ONLINE SUPPLEMENT

Obstructive sleep apnea and the progression of thoracic aortic aneurysm: a prospective cohort study

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Table E1. Patient characteristics of the per-protocol subgroup with complete data for annual aortic growth (n=160).

Anthropometrics		
Age, years		68.7 (60.0 to 73.6)
Male, n (%)		132 (83%)
BMI, kg/m^2		26.2 (24.4 to 29.1)
Height, cm		176 ± 7
Weight, kg		83.9 ± 12.9
Body surface area, m^2		2.0 ± 0.2
Neck circumference, cm		39.5 ± 3.5
Blood pressure data		
Office (average of three)	Systolic, mmHg	129.3 (119.6 to 143.4)
	Diastolic, mmHg	82.3 (75.6 to 89.5)
Home (7 day average)	Systolic, mmHg	125.4 (118.1 to 132.6)
	Diastolic, mmHg	77.0 (70.4 to 83.7)
Comorbidities		
Active / Ex- / Never-Smokers, n (%)		18 (11%) / 75 (47 %) / 67 (42%)
History of hypertension, n (%)		116 (73%)
History of diabetes mellitus type 2, n (%)		10 (7%)
HbA_{1c}, %		5.7 ± 0.7
History of dyslipidemia, n (%)		92 (58%)
Cholesterol, mmol/l		4.7 ± 1.2
Triglycerides, mmol/l		1.5 (1.0 to 2.0)
High-density lipoprotein, mmol/l		1.4 (1.0 to 1.6)
Low-density lipoprotein, mmol/L		2.6 (1.9 to 3.2)

Data are n (%), median (interquartile range), or mean ± SD as appropriate. BMI, body mass index.

Table E2. Medication of the final TAA cohort at baseline (n=230).

Drugs	**Baseline, all participants** (n=230)	**Baseline, complete cases** (n=160)	**Absolute changes during follow-up**	**Follow-up 3 yrs, complete cases** (n=160)
β-Adrenoreceptor antagonists	120 (52.2%)	82 (51.2%)	+4 / -2	84 (52.5%)
α-Adrenoreceptor antagonists	16 (7.0%)	8 (5.0%)	+0 / -0	8 (5.0%)
Angiotensin-converting-enzyme inhibitors	78 (33.9%)	59 (36.9%)	+4 / -1	62 (38.8%)
Calcium channel antagonists	56 (24.3%)	38 (23.7%)	+5 / -1	42 (26.3%)
Angiotensin-II-receptor blockers	59 (25.7%)	36 (22.5%)	+2 / -1	37 (23.1%)
Aldosterone antagonists	9 (3.9%)	6 (3.8%)	+0 / -0	6 (3.8%)
Diuretics	74 (32.2%)	45 (28.1%)	+2 / -1	46 (28.8%)
Statins	129 (56.1%)	94 (58.8%)	+5 / -1	98 (61.3%)
Insulin	4 (1.7%)	3 (1.9%)	+3 / -0	6 (3.8%)
Oral antitiabetics	16 (7.0%)	11 (6.9%)	+4 / -0	15 (9.4%)
Oral anticoagulation	78 (33.9%)	58 (36.2%)	+5 / -1	62 (38.8%)
Aspirin	88 (38.3%)	64 (40.0%)	+0 / -0	64 (40.0%)
Total number of antihypertensive drugs				
0 antihypertensive drugs	37 (16.1%)	26 (16.3%)	+0 / -2	24 (15.0%)
1 antihypertensive drug	64 (27.8%)	48 (30.0%)	+1 / -3	46 (28.8%)
2 antihypertensive drugs	64 (27.8%)	45 (28.1%)	+4 / -2	46 (28.8%)
3 antihypertensive drugs	43 (18.7%)	28 (17.5%)	+4 / -3	29 (18.1%)
4 antihypertensive drugs	19 (8.3%)	13 (8.1%)	+4 / -2	15 (9.4%)
5 antihypertensive drugs	3 (1.3%)	0 (0%)	+0 / -0	0 (0%)

All data are n (%)

Table E3. Average TAA growth rates and blood pressure data by changes in overall number of antihypertensive drugs.

	Less antihypertensive drugs at the end of follow-up	**No change of** antihypertensive drugs at the end of follow-up	**More** antihypertensive drugs at the end of follow-up	ANOVA p-value
n	2	146	12	
Aortic sinus growth rate, mm	0.00 ± 0.05	0.54 ± 1.26	0.50 ± 1.98	0.259
Ascending aorta growth rate, mm	1.00 ± 0.9	0.59 ± 1.13	0.68 ± 1.20	0.586
Systolic blood pressure (office), mmHg	126.0 (121.0 to 131.0)	129.2 (119.3 to 144.3)	130.5 (120.0 to 136.0)	0.682
Diastolic blood pressure (office), mmHg	80.0 (75.0 to 85.0)	81.5 (74.9 to 89.3)	81.3 (76.3 to 88.3)	0.568

Figure E1. Absolute aortic sinus and ascending aorta measurements over three years of complete cases (n=160).

