Supplementary Appendix

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

SUPPLEMENTARY APPENDIX

Contents

PEDIATRIC HEART NETWORK INVESTIGATORS

In addition to the authors, the following investigators participated in the Pediatric Heart Network Marfan Trial:

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* no longer at the institution listed

Supplementary Results

Secondary Analyses

A secondary analysis excluded 36 subjects identified after randomization as having a major eligibility violation, and adjusted for medical history of endocrine disorder/treatment, as its prevalence was unequal in the 2 treatment arms. Inferences regarding treatment effect on aortic-root z-score and dimension were unchanged by the secondary covariate-adjusted analysis of these fully eligible subjects (−0.144±0.014 SD units/year in the atenolol group and −0.113±0.014 SD units/year in the losartan group, P=0.11). The 608 subjects were from 549 families. Adjustment for correlation among family members did not affect study inferences (−0.139±0.013 SD units/year in the atenolol group and −0.107±0.013 SD units/year in the losartan group, P=0.08).

Less than six percent of the expected primary outcome measurements were missing. Almost 80% of the 171 missing observations arose from the 65 subjects who withdrew during the course of the trial. Table S6 shows that these subjects were older and had larger baseline aortic-root size than those who did not withdraw, factors that might affect the rate of change in aortic-root z-score. The P value for the primary outcome using multiple imputation is P=0.11 (Table S7). We also conducted sensitivity analyses that exclude the subjects withdrawn from trial and the subset of 29 withdrawn subjects who had a clinical event (Table S7). These analyses did not affect study inferences. In all of these analyses, the annual rate of change in aortic-root z-score was between −0.14 and −0.13 for the atenolol group and between −0.11 and −0.10 for the losartan group, with P values ranging from 0.07 to 0.11.

Description of Subjects with Adverse Clinical Outcomes of Death, Aortic-Root Surgery or Dissection

The only death occurred in the losartan group, and was caused by heart failure and not by aortic complications. Both dissections occurred in the losartan group, but one dissection occurred in the context of pregnancy without progressive aortic-root enlargement, a known risk in Marfan syndrome. Although this subject was randomized to losartan, she became pregnant shortly thereafter and was treated with atenolol for several months before dissection. The other dissection was noted at the six-month follow-up visit at an aortic-root dimension of 6.27 cm in an individual who was randomized with an aortic-root dimension of 4.75 cm.

Anthropometric Outcomes

There was no treatment effect on any of the anthropometric outcomes (Table S8) and no differential treatment effect according to pre-specified subgroups.

Adverse Events and Subject-Reported Symptoms

At the end of uptitration, hematocrit (P=0.03), leukocyte count (P=0.004), and potassium (P=0.04) were higher in the atenolol group compared to the losartan group, but all values were within normal ranges.

Many mild symptoms, particularly headache, fatigue, and nasal congestion, were reported at baseline but these did not differ between treatment groups (Table S9). During maintenance, dysgeusia, nausea, and muscle pain or cramps were slightly more common in the atenolol group. Very few subjects reported bothersome symptoms (3 to 4 rating on a 1 to 4 scale) either at baseline or during maintenance, but significantly more subjects taking atenolol reported bothersome chest pain and orthostatic dizziness.

