Effect of Losartan or Atenolol on Children and Young Adults With Bicuspid Aortic Valve and Dilated Aorta

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Bicuspid aortic valve aortopathy is defined by dilation of the aortic root (AoRt) and/or ascending aorta (AsAo), and increases risk for aortic aneurysm and dissection. The effects of medical prophylaxis on aortic growth rates in moderate to severe bicuspid aortopathy have not yet been evaluated. This was a single-center retrospective study of young patients (1 day to 29 years) with bicuspid aortopathy (AoRt or AsAo z-score ≥ 4 SD, or absolute dimension ≥ 4 cm), treated with either losartan or atenolol. Maximal diameters and BSA-adjusted z-scores obtained from serial echocardiograms were utilized in a mixed linear effects regression model. The primary outcome was the annual rate of change in AoRt and AsAo z-scores during treatment, compared with before treatment. The mean ages (years) at treatment initiation were 14.2 ± 5.1 (losartan; n = 27) and 15.2 ± 4.9 (atenolol; n = 18). Median treatment duration (years) was 3.1 (IQR 2.4, 6.0) for losartan, and 3.7 (IQR 1.4, 6.6) for atenolol. Treatment was associated with decreases in AoRt and AsAo z-scores (SD/year), for both losartan and atenolol (pre- vs post-treatment): losartan/AoRt: +0.06 ± 0.02 vs -0.14 ± 0.03, p < 0.001; losartan/AsAo: +0.20 ± 0.03 vs -0.09 ± 0.05, p < 0.001; atenolol/AoRt: +0.07 ± 0.03 vs -0.02 ± 0.04, p = 0.04; atenolol/AsAo: +0.21 ± 0.04 vs -0.06 ± 0.06, p < 0.001. Treatment was also associated with decreases in absolute growth rates (cm/year) for all comparisons (p ≤ 0.02). Medical prophylaxis reduced proximal aortic growth rates in young patients with at least moderate and progressive bicuspid aortopathy. **(Am J Cardiol 2021;144:111−117)**

Bicuspid (bicommissural) aortic valve (BAV) is a very common congenital heart defect,[1−3] is highly heritable,[4−8] and is often accompanied by proximal aortic disease (aortopathy).[9−12] BAV aortopathy is defined as dilation of the aortic root (AoRt) and/or ascending aorta (AsAo). This aortopathy is frequently present and persistent throughout childhood and adolescence,[13] AoRt and AsAo dilation may also be present without clinically significant aortic valve stenosis or insufficiency,[13,14] and progresses more rapidly compared with the normal population.[13,15,16] More severe dilation is associated with increased risk for aortic aneurysm, dissection, and death during adulthood.[17−19] Although prophylactic medical therapy is an integral part of management for other forms of aortopathy,[5,20] the utility of medical prophylaxis for BAV-associated aortopathy is not yet known. Both beta blockers and angiotensin receptor blockers have been shown to stabilize aortic growth in patients with the Marfan syndrome.[21−23] The primary study objective was to assess the aortic growth, expressed as annual rates of change in AoRt and AsAo z-scores (SD/year) during treatment compared with before treatment, in a cohort of young patients with BAV.

Methods

We conducted a single-center, retrospective pilot study of patients with BAV and aortic dilation (aged 1 day to 29 years) followed at Boston Children's Hospital (BCH) from 1990 to 2018. Management of BAV aortopathy was organized by a center-specific, quality-improvement Standardized Clinical Assessment and Management Plan (SCAMP).[24] The SCAMP specified medical prophylaxis with either losartan or atenolol for patients with severe dilation of the AoRt and/or AsAo. The treating physician determined the treatment plan for individual patients. For this study, eligible patients were identified via the BCH SCAMP database. Study inclusion criteria were (1) bicuspid or unicuspid aortic valve and related variants (Figure 1), (2) moderate to severe aortopathy defined as AoRt or AsAo z-score ≥ 4 SD and/or absolute AoRt or AsAo diameter ≥ 4 cm (Figure 1), and (3) history of medical prophylaxis with losartan or atenolol. Patients with complex congenital heart disease or known connective tissue disorders were excluded.