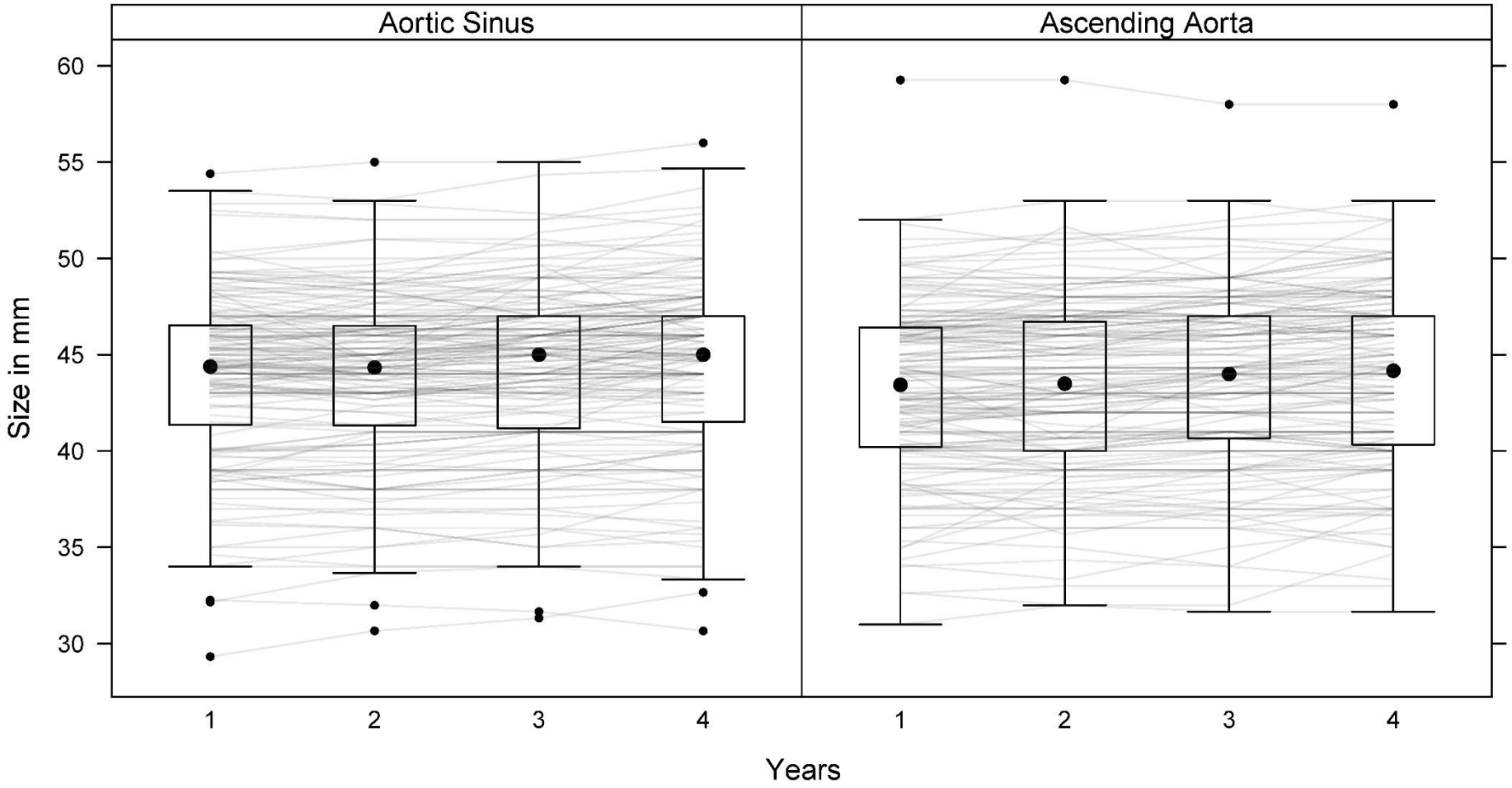

Table E4. Normal linear regression model based on TAA expansion as the primary outcome (n=160) and controlling for baseline value and pre-defined cardiovascular confounders. Model 1 ($\beta_{1\ AHI}$) was conducted according to the study protocol. Model 2-4 ($\beta_{1\ ODI}$ / $\beta_{1\ T90a}$ / $\beta_{1\ T90r}$) are post-hoc analysis exploring potential association of alternative severity parameters of OSA. Model 5 ($\beta_{1\ AHI}$) limited the analysis to subjects who did not effectively initiate CPAP-therapy during the course of the study.