Figure S1. Resting and Average 24-hour Heart Rate vs. Prescribed Dose in Children at 36 month visit, According to Treatment Assignment.
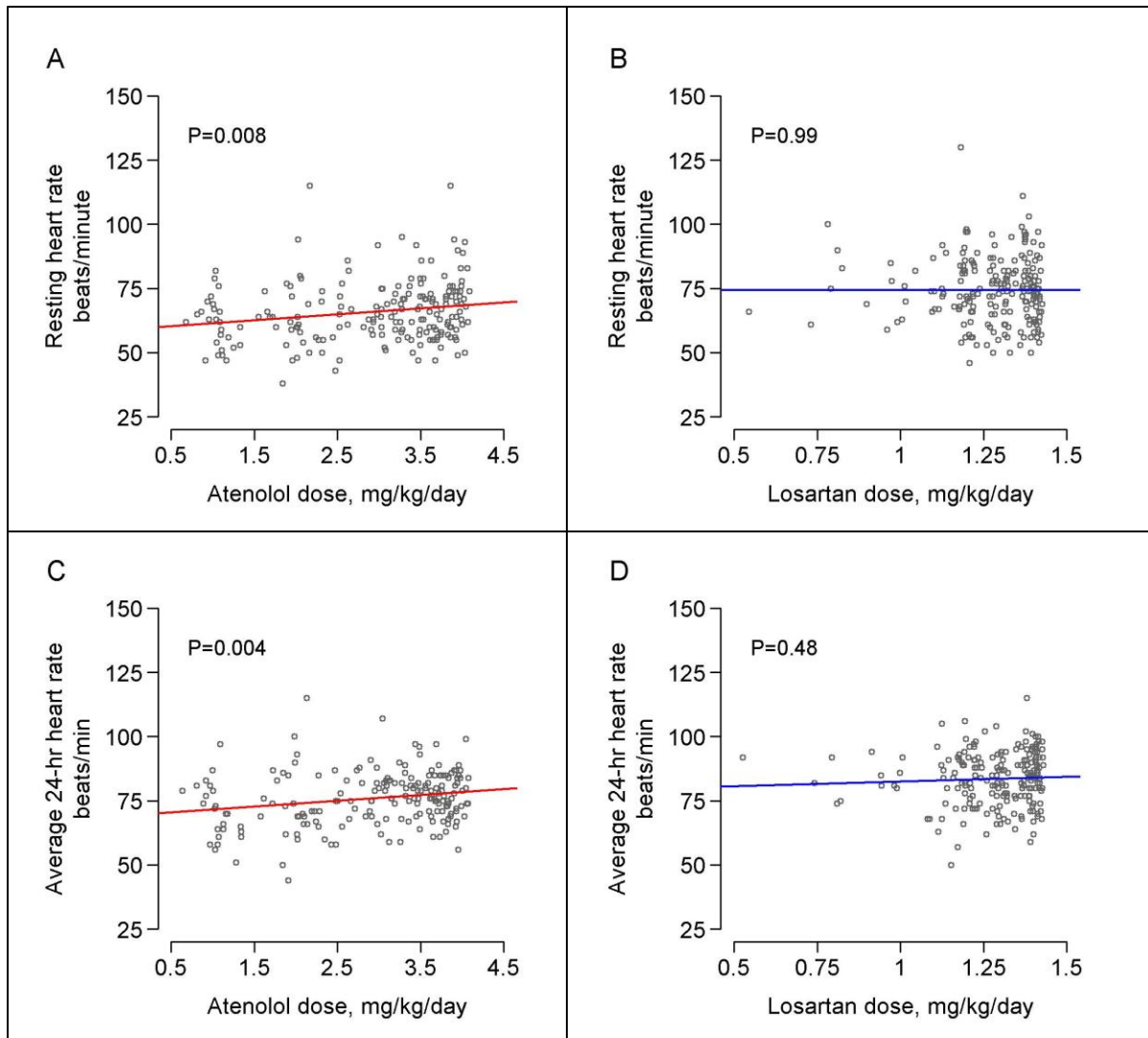
Panel A shows actual and predicted resting heart rate by prescribed dose of atenolol in mg/kg/day. Panel B shows actual and predicted resting heart rate by prescribed dose of losartan in mg/kg/day. Panel C shows actual and predicted average 24-hour heart rate by prescribed dose of atenolol in mg/kg/day. Panel D shows actual and predicted average 24-hour heart rate by prescribed dose of losartan in mg/kg/day.