Baseline pre-treatment characteristics included clinical and echocardiographic data closest to the start of medical prophylaxis, and after treatment characteristics included most recent follow-up data. Postoperative data were excluded for patients with history of AoRt or AsAo surgery.

Maximal mid-systolic (inner edge to inner edge)[25,26] AoRt and AsAo diameters and body surface area (BSA)-adjusted z-scores were obtained from 2D echocardiograms before and during treatment utilizing the BCH echocardiographic database and normative echocardiographic values for cardiovascular structures.[27]

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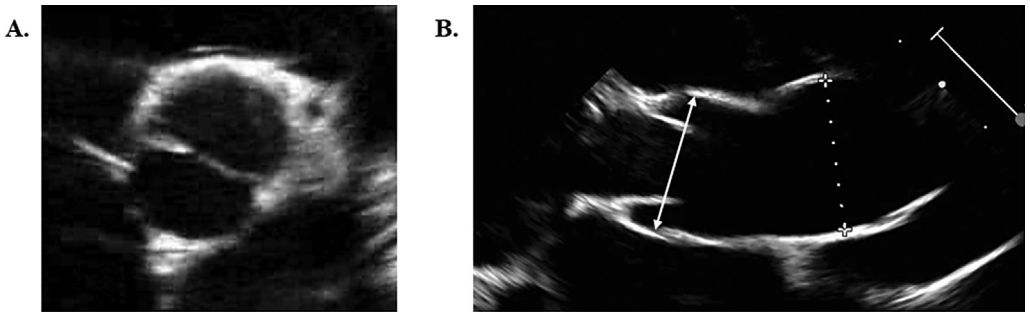

Figure 1. Bicuspid aortopathy patient inclusion criteria. Study inclusion criteria were bicuspid aortic valve (1A) and related variants, and moderate to severe aortopathy, defined as aortic root (1B, solid double arrow) or ascending aorta (1B, dashed line) z-score ≥ 4 standard deviations and/or absolute diameter ≥ 4 centimeter. All patients had a history of medical prophylaxis with either losartan or atenolol.

The primary outcomes of interest were the annual rates of change in maximal AoRt and AsAo diameter z-scores (SD/yr) during medical treatment, compared with those before treatment. The secondary outcomes were the annual rates of change in maximal AoRt and AsAo diameters (cm/yr) during treatment compared with those before treatment.

Patient characteristics were described using mean (standard deviation) or median (interquartile range) as appropriate. Diameters and z-scores for the AoRt and AsAo were assessed as continuous variables in primary analyses, and categorical variables when employed as a subgroup factor (AoRt z-score ≥ 5 SD, AsAo z-score ≥ 5 SD). Mean changes (slopes over time) in aortic diameters and BSA-adjusted z-scores for the 2 treatments were estimated using a mixed effects linear regression model with an unstructured covariance matrix (selected using the Bayesian information criterion [BIC]), with a treatment timing (pre- vs after treatment) x time interaction effect and drug x treatment timing x time effect. After treatment slopes of aortic diameters by patient subgroups, separately for each treatment, were estimated and compared using mixed effects linear regression with a compound symmetric covariance structure (selected based on the BIC), with a patient subgroup x time interaction effect. Subgroups examined included gender, age at treatment initiation (<15 vs ≥ 15 years), AoRt z-score ≥ 5 SD vs < 5 SD, AsAo z-score ≥ 5 SD vs < 5 SD, history of coarctation surgery, presence vs absence of at least moderate aortic insufficiency, and presence vs absence of at least moderate aortic stenosis. A p-value of < 0.05 was considered significant. Analyses were conducted with SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) and R version 3.5.1. All authors had access to the study data and shared responsibility for its integrity, analysis, and interpretation. All study activities were approved by the Cardiology Scientific Review Committee and the Institutional Review Board at BCH. Due to the retrospective design, a waiver of informed consent was granted.

