

ORIGINAL ARTICLE

# Angiotensin II Blockade and Aortic-Root Dilation in Marfan's Syndrome

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## ABSTRACT

### BACKGROUND

Progressive enlargement of the aortic root, leading to dissection, is the main cause of premature death in patients with Marfan's syndrome. Recent data from mouse models of Marfan's syndrome suggest that aortic-root enlargement is caused by excessive signaling by transforming growth factor  $\beta$  (TGF- $\beta$ ) that can be mitigated by treatment with TGF- $\beta$  antagonists, including angiotensin II-receptor blockers (ARBs). We evaluated the clinical response to ARBs in pediatric patients with Marfan's syndrome who had severe aortic-root enlargement.

### METHODS

We identified 18 pediatric patients with Marfan's syndrome who had been followed during 12 to 47 months of therapy with ARBs after other medical therapy had failed to prevent progressive aortic-root enlargement. The ARB was losartan in 17 patients and irbesartan in 1 patient. We evaluated the efficacy of ARB therapy by comparing the rates of change in aortic-root diameter before and after the initiation of treatment with ARBs.

### RESULTS

The mean ( $\pm$ SD) rate of change in aortic-root diameter decreased significantly from  $3.54 \pm 2.87$  mm per year during previous medical therapy to  $0.46 \pm 0.62$  mm per year during ARB therapy ( $P < 0.001$ ). The deviation of aortic-root enlargement from normal, as expressed by the rate of change in z scores, was reduced by a mean difference of 1.47 z scores per year (95% confidence interval, 0.70 to 2.24;  $P < 0.001$ ) after the initiation of ARB therapy. The sinotubular junction, which is prone to dilation in Marfan's syndrome as well, also showed a reduced rate of change in diameter during ARB therapy ( $P < 0.05$ ), whereas the distal ascending aorta, which does not normally become dilated in Marfan's syndrome, was not affected by ARB therapy.

### CONCLUSIONS

In a small cohort study, the use of ARB therapy in patients with Marfan's syndrome significantly slowed the rate of progressive aortic-root dilation. These findings require confirmation in a randomized trial.

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**M**ARFAN'S SYNDROME, AN AUTOSOMAL dominant connective-tissue disorder affecting approximately 1 in 5000 people, is caused by mutations in the gene encoding fibrillin-1 (*FBN1*).<sup>1,2</sup> *FBN1* mutations lead to defects in multiple organ systems, of which the most life-threatening is progressive enlargement and dissection of the aortic root.<sup>3,4</sup> Current medical management of Marfan's syndrome is focused on serial cardiac-imaging studies and the use of pharmacologic agents to reduce hemodynamic stress on the aortic wall. Pharmacologic treatment often involves the use of beta-adrenergic-receptor antagonists (beta-blockers), although other agents, such as angiotensin-converting-enzyme (ACE) inhibitors and calcium-channel blockers, have been used in patients who have unacceptable adverse events or no response to beta-blockers.<sup>5-7</sup>

Studies in a mouse model of Marfan's syndrome have shown that a deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor  $\beta$  (TGF- $\beta$ ), an event that probably contributes to the pathogenesis of multiple phenotypic features of Marfan's syndrome, including progressive enlargement of the aortic root.<sup>8-11</sup> These genetically engineered mice, in which the pathologic changes in the aortic root closely mimic those seen in humans, were subsequently used to demonstrate the therapeutic benefit of treatment with TGF- $\beta$  antagonists *in vivo*. The development of pathologic changes in the aortic wall and the progressive dilation of the aortic root were attenuated or prevented by systemic treatment with a TGF- $\beta$ -neutralizing antibody or the angiotensin II-receptor blocker (ARB) losartan, an antihypertensive medication known to inhibit TGF- $\beta$  signaling.<sup>10,12</sup> In comparison, mutant mice treated with the beta-blocker propranolol continued to show substantial aortic-wall pathologic changes and had only a moderate reduction in the rate of aortic-root dilation. These findings led us to hypothesize that treatment with ARBs might be effective for the prevention of aortic-root enlargement and associated cardiovascular pathologic changes in patients with Marfan's syndrome.