Figure S2. Treatment Group Differences in Change in Aortic-Root Z-Score by Subgroup
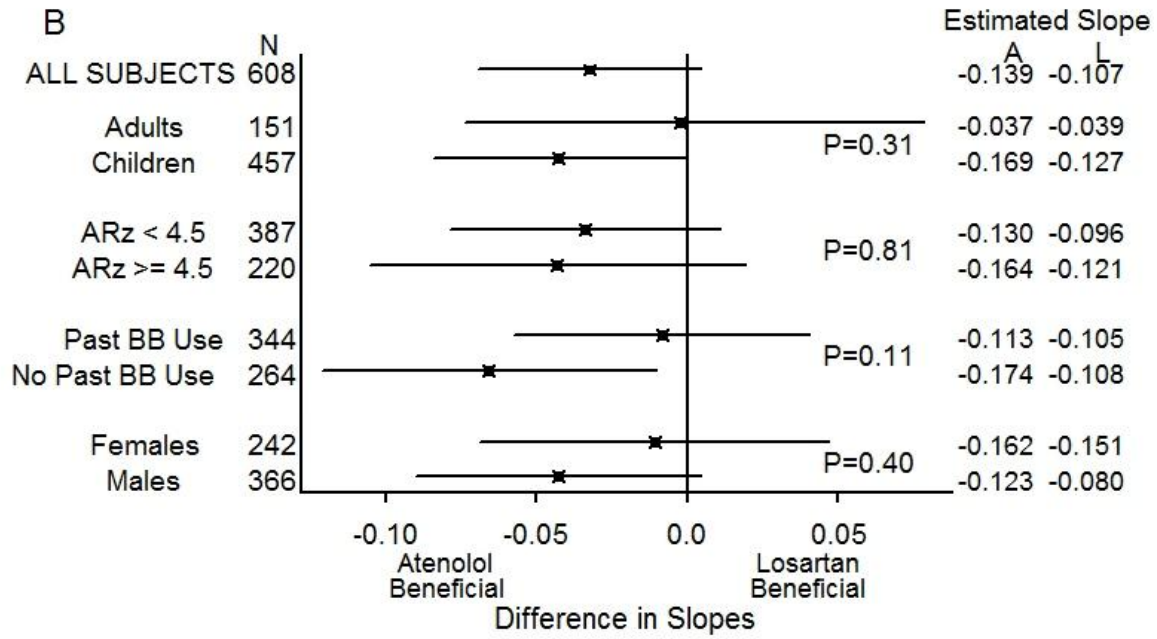
Treatment group differences in baseline-adjusted change in aortic-root z-score over 3 years are shown by pre-specified subgroup. Bars represent 95% confidence intervals for the group difference. Adult is defined as males ≥16 years and females ≥15 years. A denotes atenolol, ARz body-surface area-adjusted maximum aortic-root dimension z-score, BB β-blocker, and L losartan.

