

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC III. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med* 2008;358:2787-95.

Supplemental Appendix Table 1. Summary of Individual Ocular Phenotype, Mutation Analysis, Rate of Change in Aortic Root Diameter, and Medication Therapy Before and After Starting ARB Therapy Among Entire Patient Cohort (n=18).*

Pt. No.	Ghent Criteria†	Ocular Disease§	Mutation Analysis	Rate of Change in Aortic Root (mm/yr)			Medical Therapy¶	
				Pre-ARB	Post-ARB	% Change	Pre-ARB	Post-ARB
1.	Yes	Ectopia Lentis	Not Tested	1.26	<0.01	>99	BB	BB + ARB ²
2.	Yes	Ectopia Lentis	Not Tested	4.11	0.87	79	BB	BB + ARB ¹
3.	Yes	Ectopia Lentis	Not Tested	3.43	1.59	53	BB + ACEi	BB + ARB ¹
4.	Yes	Ectopia Lentis	<i>FBN1</i> Mutation	4.28	0.88	79	BB + ACEi	BB + ARB ¹
5.	Yes	Ectopia Lentis	Not Tested	1.23	0.39	68	BB → CCB	ARB ³
6.	Yes	Ectopia Lentis	<i>FBN1</i> Mutation	1.77	0.52	71	BB	BB + ARB ²
7.	Yes	Ectopia Lentis	Not Tested	2.68	<0.01	>99	BB	BB + ARB ¹
8.	Yes	Early Myopia	Not Tested	2.02	0.39	81	BB → CCB	ARB ²
9.	Yes	Ectopia Lentis	Not Tested	1.41	0.36	74	BB	BB + ARB ¹
10.	Yes	Ectopia Lentis	Not Tested	3.25	0.60	81	BB	BB + ARB ¹
11.	Yes	None	<i>FBN1</i> Mutation	2.01	1.17	42	BB	BB + ARB ²
12.	Yes	Early Myopia	Not Tested	1.32	<0.01	>99	BB	ARB ²
13.	Yes	Ectopia Lentis	<i>FBN1</i> Mutation	3.13	0.34	89	BB	BB + ARB ¹
14.	Yes	Ectopia Lentis	Not Tested	10.69	0.65	94	BB	BB + ARB ¹
15.	Yes	Ectopia Lentis	<i>FBN1</i> Mutation	11.04	0.73	93	BB + ACEi	BB + ARB ¹
16.	Yes	Ectopia Lentis	<i>FBN1</i> Mutation	2.38	<0.01	>99	BB	BB + ARB ²
17.	Yes	Ectopia Lentis	Not Tested	4.67	1.13	76	BB + ACEi	BB + ARB ¹

18.	Yes	Ectopia Lentis	Not Tested	3.03	0.15	95	BB	BB + ARB ¹
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* Data represent a summary of diagnostic criteria for all 18 pediatric patients in the retrospective cohort, with the corresponding mean rate of change in aortic root diameter and the medical therapy used before and after starting ARB therapy. ARB denotes angiotensin receptor blocker; ACEi angiotensin converting enzyme inhibitor; BB Beta-Blocker; CCB calcium channel blocker

† Ghent diagnostic criteria for Marfan syndrome include major & minor criteria for disease involvement of the skeletal, ocular, cardiovascular, pulmonary organ systems, skin, and dura, as well as the contribution of family or genetic history.¹⁴

§ Ocular disease established in all patients following examination by a board-trained ophthalmologist.

¶ Medical therapy prior to starting ARB therapy involved BB used alone or in combination with an ACEi. BB agents included atenolol and propranolol, typically started at an empiric weight-based dose between 0.5 to 1.0mg/kg/day before increasing the dose sufficient to keep the heart rate after submaximal exercise below 100 or 110 for children above or below the age of 5-years, respectively, or until side effects occurred. The ACEi captopril had been started at a dose of 0.3mg/kg/day and increased to a goal dose of 1.0mg/kg/day. The CCB verapamil had been prescribed for patients intolerant to beta-blockers, and was started at an initial dose of 120mg/day before increasing the dose to a goal of 240mg/day in older children. The decision to start ARB therapy in patients was made on the basis of three clinical criteria, including evidence of a rapid rate of change in aortic root diameter while on prior medical therapy¹; evidence of an aortic root diameter \geq 4.0 cm approaching need for surgical intervention²; or evidence of intolerance to all prior medical therapy³.

Supplemental Appendix Table 2. Comparison of Annual Rate of Change in Absolute and Normalized Growth Parameters Before and After the Initiation of ARB Therapy*

Variable	<u>Pre-ARB</u>		<u>Post-ARB</u>		P-value†
	Median	Mean(±SD)	Median	Mean(±SD)	
Change in Body Mass					
Weight (kg/yr)	3.4	3.62(1.59)	2.6	3.05(1.49)	0.42
Weight Z-score/yr	+0.3	+0.61(2.54)	+0.4	+0.61(2.05)	0.45
BMI (kg/m ² /yr)	0.3	0.48(1.10)	0.4	0.47(0.54)	0.47
BMI Z-score/yr	+0.1	+0.21(0.53)	+0.4	+0.54(0.70)	0.28
Change in Linear Growth					
Height (cm/yr)	9.0	9.63(7.47)	4.4	5.01(3.31)	<0.05
Height Z-score/yr	-0.1	+0.14(0.61)	-0.2	-0.06(0.69)	0.06
Height Velocity Z-score	+0.7	+0.98(1.64)	-1.3	-1.02(2.16)	<0.05

* Measurements of height and weight were made at the time of echocardiography and used to calculate body mass index (BMI) and height velocity before converting into absolute and normalized growth rates. Z-scores for weight, height, and BMI were calculated using Center for Disease Control 2000 reference standards.

† P values were calculated by the Wilcoxon signed-rank test