## METHODS

### STUDY DESIGN AND PATIENTS

We retrospectively reviewed the records of all pediatric patients treated in the medical genetics clinic of Johns Hopkins Hospital who met the

Ghent diagnostic criteria<sup>13</sup> for Marfan's syndrome and who were followed prospectively from October 1996 through November 2007. The diagnosis of Marfan's syndrome was confirmed in each patient after exclusion of other known congenital aneurysm syndromes on the basis of distinguishing phenotypic features, molecular mutation analysis, or both (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). This retrospective study was approved by the institutional review board of Johns Hopkins University, which waived the requirement for informed consent.

We identified a cohort of 18 patients with Marfan's syndrome, 14 months to 16 years of age, who had begun ARB therapy between November 2003 and May 2006 and had continued to receive the therapy for at least 1 year of follow-up. An additional patient was identified who was prescribed an ARB, but this patient was excluded from the analysis after we found documented periods of nonadherence to therapy. The decision to initiate ARB therapy in these patients was made on clinical grounds during routine visits. Although no formal inclusion criteria were applied, factors that influenced the decision to prescribe ARBs included evidence of a rapid rate of change in aortic-root diameter despite other medical therapy, including beta-blockers with or without ACE inhibitors (11 patients); an aortic-root diameter of at least 4.0 cm, approaching the threshold for surgical intervention (6 patients); and unacceptable adverse events associated with conventional pharmacologic agents (1 patient). Details of therapy before the initiation of ARB treatment are provided in the Supplementary Appendix.

We identified 65 additional pediatric patients with Marfan's syndrome who had undergone echocardiography at least three times at Johns Hopkins Hospital during the study period, had not had aortic-root surgery, and had not received ARB therapy. All patients in this cohort had received beta-blockers according to a dosing regimen similar to that used in the recipients of ARBs before the initiation of ARB therapy.

### THERAPY WITH ARBs

Therapy was initiated in 17 patients with the ARB losartan (Cozaar, Merck) at an initial oral dose of 0.6 mg per kilogram of body weight per day; therapy with ACE inhibitors or calcium-channel blockers was discontinued at this time. The patients

were assessed for adverse events at this starting dose over a 3-week period before the dose was gradually increased to a sustained dose of 1.4 mg per kilogram per day. Therapy was initiated in one additional patient with the ARB irbesartan (Avapro, Bristol-Myers Squibb) at an initial dose of 1.4 mg per kilogram per day and a final dose of 2.0 mg per kilogram per day. The blood urea nitrogen and creatinine levels (i.e., renal function) and electrolyte levels were assessed after the patients had received ARB therapy for 3 months. Beta-blocker therapy was not decreased or discontinued unless the patient had adverse events in association with both medications (see the Supplementary Appendix).

#### ECHOCARDIOGRAPHY

Two-dimensional transthoracic echocardiograms were obtained every 3 to 12 months as part of routine clinical care, with the use of transducers appropriate for the patient's size. Complete orthogonal sweeps from the subxiphoid, apical, parasternal, and suprasternal-notch windows were obtained during each study. Measurements of maximal aortic diameter were taken at the aortic annulus, sinotubular junction, ascending thoracic aorta, and aortic root at the sinuses of Valsalva with the use of a parasternal long-axis view. The maximal diameter of these segments was determined by measuring from internal edge to internal edge of the aortic wall during ventricular systole on an axis perpendicular to the path of blood flow.

All echocardiograms obtained at Johns Hopkins Hospital were read by attending cardiologists who were not involved in the study and who were unaware of the patient's treatment status. A subgroup of studies was performed on selected patients, and the results were interpreted at other institutions. The majority of the echocardiograms were reviewed at Johns Hopkins to ensure standardization of measurement practices.

A z score was calculated for each echocardiographic measurement with the use of standard algorithms. The z score represented the standard deviation from the mean aortic diameter normalized for the patient's body-surface area and age.<sup>14</sup> In addition, measurements of heart rate, blood pressure, height, and weight were obtained at the time of each echocardiogram. Measurements of height and weight were used to calculate the body-mass index and were converted into z scores normalized for sex and age.