Results

A total of 41 patients who met study criteria were identified. Four patients were included in both treatment groups, having received each drug at different times, resulting in 27 patients in the losartan group and 18 in the atenolol group. Baseline pre-treatment characteristics (Table 1A) were generally similar in the 2 treatment groups, excluding patients from the losartan (n = 5) and atenolol (n = 4) groups without serial pre-treatment echocardiographic data. The mean age at initiation of treatment was 14.2 ± 5.1 and 15.2 ± 4.9 years in the losartan and atenolol groups, respectively, and approximately 1 quarter of patients in both groups were female. There were few patients with history of coarctation surgery (n = 3/41) or moderate or more aortic valve dysfunction (n = 4/41 stenosis, n = 10/41 insufficiency) in the overall cohort. Most patients had predominant dilation of the AsAo (Table 2). Severe dilation of the AsAo (z-score ≥ 5) was common (85% in the losartan group and 56% in the atenolol group), and severe dilation of the AoRt was uncommon (11% in each group).

After treatment characteristics, duration of treatment follow-up, and final medication dose are described in Table 1B. Median follow-up during treatment was 3.1 (Interquartile Range 2.4, 6.0) and 3.7 (Interquartile Range 1.4, 6.6) years in the losartan and atenolol groups, respectively. There were no deaths.

Four patients in the losartan group and 5 in the atenolol group had aortic surgery at age 18.4 ± 4.8 years (median 19.6 years) after treatment follow-up of 3.3 ± 1.8 years (median 3.1 years). All but one were ≥ 15 years old, and all but 1 (89%) were male. One patient in the atenolol group had repair of a fistula between the noncoronary sinus of Valsalva and the right atrium with reduction of the noncoronary sinus, without valve intervention. Of the remaining 8 patients, only 2 had surgery primarily for aortic size: a 20 years old male with mild to moderate aortic insufficiency and AsAo diameter of 5.0 cm, and a 7 years old male with normal valve function and an AoRt diameter of 3.7 cm (z-score + 8.0 SD) and an AsAo diameter of 3.9 cm (z-score + 10.3 SD). The primary surgical indication for the remaining 6 patients was progressive aortic insufficiency; 5 of these patients had AoRt or AsAo diameter between 4.6 and 4.9 cm. Excluding the patient with the sinus of Valsalva aneurysm, 7 of 8 had aortic valve repair or replacement, and all 8 had replacement or reduction of the AoRt and/or AsAo.

The pre- and post-treatment annual rates of change in AoRt and AsAo diameter z-scores for each treatment group are shown in Table 3A. Pre- and post-treatment AoRt and AsAo z-score trajectories for individual patients are depicted for losartan in Figure 2 and for atenolol in Figure 2, respectively. Before treatment, there was a significant

Table 1A.
Patient Characteristics at Initiation of Treatment

Characteristic	Losartan (n = 27)	Atenolol (n = 18)
Age (years) [range]	14.2 ± 5.1 [4.7, 23.0]	15.2 ± 4.9 [6.4, 23.2]
Female	7 (26%)	5 (28%)
Body mass index (kg/m^2)	19.1 ± 3.8	19.3 ± 4.2
Systolic blood pressure (mm Hg)	103 ± 13 [n = 24]	112 ± 14 [n = 15]
≥ Moderate aortic stenosis	2 (7%)	2 (11%)
≥ Moderate aortic insufficiency	5 (19%)	5 (28%)
Aortic coarctation surgery	1 (4%)	2 (11%)
Aortic root diameter (cm)	3.2 ± 0.6	3.4 ± 0.7
Ascending aorta diameter (cm)	3.7 ± 0.6	3.5 ± 0.5
Aortic root diameter z-score (SD)	3.0 ± 1.8	3.1 ± 1.6
Ascending aorta diameter z-score (SD)	6.3 ± 1.4	5.2 ± 2.1
Aortic root z-score ≥ 5	3 (11%)	2 (11%)
Ascending aorta z-score ≥ 5	23 (85%)	10 (56%)
Median years pre-treatment (IQR) *	7.7 (6.5, 9.6) [n = 22]	9.9 (6.1, 13.5) [n = 14]

Abbreviations: cm: centimeters; IQR: interquartile range; kg: kilograms; SD: standard deviation.
Values are mean±SD unless otherwise noted.
Four patients were included (at different times) in both treatment groups.
* Excluding patients from the losartan (n = 5) and atenolol (n = 4) groups without serial pre-treatment echocardiographic data.