Substitution of $\beta_{1\ AHI}$

			Aortic sinus			Ascending aorta		
			Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Model 1 (n=160) $\beta_0 + \beta_{1\ AHI} + \beta_{2\text{-}8}$	β_0	Intercept	0.547	-2.663 to 3.757	0.74	-0.812	-3.901 to 2.278	0.60
	$\beta_{1\ AHI}$	Apnea-hypopnea index, hr^{-1}	0.025	0.009 to 0.040	**0.002**	0.026	0.011 to 0.041	**0.001**
	β_2	Age, years	-0.001	-0.022 to 0.021	0.97	0.001	-0.019 to 0.022	0.91
	β_3	Male (Reference level: female)	0.604	-0.060 to 1.268	0.074	0.208	-0.430 to 0.847	0.52
	β_4	Body surface area, m^2	-0.706	-2.380 to 0.968	0.41	0.331	-1.280 to 1.943	0.68
	β_5	n of antihypertensives (0 to 5), n	0.036	-0.141 to 0.213	0.69	-0.003	-0.173 to 0.167	0.97
	β_6	BMI, kg/m^2	0.010	-0.053 to 0.072	0.76	-0.005	-0.066 to 0.055	0.86
	β_7	History of dyslipidemia (yes/no)	0.076	-0.094 to 0.246	0.38	0.071	-0.092 to 0.235	0.39
	β_8	Active smoker (yes/no)	-0.162	-0.767 to 0.442	0.60	-0.016	-0.598 to 0.566	0.96
Alternative OSA severity parameters (substitution of β_1)								
Model 2 (n=160) $\beta_0 + \beta_{1\ ODI} + \beta_{2\text{-}8}$	$\beta_{1\ ODI}$	Oxygen-desaturation index, hr^{-1}	0.023	0.008 to 0.038	**0.001**	0.019	0.004 to 0.034	**0.002**
Model 3 (n=160) $\beta_0 + \beta_{1\ T90a} + \beta_{2\text{-}8}$	$\beta_{1\ T90a}$	Absolute time SpO_2 <90%, minutes	-0.001	-0.003 to 0.006	0.563	0.001	-0.003 to 0.006	0.910
Model 4 (n=160) $\beta_0 + \beta_{1\ T90r} + \beta_{2\text{-}8}$	$\beta_{1\ T90r}$	Relative time SpO_2 <90%, % of recording time	-0.001	-0.213 to 0.191	0.917	-0.010	-0.330 to 0.824	0.276
Limitation to subjects who did not effectively initiate CPAP during the trial (restriction of n)								
Model 5 (n=146) $\beta_0 + \beta_{1\ AHI} + \beta_{2\text{-}8}$	$\beta_{1\ AHI}$	Apnea-hypopnea index, hr^{-1}	0.029	0.012 to 0.049	**0.005**	0.028	0.009 to 0.050	**0.004**

Bold values denote statistical significance at the $p<0.05$ level. Model 1: $R^2=0.127$. BMI, body mass index; CI, confidence interval
Akaike's information criterion (AIC): Model 1 (-212.9) < Model 2 (-212.1) < Model 4 (-206.2) < Model 3 (-205.6) < Model 5 (-203.6)

Table E5. Average growth rates by AHI categories above and below 15 events per hour.

	AHI <15 events/hour	AHI ≥15 events/hour	p-value
n	105	55	
Aortic sinus, mm	0.35 ± 1.05	0.95 ± 1.49	0.005
Ascending aorta, mm	0.44 ± 1.19	0.90 ± 1.23	0.016

Quality control

Table E6. Aortic sinus and ascending aorta dimensions measured by the same observer and corresponding absolute and relative measures of intraobserver variability cumulatively 1,920 measurements (160 subjects x 4 visits x 3 measurements).

	Absolute intraobserver variability			**Relative intraobserver variability**		
	Absolute difference (mm)*	Difference (mm)*	Individual SD (mm)	Absolute differene (%)*	Difference (%)*	SD (%)
Aortic Sinus, average	0.62	+0.01	0.34	1.43	+0.20	0.79
Ascending aorta, average	0.57	-0.01	0.32	1.34	-0.21	0.74

* for the difference the two most extreme values (minimum, maximum) were considered

Table E7. Intraclass correlation coefficient using one-way ANOVA from 1,920 measurements at the aortic sinus (160 subjects x 4 visits x 3 measurements).

Source of variation	**Sum of squares**	**Degr. of freedom**	**Mean squares**	**p-value**	**ICC (95%CI)**
Subjects	37,263.5	639	58.3	<0.001	0.982 (0.980-0.984)
Error	463.2	1,280	0.4	-	
Total	37,726.7	1,919	19.7	-	

95% CI, Confidence interval; ICC, Intraclass correlation coefficient

Table E8. Intraclass correlation coefficient using one-way ANOVA from 1,920 measurements at the ascending aorta (160 subjects x 4 visits x 3 measurements).

Source of variation	Sum of squares	Degr. of freedom	Mean squares	p-value	ICC (95%CI)
Subjects	38,915.1	639	60.4	<0.001	0.987 (0.985 – 0.989)
Error	334.9	1,280	0.3	-	
Total	38,915.1	1,919	20.3	-	

95% CI, Confidence interval; ICC, Intraclass correlation coefficient

Table E9. Average aortic sinus and ascending aorta growth rates measured by three different observers in 480 growth rate calculations (160 subjects x 3 annual growth rates).

	Observer 1	Observer 2	Observer 3	p-value (global)
Measurements, n (%)	288 (60.0%)	180 (37.5%)	12 (2.5%)	-
Aortic sinus	0.17±0.88	0.21±0.84	0.29±1.02	0.743
Ascending aorta	0.22±0.98	0.25±0.83	0.18±0.96	0.160