#### STATISTICAL ANALYSIS

The Wilcoxon signed-rank test was used to compare the rates of change in aortic diameter before and after the initiation of ARB therapy in individual patients. The one-sample proportion test (sign test) was used to test for a consistent decrease in the rate of change in aortic-root diameter after the initiation of ARB therapy, with a null hypothesis of equal proportions. Linear regression models were fitted with the use of generalized estimating equations<sup>15</sup> with a breakpoint to compare the rates of aortic enlargement before and after the initiation of ARB therapy, after adjustment for age and sex. The last model takes into account the correlation between repeated measures within individual patients. The Mann-Whitney U test was used to compare the changes in absolute and normalized aortic-root diameter between patients treated with ARBs and those treated with beta-blockers alone. Two-sided P values of less than 0.05 were considered to indicate statistical significance for all statistical tests and models. Stata statistical software, version 9.0, was used for all analyses.

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## RESULTS

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#### CHARACTERISTICS OF PATIENTS RECEIVING ARB THERAPY

Demographic data, diagnostic criteria, and treatment information for the 18 pediatric patients receiving ARB therapy are given in Table 1 (and in Table 1 in the Supplementary Appendix). All patients had evidence of severe aortic-root enlargement, with a mean ( $\pm$ SD) aortic-root diameter of  $3.67\pm 0.53$  cm and a mean aortic-root-diameter z score of  $7.21\pm 2.69$  at the time ARB therapy was initiated. The median duration of treatment before the initiation of ARB therapy was 48.6 months, with a median of seven echocardiograms per patient. The age at initiation of ARB therapy ranged from 14 months to 16 years. All patients were receiving the maximal weight-based dose within 6 months after the initiation of therapy. The patients were followed for a median of 26.1 months while receiving ARB therapy and had a median of five echocardiograms during that period.

At the time of data analysis, two patients, both of whom had severe aortic-root enlargement at the time of initiation of ARB therapy (4.2 cm in one and 4.4 cm in the other), had undergone previously planned prophylactic aortic-root replacement when their aortic-root diameter reached approxi-

**Table 1. Characteristics of the 18 Patients Receiving ARB Therapy.\***

Variable	Value
Age at initiation of ARB — yr	
Median	6.5
Range	1–16
Male sex — no. (%)	9 (50)
Race — no. (%)†	
White	17 (94)
Black	1 (6)
Aortic-root diameter at initiation of ARB — cm	3.67±0.53
Aortic-root-diameter z score at initiation of ARB	7.21±2.69
Previous treatment — no. (%)	
Beta-blocker alone	12 (67)
Beta-blocker plus ACE inhibitor	4 (22)
Beta-blocker plus calcium-channel blocker	2 (11)
Previous treatment dose — mg/kg/day	
Beta-blocker	1.83±0.38
ACE inhibitor	0.97±0.27
Calcium-channel blocker	4.12±1.04
No. of echocardiograms per patient	
Before initiation of ARB	
Median	7
Range	3–15
After initiation of ARB	
Median	5
Range	2–10
Duration of treatment — mo	
Before initiation of ARB	
Median	48.6
Range	12–104
After initiation of ARB	
Median	26.1
Range	12–47

\* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and ARB angiotensin II-receptor blocker.

† Race was self-assessed by the patient or parent.

mately 4.5 cm. A third patient required mitral-valve repair because of valve insufficiency and left ventricular dysfunction. The data for these three patients were censored at the time of surgery.

#### SIDE EFFECTS

There were no significant changes in mean heart rate, mean systolic blood pressure, or mean dia-

stolic blood pressure after the initiation of ARB therapy, as compared with the previous period when the patients were receiving beta-blockers, ACE inhibitors, or calcium-channel blockers (Table 2). Laboratory indicators of renal function were normal 3 months after the initiation of ARB therapy in all patients: the median blood urea nitrogen level was 15 mg per deciliter (5.4 mmol per liter) (range, 7 to 25 mg per deciliter [2.5 to 8.9 mmol per liter]), and the median serum creatinine level was 0.5 mg per deciliter (44.2  $\mu$ mol per liter) (range, 0.3 to 0.8 mg per deciliter [26.5 to 70.7  $\mu$ mol per liter]). No adverse events or side effects were documented among patients while they were receiving ARB therapy.