Table 1B.
Patient Characteristics on Treatment

Characteristic	Losartan (n = 27)	Atenolol (n = 18)
Median years of follow-up (IQR) *	3.1 (2.4, 6.0)	3.7 (1.4, 6.6)
Systolic blood pressure (mm Hg) †	109 ± 13	110 ± 12 [n = 17]
Median medication dose (mg/kg/day) (IQR) †	0.95 (0.64, 1.45)	0.67 (0.59, 0.81)

Values are mean±SD unless otherwise noted.
Four patients were included (at different times) in both treatment groups.
* Follow up is after treatment initiation, but still excluding patients from the losartan (n = 5) and atenolol (n = 4) groups without serial pre-treatment echocardiographic data.
† Blood pressure and medication dose were taken from the time of the last echocardiogram after treatment initiation.

increase in AoRt and AsAo z-scores over time in both the atenolol and losartan groups. The pre- and post-treatment slopes of AoRt and AsAo z-scores differed for both the atenolol and losartan groups ($p \leq 0.04$). There was a significant decrease over time in AoRt z-score on losartan ($p < 0.001$), whereas AoRt z-score slope on atenolol did not differ from zero. For AsAo in both treatment groups the mean z-scores stabilized (after treatment slopes did not differ from zero). Inferences regarding the magnitude of the pre- vs post-treatment difference in slopes for both AoRt and AsAo z-scores in both treatment groups remained the same after age adjustment.

In head-to-head comparison of after treatment slopes between losartan and atenolol groups, unadjusted for any patient differences between treatment groups, there was a decline in AoRt z-score over time for those who received losartan but no significant change for those who received atenolol (-0.14 ± 0.03 for losartan vs -0.02 ± 0.04 for atenolol, $p = 0.02$). Inferences were unchanged when adjusted for age ($p = 0.23$) and systolic blood pressure ($p = 0.06$). There was no significant difference between treatment groups in the slope for AsAo z-score ($p = 0.69$; neither after treatment slope differed from zero).

The pre-treatment and after treatment annual rates of change in maximal AoRt and AsAo diameters for each treatment group are shown in Table 3B and depicted in Figure 3 (losartan) and Figure 3 (atenolol). There were increases in raw aortic diameters in all pre- and post-

Table 2.
Pattern of aortic dilation (z-score ≥ 4 SD and/or diameter ≥ 4 cm)

	Losartan (n = 27)	Atenolol (n = 18)	All (n = 45)
Pattern			
Isolated Aortic Root Dilation	1 (3%)	4 (22%)	5 (11%)
Isolated Ascending Aorta Dilation	20 (74%)	12 (67%)	32 (71%)
Both Root and Ascending Dilation	6 (22%)	2 (11%)	8 (18%)

Abbreviations: cm: centimeter; SD: standard deviation.

Table 3A.
Annual rate of change in aortic diameter z-score (SD/year)

	Observations	Pre-Treatment Slope ± SE (95% CI)	Post-Treatment Slope ± SE (95% CI)	p-value
LOSARTAN (n = 27)				
Aortic Root	259	+0.06 ± 0.02* (+0.02, +0.11)	−0.14 ± 0.03* (−0.20, -0.08)	<0.001
Ascending Aorta	260	+0.20 ± 0.03* (+0.13, +0.27)	−0.09 ± 0.05 (−0.18, +0.01)	<0.001
ATENOLOL (n = 18)				
Aortic Root	157	+0.07 ± 0.03* (+0.02, +0.12)	−0.02 ± 0.04 (−0.10, +0.05)	0.04
Ascending Aorta	155	+0.21 ± 0.04* (+0.13, +0.29)	−0.06 ± 0.06 (−0.18, +0.07)	<0.001

Abbreviations: CI: confidence interval; SD: standard deviation; SE: standard error.
* Slope differs from zero, $p < 0.05$

treatment groups. However, the after treatment slopes were less positive than the pre-treatment slopes for both AoRt and AsAo in the atenolol-treated and losartan-treated patients ($p \leq 0.02$).

