makes our findings applicable to day-to-day clinical practice. The controls were followed for a slightly shorter period but by using indexation of aortic growth to the follow-up time we attempted to reduce any differential impact of the duration of follow-up both between TS and controls and within each group. Owing to the cohort size, the predictors of aortic growth (CoA/BAV) need validation in future prospective studies in larger cohorts.

Conclusion

Aortic growth rates in adult women with TS are similar to or smaller than in healthy female controls when widely treated for clinical hypertension. BAV and CoA appear to impact aortic growth. Spontaneous dissection seems rare and no mortality occurred due to aortic dissection. However, planned aortic root surgery or valve surgery, remain a considerable cause of morbidity and mortality throughout adult life.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Funding

This work was supported by grants from Lundbeck, the Danish Heart Foundation, Augustinus Foundation, Toyota Foundation, Aase og Einar

Danielsen, the Novo Nordisk Foundation (NNF13OC0003234, NNF15OC0016474), "Fonden til lægevidenskabens fremme", the Hede Nielsen foundation, and Aarhus University.

Conflict of interest: The authors report no relationships that could be construed as a conflict of interest. The authors have all contributed to and approved the final article.

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