#### BODY HEIGHT AND WEIGHT DURING ARB THERAPY

There was a decline in the rate of change of increase in body height after the initiation of ARB therapy, with significant decreases in height velocity and in height-velocity z scores, as compared with previous growth rates (see Table 2 in the Supplementary Appendix). No significant changes were found in the rate of change in body-weight measurements. This finding might be attributable, at least in part, to a reduction in linear growth and age-dependent fluctuations in the rate of change in body-mass index.

#### AORTIC-ROOT DILATION DURING ARB THERAPY

The mean rate of change in aortic-root diameter in patients before the initiation of ARB therapy was 3.54±2.87 mm per year. After the initiation of ARB therapy, this rate decreased to 0.46±0.62 mm per year, which represented a clinically and statistically significant difference in aortic dilatation ( $P<0.001$ ) (Table 3). The mean and median rates of increase in aortic-root diameter were decreased by factors of approximately 8 and 11, respectively (Fig. 1A and Table 3). Similarly, the mean rate of change in aortic-root-diameter z scores was 0.97±1.55 per year before ARB therapy and decreased to -0.50±0.43 per year after the initiation of ARB therapy ( $P<0.001$ ) (Table 3 and Fig. 1B). The z score takes into account differences in age and body-surface area among patients and thus provides a measure that controls for the effects of these variables during follow-up.<sup>14</sup>

Regression modeling with the use of generalized estimating equations, after adjustment for age and sex, showed that the initiation of ARB therapy was independently associated with an estimated

**Table 2. Comparison of Hemodynamic Measurements before and after Initiation of ARB Therapy.\***

Measurement	Before ARB Therapy		After Initiation of ARB Therapy		P Value†
	Median	Mean	Median	Mean	
Heart rate (beats/min)	79	81.3±13.0	77	79.0±14.9	0.11
Systolic blood pressure (mm Hg)	98	97.1±9.9	98	97.9±11.0	0.62
Diastolic blood pressure (mm Hg)	59	58.3±6.0	57	57.6±7.1	0.67

\* Plus–minus values are means ±SD. All hemodynamic measurements were taken at the time of the echocardiograms. ARB denotes angiotensin II–receptor blocker.

† P values for the differences in medians were calculated with the use of the Wilcoxon signed-rank test.

**Table 3. Comparison of Annual Rates of Change in Aortic-Root Diameter and z Scores in Patients with Severe Marfan's Syndrome before and after Initiation of ARB Therapy and in Patients with Mild Marfan's Syndrome Receiving Beta-Blockers Alone.\***

Variable	Severe Marfan's Syndrome (N=18)				P Value†	Mild Marfan's Syndrome (N=65)		P Value‡
	Before ARB Therapy		After Initiation of ARB Therapy			After Initiation of Therapy with Beta-Blockers		
	median	mean	median	mean		median	mean	
Aortic-root-diameter z score								
Cohort average§	6.7	6.52±2.43	NA	NA		3.0	3.25±1.52	<0.001
Last measurement¶	7.2	7.21±2.69	6.3	6.44±2.43	<0.001	NA	NA	
Change in aortic-root diameter								
Absolute change (mm/yr)	3.3	3.54±2.87	0.3	0.46±0.62	<0.001	1.3	1.71±1.24	<0.001
Normalized change (z scores/yr)	1.0	0.97±1.55	–0.5	–0.50±0.43	<0.001	0.1	0.24±0.50	<0.001

\* Plus–minus values are means ±SD. Aortic diameters were measured during echocardiography and converted into rates of enlargement expressed as millimeters per year. The z scores were calculated from aortic-root diameters normalized for age and body-surface area. ARB denotes angiotensin II–receptor blocker, and NA not applicable.

† P values for the comparison of median rates of change in aortic-root diameter before and after the initiation of ARB therapy were calculated with the use of the Wilcoxon signed-rank test.

‡ P values for the comparison of median cohort z scores and rates of change in aortic-root diameter between patients with severe and mild Marfan's syndrome were calculated with the use of the Mann–Whitney U test.