Two sensitivity analyses were performed with respect to the pre- vs post-treatment slope comparisons for each treatment. Inferences were unchanged when excluding data from 9 patients without serial pre-treatment follow-up echocardiograms (Supplemental Table 1A, 1B). Inferences were largely unchanged (i.e., some findings were significant at the 0.10 level instead of $p < 0.05$) when the data from 4 patients who were prescribed both drugs at different times were excluded (Supplemental Table 2A, 2B).

We sought to determine whether post-treatment z-score slopes (SD/yr) differed according to patient subgroup. In the losartan group the AoRt z-score decreased over time, but a greater response was observed in those with baseline severe AoRt dilation (z-score ≥ 5 SD) compared with those with z-score < 5 SD (-0.31 ± 0.10 vs -0.10 ± 0.03, $p = 0.04$). The decrease in AoRt z-score was also greater in those with baseline AsAo z-score < 5 SD compared with those with AsAo z-score ≥ 5 SD (-0.33 ± 0.09 vs -0.09 ± 0.03, $p = 0.02$). In the atenolol group the AsAo z-score decreased over time for males but not for females (-0.12 ± 0.04 vs +0.02 ± 0.03 SD, $p = 0.01$). There were no significant subgroup differences based on age at treatment initiation.

Discussion

BAV is a common heart defect associated with aortic aneurysm, dissection and death during adulthood. This pilot

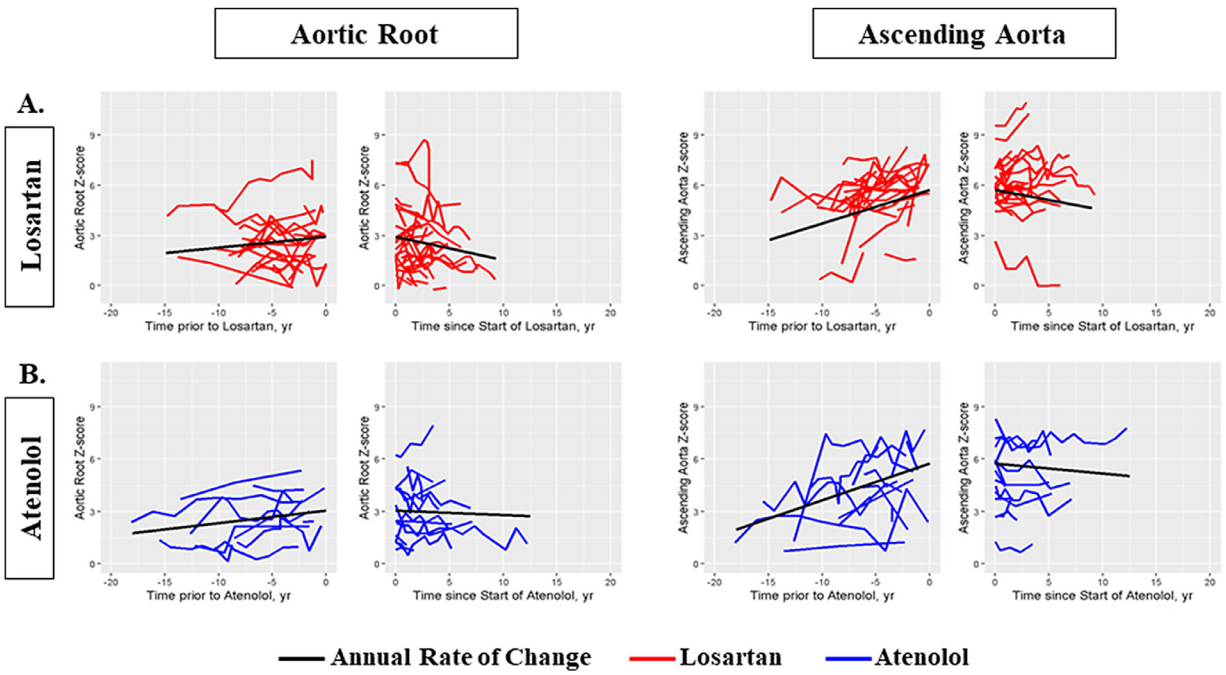

Figure 2. Annual Rate of Change in Aortic Diameter Z-Score Before and After Treatment. The annual rates of change in BSA-adjusted aortic root and ascending aorta z-scores, before and after medical treatment, are shown in black, estimated by mixed effects linear regression modeling with a treatment by time interaction effect. Individual patients are depicted in red for losartan (2A) and blue for atenolol (2B).