Figure S3. Change in Aortic-Root Z-Score and Aortic-Root Dimension in Adults vs. Children, According to Treatment Assignment.
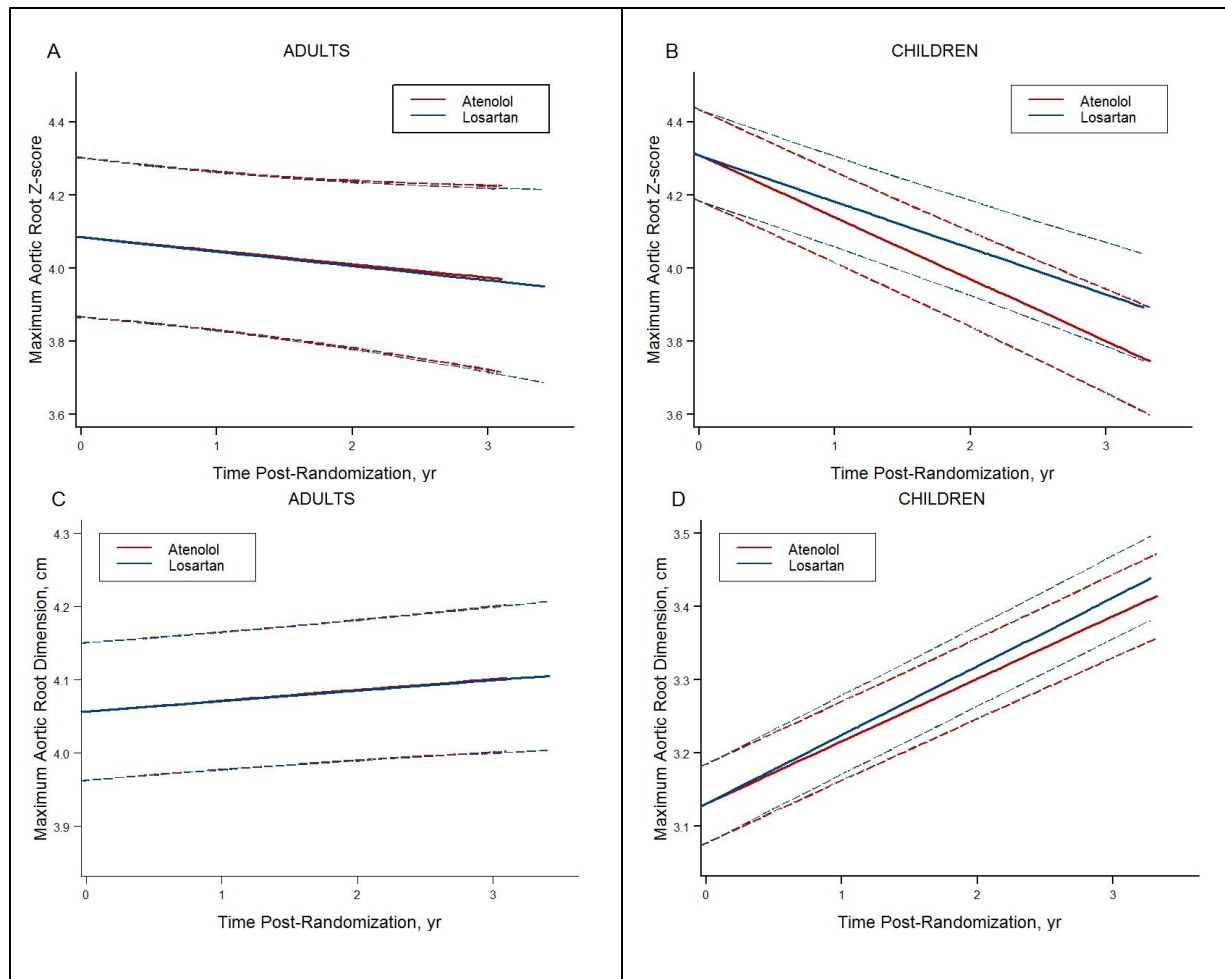
Panel A shows the baseline-adjusted rate of change in aortic-root z-score over 3 years in adults (solid lines), with pointwise 95% confidence bands (dashed lines). Panel B shows the baseline-adjusted rate of change in aortic-root z-score over 3 years in children (solid lines), with pointwise 95% confidence bands (dashed lines). The P value for differential treatment effect on aortic-root z-score in adults vs. children was 0.31. Panel C shows the baseline-adjusted rate of change in aortic-root absolute dimension over 3 years in adults (solid lines), with pointwise 95% confidence bands (dashed lines). Panel D shows the baseline-adjusted rate of change in aortic-root absolute dimension over 3 years in children (solid lines), with pointwise 95% confidence bands (dashed lines). The P value for differential treatment effect on aortic-root dimension in adults vs. children was 0.43. Adult is defined as males ≥16 years and females ≥15 years. Aortic-root Z-score denotes body-surface area-adjusted maximum aortic-root dimension z-score.