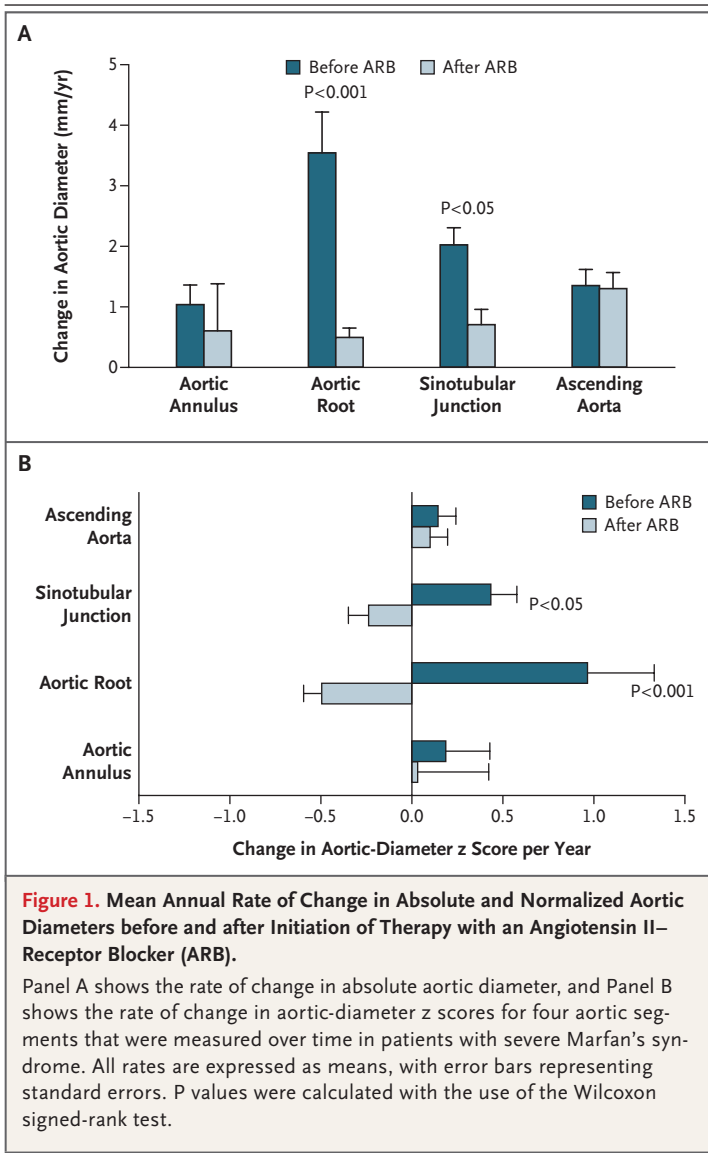
§ The mean and median z scores were calculated from all echocardiograms obtained before the initiation of ARB therapy for patients with severe Marfan's syndrome or from all echocardiograms obtained during childhood for patients with mild Marfan's syndrome.

¶ The mean and median z scores were calculated from aortic-root diameters measured at the last echocardiogram obtained before the initiation of ARB therapy and at the most recent echocardiogram obtained during ARB therapy.

decrease in the rate of change in aortic-root diameter of 2.75 mm per year (95% confidence interval [CI], 1.65 to 3.84 mm per year;  $P<0.001$ ) and an estimated decrease of 1.27 aortic-root-diameter z scores per year (95% CI, 0.57 to 1.97;  $P<0.001$ ). The rate of change in aortic-root diameter was reduced among all patients after initiation of ARB therapy ( $P<0.001$ ) (Fig. 2A, and Table 1 in the Supplementary Appendix), including the single patient treated with irbesartan (Fig. 2B).