Table 3B.
Annual rate of change in absolute aortic diameter (cm/year)

	Observations	Pre-Treatment Slope ± SE (95% CI)	Post-Treatment Slope ± SE (95% CI)	p-value
LOSARTAN (n = 27)				
Aortic Root	259	+0.11 ± 0.01* (+0.09, +0.13)	+0.04 ± 0.01* (+0.02, +0.06)	<0.001
Ascending Aorta	260	+0.14 ± 0.01* (+0.12, + 0.16)	+0.07 ± 0.01* (+0.04, + 0.09)	<0.001
ATENOLOL (n = 18)		Pre-Treatment	Post-Treatment	
Aortic Root	157	+0.10 ± 0.01* (+0.08, + 0.12)	+0.07 ± 0.01* (+0.04, + 0.10)	0.02
Ascending Aorta	155	+0.12 ± 0.01* (+0.10, + 0.15)	+0.06 ± 0.02* (+0.03, + 0.10)	<0.001

Abbreviations: CI: confidence interval; cm: centimeter; SE: standard error.
* Slope differs from zero, $p < 0.05$.

study addresses the utility of medical prophylaxis for proximal aortic enlargement in young patients with BAV aortopathy. Our study results suggest that both angiotensin II receptor blockers and beta blockers reduce the rate of growth of the proximal aorta in patients with moderate to severe BAV-associated aortopathy. Before initiation of medical prophylaxis, AoRt and AsAo z-scores increased in both treatment groups, consistent with previous natural history studies showing progressive aortic dilation during childhood reporting z-score slopes ranging from 0.2 to 0.4SD/yr.[13,15,16] In the losartan group, treatment was associated with a reduction in AoRt z-score over time, and zero change (stabilization) in AsAo z-score. In the atenolol group, both AoRt and AsAo z-scores stabilized on treatment. Similarly, for both treatment groups, medical therapy was associated with a ≥ 30% reduction in growth rate (cm/yr) at the AoRt and AsAo compared with pre-treatment (Table 3B).

Although medical prophylaxis is an integral part of aortopathy management for the Marfan syndrome, its efficacy for BAV aortopathy has not been studied formally. An unpublished survey of pediatric cardiologists in New England revealed that a vast majority of pediatric cardiologists prescribe medications such as losartan or atenolol for patients with BAV and severe (z-score > 5) aortic dilation (Flyer JN, Hidestrand PM and Lacro RV. New England Congenital Cardiology Association BAV Aortopathy Working Group Clinical Cases. *Unpublished survey data*. 2017.) Patients with BAV are at increased risk for aortic dissection compared with the general population.[6,18,28,29] In