Table S1. Ghent Diagnostic Criteria for Marfan Syndrome

Diagnostic Rules

For the index case:

- If family or genetic history is not contributory, major criteria in at least 2 different organ systems AND involvement of a third organ system.
- If a mutation known to cause Marfan syndrome in others or a mutation involving a highly conserved amino acid is detected, one major criterion in an organ system AND involvement of a second organ system.

For a relative of an index case:

- Presence of a major criterion in the family or genetic history AND one major criterion in an organ system AND involvement in second organ system.

SKELETAL

> Major (Presence of at least 4 of the following): pectus carinatum, pectus excavatum (moderate to-severe), reduced upper-to-lower-segment ratio for age or arm span-to-height ratio greater than 1.05, wrist and thumb signs, scoliosis > 20° or spondylolisthesis, reduced extension at the elbow (<170°), medial rotation of the medial malleolus causing pes planus, protrusio acetabuli.
>
> Minor: pectus excavatum of moderate severity, joint hypermobility, high arched palate with crowding of teeth, facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, down-slanting palpebral fissures, retrognathia). INVOLVEMENT: 2 major criteria OR 1 major and 2 minor criteria

OCULAR

> Major: ectopia lentis
>
> Minor: flat cornea, increased axial length of the globe, hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis. INVOLVEMENT: 2 minor criteria

CARDIOVASCULAR

> Major: dilatation of the ascending aorta involving the sinuses of Valsalva and/or dissection of the ascending aorta
>
> Minor: mitral valve prolapse, dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis below the age of 40 years, calcification of the mitral annulus below the age of 40 years, dilatation or dissection of the thoracic or abdominal aorta below the age of 50 years. INVOLVEMENT: 1 minor criterion

PULMONARY

> Minor only: spontaneous pneumothorax, apical blebs. INVOLVEMENT: 1 minor criterion

SKIN AND INTEGUMENT

> Minor only: striae atrophicae, recurrent or incisional hernia. INVOLVEMENT: 1 minor criterion

DURA

> Major: lumbosacral dural ectasia by CT or MRI

FAMILY/GENETIC HISTORY

> Major (any 1 of the following 3 observations): first degree relative who independently meets the diagnostic criteria, presence of a mutation in *FBN1* that is known to cause Marfan syndrome or that involves a highly conserved amino acid, presence of a haplotype around *FBN1* that is inherited by descent and unequivocally associated with MFS in the family

Table S2. Dose of Treatment Medication

Dose of treatment medication (mg/kg/day)	N	Atenolol Mean ± SD	Range	N	Losartan Mean ± SD	Range
All	291	2.70±1.09	0.50-4.00	298	1.26±0.18	0.30-1.40
Children	219	2.83±1.03	0.50- 4.00	224	1.27±0.18	0.30-1.40
Adult*	72	2.31±1.17	0.50-4.00	74	1.23±0.16	0.70-1.40

*Adult is defined as ≥15 years for females and ≥16 years for males. SD, standard deviation.

Table S3. Blood Pressure and Heart Rate

Measure	N	Baseline Atenolol	N	Losartan	P Value	N	3 Years Atenolol	N	Losartan	P Value
Blood pressure (mm Hg, mean ± SD)										
Systolic	303	97±13	303	98±12	0.53	268	95±12	268	96±13	0.44
Systolic-for-age z-score	303	-0.7±1.0	303	-0.6±1.0	0.29	268	-1.1±0.9	268	-1.0±1.0	0.33
Diastolic	303	59±10	303	59±8	0.46	268	54±8	268	56±8	0.04
Diastolic-for-age z-score	303	0.3±1.0	303	0.3±0.9	0.59	268	-0.3±0.9	268	-0.2±0.8	0.02
Mean	298	72±11	297	71±9	0.61	266	68±10	268	69±9	0.13
Mean-for-age z-score	298	-0.2±1.0	297	-0.3±0.9	0.84	266	-0.8±0.9	268	-0.7±0.9	0.07
Heart Rate (beats/min, mean + SD)										
Resting heart rate	303	79±17	301	79±18	0.75	268	64±12	268	73±13	<0.001
Resting heart rate-for-age z-score	303	-0.02±0.90	301	-0.0±0.9	0.83	268	-0.9±0.8	268	-0.3±0.9	<0.001
Average 24-hour heart rate	303	88±15	305	88±15	0.85	245	73±11	254	82±11	<0.001

SD, standard deviation; z-score, z-score indexed to body-surface area unless otherwise specified.