The sinotubular junction, an aortic segment that is also prone to dilation in patients with severe Marfan's syndrome, also benefited from ARB therapy. The mean rate of change in absolute si-

notubular-junction diameter was  $2.02\pm 1.13$  mm per year before the initiation of ARB therapy and was reduced to  $0.70\pm 1.01$  mm per year during ARB therapy ( $P<0.05$ ) (Table 4 and Fig. 1A). The normalized rate of sinotubular-junction enlargement decreased from  $0.43\pm 0.57$  z score per year during previous therapy to  $-0.24\pm 0.44$  z score per year during ARB therapy ( $P<0.05$ ) (Table 4 and Fig. 1B). In comparison, more distal segments of the ascending aorta past the sinotubular junction, which are not generally affected by pathologic dilatation in Marfan's syndrome, showed no change in growth measurements after the initiation of ARB therapy. Both the mean rate of change in as-



ending-aorta diameter and the mean rate of change in ascending-aorta-diameter z score were essentially unchanged after the initiation of ARB therapy (Table 4). Finally, the rates of change in absolute aortic-annulus (aortic-valve) diameter and aortic-valve-diameter z score were also unaffected by the initiation of ARB therapy (Table 4).

#### AORTIC-ROOT DILATION DURING TREATMENT WITH BETA-BLOCKERS ALONE

Of the 65 patients with Marfan's syndrome who received beta-blocker therapy alone throughout the study period, 36 (55%) were female, 3 (5%) were black, and the median age was 12.0 years (range,

4 months to 19 years). Overall, this population had milder aortic-root disease, as evidenced by a reduced mean aortic-root-diameter z score for all echocardiograms obtained during childhood as compared with the mean z score of the cohort receiving ARB therapy ( $3.25 \pm 1.52$  vs.  $6.52 \pm 2.43$ ,  $P < 0.001$ ). The mean rates of change in aortic-root diameter ( $1.71 \pm 1.24$  mm per year) and in aortic-root-diameter z score ( $0.24 \pm 0.50$  per year) in patients receiving beta-blockers alone were significantly higher than those in severely affected patients receiving ARB therapy ( $P < 0.001$  for both comparisons) (Table 3).

#### DISCUSSION

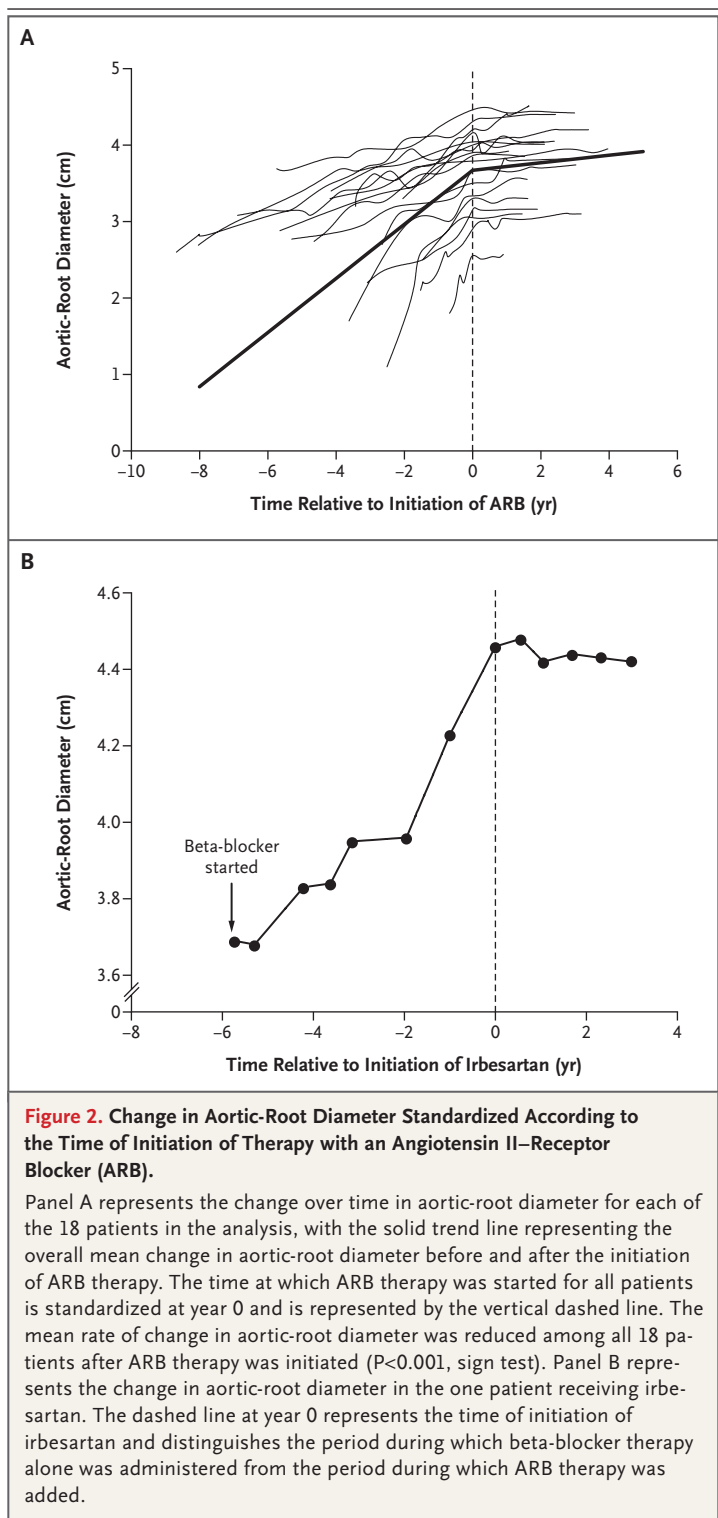
The current study provides early evidence suggesting that the addition of losartan or another ARB to the traditional regimen used to treat aortic aneurysm in patients with Marfan's syndrome may be beneficial. The initiation of ARB therapy resulted in a significant reduction in the rate of change in aortic-root diameter as compared with beta-blocker therapy alone. The therapeutic effect extended to the sinotubular junction, a site also affected by Marfan's syndrome. In comparison, aortic segments not typically affected in Marfan's syndrome (e.g., the ascending aorta above the sinotubular junction) continued to show an annual rate of change in diameter that was appropriate for age and body size. Together, these findings suggest that ARBs do not arrest aortic growth but specifically reduce the pathologic rate of increase in the diameter of aortic segments that are already of sufficient size to accommodate the physiologic demands of the tissues for blood flow.