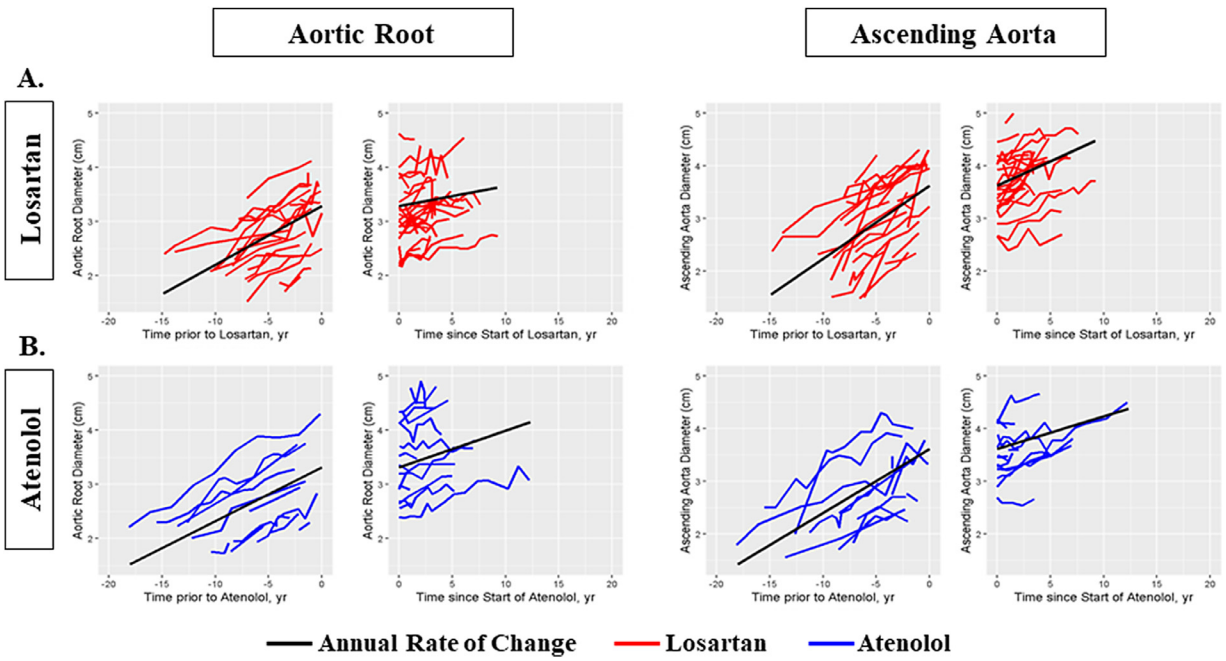

Figure 3. Annual Rate of Change in Absolute Aortic Diameter Before and After Treatment. The annual rates of change in absolute aortic diameter (cm/year) for aortic root and ascending aorta, before and after medical treatment, are shown in black, estimated by mixed effects linear regression modeling with a treatment by time interaction effect. Individual patients are depicted in red for losartan (3A) and blue for atenolol (3B).

a necropsy study of 161 cases of aortic dissection, 15% had BAV.[28] In 1 single-center experience, 12.5% of patients with BAV and aortic dissection suffered the event with an aortic diameter < 5 cm, compared with 15% of patients with the Marfan syndrome and aortic dissection.[30,31] Although concurrent prophylactic aortic repair has been suggested for patients with BAV undergoing valve surgery,[5,6,30,32] there is no consensus about indications for medical therapy or the threshold for surgical intervention to prevent dissection for patients with BAV.[5,6]

Aortic dissection is extremely rare in children with BAV[9,10]; however, prophylactic medical treatment of children may reduce vascular complications during adulthood. This study builds on the premise that earlier intervention with prophylactic medication during more youthful periods of rapid somatic growth may decrease the progression of aortic vascular disease.

In this study, median medication doses were modest for both losartan and atenolol when compared with recently reported aortopathy trials,[21] perhaps diminishing treatment effects. However, statistically significant short-term changes were still noted for both AoRt and AsAo growth rates in both medication groups, suggesting therapeutic value even with lower dosing. Future studies should investigate whether higher medication dosing or use of other agents such as irbesartan might lead to greater magnitude of benefit.

There were several limitations to the study. This was a non-randomized single-center experience with retrospective chart review, and without centralized blinded echocardiographic interpretation. Medication dosing and duration of therapy were variable, likely based on patient tolerance and/or individual prescriber. Medication compliance was not directly assessed. This study was limited to patients with moderate to severe progressive aortopathy, and results may not be generalizable to all patients with BAV. There were small numbers of patients available for subgroup analyses, in particular those with history of coarctation surgery and/or moderate valvar dysfunction (aortic stenosis/insufficiency). This study was not a randomized trial, therefore comparisons between losartan and atenolol may be biased and should be interpreted cautiously. Finally, this study did not elucidate the possible mechanisms (for example, changes in blood pressure) by which medical therapy was associated with an attenuated aortic growth rate.

This study demonstrates that medical prophylaxis with angiotensin II receptor blockers (losartan) and beta blockers (atenolol) stabilizes proximal aortic growth rates in young patients with BAV who have moderate to severe aortopathy, which is contrary to natural history studies showing continued dilation during childhood. Additional larger clinical studies are warranted to confirm this finding and to determine if early medical prophylaxis can decrease the rate of serious aortic events during adulthood, including aortic surgery, aortic dissection, and sudden death.

Disclosures

None

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.050.

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