Table S4. Change over Time in Aortic-Root Z-Score: Effect of Baseline Age

Age (yrs)	Annual Rate of Aortic-Root Z-Score Change*	
	Atenolol	Losartan
1	-0.232±0.025	-0.171±0.024
5	-0.195±0.018	-0.144±0.018
10	-0.149±0.013	-0.111±0.013
15	-0.103±0.016	-0.077±0.016
20	-0.056±0.023	-0.044±0.024

*SD units/year ± SE.

The association of baseline age with annual rate of change in aortic-root z-score did not depend on treatment group (P=0.38). Younger baseline age was associated with a greater decrease in aortic-root z-score over time in both the atenolol (P<0.001) and losartan (P=0.002) groups.

Aortic-root z-score, body-surface area-adjusted maximum aortic-root dimension z-score; SD, standard deviation; SE, standard error.

Table S5. Change in Aortic-Root Z-Score: Association with Prescribed Dose*

	Atenolol†		Losartan‡	
Dose*	Rate of Aortic-Root Z-Score Change¶	Dose*	Rate of Aortic-Root Z-Score Change¶	
1.8 mg/kg	-0.143±0.018	1.2 mg/kg	-0.110±0.014	
3.0 mg/kg	-0.133±0.014	1.3 mg/kg	-0.112±0.014	
3.7 mg/kg	-0.127±0.018	1.4 mg/kg	-0.114±0.017	

*Doses are quartiles of prescribed maintenance dose.

†Rate of aortic-root z-score change does not depend on prescribed atenolol dose, time x dose interaction, P=0.51.

‡Rate of aortic-root z-score change does not depend on prescribed losartan dose, time x dose interaction, P=0.78.

¶SD units/year ± SE

Aortic-root z-score, body-surface area-adjusted maximum aortic-root dimension z-score; SD, standard deviation; SE, standard error.

Table S6. Baseline Characteristics by Withdrawal Status

Baseline Characteristic	Withdrawn From Trial	Not Withdrawn From Trial	P value
N	65	543	
Adult	43%	23%	<0.001
Age, years*	15.0±6.4	10.8±6.2	<0.001
Male	58%	60%	0.79
Aortic-root z-score ≥4.5	60%	33%	<0.001
Aortic-root z-score*	5.0±1.5	4.2±1.3	<0.001
Past β-blocker use	58%	56%	0.79

*Data shown as mean ± SD. SD, standard deviation.

Table S7. Primary Endpoint Sensitivity Analyses

Analysis of Primary Endpoint	Number of Observations	Annual Rate of Change*		P value
		Atenolol	Losartan	
Primary analysis	2869	-0.139±0.013	-0.107±0.013	0.08
Secondary analysis, multiple imputation	3040	-0.132±0.013	-0.102±0.013	0.11
Secondary analysis, excluding 29 with adverse clinical outcome	2773	-0.142±0.013	-0.111±0.013	0.09
Secondary analysis, excluding 65 withdrawals from trial	2678	-0.144±0.013	-0.110±0.013	0.07

*Estimated slopes of z-scores in SD units/year ± SE. SD, standard deviation; SE, standard error.