Losartan and irbesartan belong to the ARB class of antihypertensive medications that work by selectively blocking the angiotensin II type 1 (AT1) receptor within the renin-angiotensin-aldosterone system.<sup>16</sup> In addition to antihypertensive and other effects, AT1-receptor blockade induces a clinically relevant decrease in TGF- $\beta$  signaling.<sup>12,17,18</sup> This antagonism results in reduced plasma levels of free TGF- $\beta$ , reduced tissue expression of TGF- $\beta$ -responsive genes, and reduced levels of intracellular mediators within the TGF- $\beta$  signaling cascade, such as phosphorylated Smad2. In a prospective study of renal-transplant recipients, treatment with normal antihypertensive doses of losartan decreased plasma levels of TGF- $\beta$  by more than 50% within 2 weeks.<sup>18</sup>

The effects of angiotensin II are mediated by two receptors, the AT1 receptor and the angiotensin II type 2 (AT2) receptor.<sup>16</sup> AT1-receptor signaling can increase the production of TGF- $\beta$  ligands and receptors, as well as activators such as thrombospondin-1.<sup>19</sup> Cellular events observed in the tissues of persons with Marfan's syndrome, including proliferation of vascular smooth-muscle cells, fibrosis, and increased expression of matrix metalloproteinases 2 and 9, are plausibly attributable to increased TGF- $\beta$  activity.<sup>8-10</sup> In contrast, the AT2 receptor is thought to induce cellular effects opposite to those of the AT1 receptor, including antiproliferative and antiinflammatory effects that are beneficial in aortic-wall homeostasis.<sup>20</sup>

Given these mechanisms, the beneficial effects of ACE inhibitors and ARBs in this setting might be expected to differ. ACE inhibitors limit the production of angiotensin II and hence limit signaling through both the detrimental AT1-receptor pathway and the potentially protective AT2-receptor pathway and would not influence alternative mechanisms for angiotensin II production, such as the activity of mast-cell chymase. In contrast, ARBs cause selective blockade of the AT1 receptor, resulting in overactivation of the AT2-receptor pathway.<sup>10</sup> In keeping with these mechanistic hypotheses, Daugherty and colleagues observed that AT1-receptor-blocking agents could prevent abdominal aortic aneurysms induced by the infusion of angiotensin II in apolipoprotein E-deficient mice, whereas selective AT2-receptor antagonists increased both the incidence and the severity of abdominal aneurysms in this model.<sup>21,22</sup>

On balance, however, it seems possible that the benefit of AT1-receptor antagonism achieved with ACE inhibitors could outweigh the potential negative influence of AT2-receptor blockade. A small, randomized, controlled trial of the ACE inhibitor perindopril as compared with placebo in adult patients with Marfan's syndrome who were receiving beta-blockers showed a reduced rate of change in aortic-root diameter that correlated with decreased circulating TGF- $\beta$  levels over a relatively short period of follow-up (24 weeks).<sup>23</sup> Nevertheless, our recent observation of accelerated aortic-root enlargement in fibrillin-1-deficient mice after targeted disruption of the gene encoding the AT2 receptor further supports our hypothesis that selective AT1-receptor antagonists will provide superior protection in preventing aneurysmal dilation of the aortic root (unpublished data).



There are several limitations of our study. This was a nonrandomized, retrospective, observational study that evaluated only a small subgroup of pe-

**Table 4. Comparison of Annual Rates of Change in Aortic Diameter and z Scores before and after the Initiation of ARB Therapy.\***

Aortic Segment	Before ARB Therapy		After Initiation of ARB Therapy		P Value†
	Median	Mean	Median	Mean	
Aortic annulus					
Absolute change (mm/yr)	1.0	1.04±1.30	1.1	0.60±0.31	0.53
Normalized change (z scores/yr)	0.2	0.19±0.97	0.1	0.03±1.56	0.18
Sinotubular junction					
Absolute change (mm/yr)	1.8	2.02±1.13	0.5	0.70±1.01	<0.05
Normalized change (z scores/yr)	0.3	0.43±0.57	-0.2	-0.24±0.44	<0.05
Ascending aorta					
Absolute change (mm/yr)	0.9	1.35±1.07	0.9	1.30±1.06	0.86
Normalized change (z scores/yr)	0.1	0.14±0.39	0.1	0.10±0.38	0.57

\* Plus–minus values are means ±SD. Aortic diameters were measured during echocardiography and converted into rates of enlargement expressed as millimeters per year. The z scores were calculated from aortic-segment diameters normalized for age and body-surface area and converted into rates expressed as z scores per year. ARB denotes angiotensin II–receptor blocker.

† P values for the differences in medians were calculated with the use of the Wilcoxon signed-rank test.

diatric patients with Marfan's syndrome who had evidence of severe aortic-root enlargement or rapid increase in aortic diameter. Selection bias may have resulted in the identification of patients who were more adherent to, and therefore more likely to have a response to, ARB therapy, although it could also be hypothesized that patients with established severe disease would be less likely to have a response to ARB therapy than would patients with milder disease. Although all patients in this study had a reduction in the rate of change of aortic-root diameter while receiving ARB therapy, there was variability in this therapeutic response (Fig. 2A, and Table 2 in the Supplementary Appendix) that may be correlated with the pre-existing degree of pathologic change or other individually specific factors, such as genotype. This variability may alter the effectiveness of TGF- $\beta$  antagonism, which was not assessed in this study. It is also possible that up-regulation of AT1 receptors in response to chronic receptor antagonism may limit the long-term therapeutic effect of ARBs.

Despite the encouraging results of this observational study, equipoise is maintained regarding

a role for ARB therapy in the treatment of patients with Marfan's syndrome; our findings must be confirmed by a prospective, randomized trial. A trial coordinated by the Pediatric Heart Network of the National Heart, Lung, and Blood Institute, comparing losartan with atenolol in patients with Marfan's syndrome, began enrolling patients in the winter of 2007, and we encourage all eligible patients to enroll in this trial.<sup>24,25</sup> Until data from this trial are available, evidence for the potential efficacy of ARB therapy in this setting should be considered preliminary.

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No potential conflict of interest relevant to this article was reported.

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