Table S8. Anthropometric Measures

Measure	N	Baseline Mean±SD Atenolol	N	Baseline Mean±SD Losartan	P Value	N	3 Years Mean±SD Atenolol	N	3 Years Mean±SD Losartan	Annual Rate of Change* Atenolol	Annual Rate of Change* Losartan	P Value
Weight, kg	303	41.7±22.4	305	40.5±22.4	0.51	269	50.2±22.5	270	48.9±22.9	0.239±0.153	0.229±0.154	0.96¶
Weight-for-age z-score†	270	0.2±1.2	278	0.3±1.1	0.32	223	0.4±1.1	223	0.4±1.2	0.011±0.013	0.019±0.013	0.45
Weight-for-height z-score‡	58	-1.1±1.6	61	-1.0±1.6	0.75	19	-1.3±2.1	14	-1.0±1.7	-0.001±0.072	-0.157±0.076	0.13
Height, cm	303	151.3±33.2	305	149.7±32.5	0.55	269	164.1±24.9	270	162.2±24.5	0.822±0.204	0.935±0.202	0.65‡
Height-for-age z-score†	269	1.9±1.1	272	2.0±1.2	0.39	223	2.1±1.1	222	2.1±1.2	0.046±0.013	0.019±0.013	0.13
BMI, kg/m2	283	16.8±3.7	295	16.6±3.6	0.44	267	17.7±4.3	269	17.5±4.3	0.063±0.044	0.076±0.044	0.82‡
BMI for age z-score†	250	-1.2±1.7	263	-1.2±1.6	0.81	221	-1.2±1.8	222	-1.1±1.7	0.007±0.022	0.021±0.022	0.64
Arm span to height ratio	301	1.03±0.04	303	1.03±0.04	0.98	268	1.03±0.03	269	1.03±0.04	0.001±0.001	0.001±0.001	0.49
Upper to lower segment ratio	301	0.91±0.15	301	0.91±0.16	0.50	268	0.87±0.11	269	0.87±0.11	-0.014±0.002	-0.015±0.002	0.59

*SD units/year ± SE

†CDC 2000 weight for age z-score, height for age z-score and BMI for age z-score calculations are available for patients between 0-20 years of age.

‡Weight for height z-score calculation is available for height < 120 cm.

¶Regression model adjusted for age at study visit.

SD, standard deviation; SE, standard error; BMI, body mass index.

Table S9. Reported Symptoms at Baseline and During Maintenance

	Any Severity						Bothersome*					
	At Baseline†			Anytime 6 mo to 3 yr			At Baseline			Anytime 6 mo to 3 yr		
Reaction	Atenolol (N=303)	Losartan (N=305)	P Value‡	Atenolol (N=291)	Losartan (N=297)	P Value‡	Atenolol (N=303)	Losartan (N=305)	P Value‡	Atenolol (N=291)	Losartan (N=297)	P Value‡
Headache	112 (37%)	114 (37%)	0.93	202 (69%)	208 (70%)	0.93	10 (3%)	10 (3%)	1.00	27 (9%)	20 (7%)	0.29
Fatigue	**84 (28%)**	**105 (34%)**	**0.08**	152 (52%)	153 (52%)	0.87	0	0	-	7 (2%)	5 (2%)	0.57
Mood alterations	54 (18%)	49 (16%)	0.59	89 (31%)	86 (29%)	0.72	7 (2%)	3 (1.0%)	0.22	13 (4%)	13 (4%)	1.00
Behavior changes	21 (7%)	23 (8%)	0.88	51 (18%)	46 (15%)	0.58	2 (0.7%)	1 (0.3%)	0.62	5 (2%)	8 (3%)	0.58
Insomnia	60 (20%)	61 (20%)	1.00	108 (37%)	107 (36%)	0.80	2 (0.7%)	2 (0.7%)	1.00	6 (2%)	4 (1%)	0.54
Nightmares	52 (17%)	53 (17%)	1.00	100 (34%)	94 (32%)	0.54	2 (0.7%)	3 (1.0%)	1.00	7 (2%)	4 (1%)	0.38
Dizziness with standing	60 (20%)	58 (19%)	0.84	119 (41%)	105 (35%)	0.17	0	2 (0.7%)	0.50	**6 (2%)**	**0**	**0.01**
Dizziness - other	25 (8%)	27 (9%)	0.88	60 (21%)	61 (21%)	1.00	0	1 (0.3%)	1.00	2 (0.7%)	0	0.24
Fainting with loss of consciousness§	5 (2%)	9 (3%)	0.42	21 (7%)	16 (5%)	0.40	5 (2%)	9 (3%)	0.42	21 (7%)	16 (5%)	0.40
Palpitations¶	60 (20%)	53 (17%)	0.47	86 (30%)	101 (34%)	0.25	0	0	-	0	0	-
Chest pain	54 (18%)	58 (19%)	0.75	114 (39%)	106 (36%)	0.40	1 (0.3%)	5 (2%)	0.22	**14 (5%)**	**1 (0.3%)**	**<.001**
Dyspnea	43 (14%)	38 (12%)	0.55	75 (26%)	72 (24%)	0.70	3 (1.0%)	0	0.12	1 (0.3%)	3 (1%)	0.62
Wheezing	15 (5%)	14 (5%)	0.85	36 (12%)	32 (11%)	0.61	2 (0.7%)	1 (0.3%)	0.62	2 (0.7%)	5 (2%)	0.45
Upper respiratory/Nasal congestion	106 (35%)	117 (38%)	0.40	188 (65%)	186 (63%)	0.67	0	2 (0.7%)	0.50	3 (1%)	3 (1%)	1.00
Cough	47 (16%)	59 (19%)	0.24	117 (40%)	113 (38%)	0.61	1 (0.3%)	0	0.50	1 (0.3%)	1 (0.3%)	1.00

-Continued on next page-

	Any Severity						Bothersome*					
	At Baseline†			Anytime 6 mo to 3 yr			At Baseline			Anytime 6 mo to 3 yr		
Reaction	Atenolol (N=303)	Losartan (N=305)	P Value‡	Atenolol (N=291)	Losartan (N=297)	P Value‡	Atenolol (N=303)	Losartan (N=305)	P Value‡	Atenolol (N=291)	Losartan (N=297)	P Value‡
Dysgeusia¶	**10 (3%)**	**3 (1.0%)**	**0.05**	**29 (10%)**	**16 (5%)**	**0.04**	0	0	-	0	0	-
Stomach pain/Indigestion	47 (16%)	61 (20%)	0.17	119 (41%)	121 (41%)	1.00	0	1 (0.3%)	1.00	2 (0.7%)	8 (3%)	0.11
Nausea	30 (10%)	35 (11%)	0.60	**99 (34%)**	**78 (26%)**	**0.05**	1 (0.3%)	0	0.50	0	0	-
Vomiting	23 (8%)	23 (8%)	1.00	81 (28%)	75 (25%)	0.51	0	0	-	1 (0.3%)	2 (0.7%)	1.00
Diarrhea	35 (12%)	43 (14%)	0.40	94 (32%)	90 (30%)	0.66	1 (0.3%)	1 (0.3%)	1.00	1 (0.3%)	3 (1%)	0.62
Constipation	44 (15%)	35 (11%)	0.28	77 (26%)	66 (22%)	0.25	0	0	-	1 (0.3%)	0	0.49
Vascular (hands, feet)	35 (12%)	34 (11%)	0.90	73 (25%)	66 (22%)	0.44	0	1 (0.3%)	1.00	0	0	-
Muscle pain or cramps	59 (19%)	58 (19%)	0.92	**148 (51%)**	**124 (42%)**	**0.03**	2 (0.7%)	4 (1%)	0.69	6 (2%)	7 (2%)	1.00
Back pain	60 (20%)	67 (22%)	0.55	137 (47%)	134 (45%)	0.68	3 (1.0%)	2 (0.7%)	0.69	5 (2%)	8 (3%)	0.58
Periorbital edema	13 (4%)	15 (5%)	0.85	22 (8%)	27 (9%)	0.55	0	0	-	0	1 (0.3%)	1.00
Other‖	21 (7%)	16 (5%)	0.40	105 (36%)	108 (36%)	1.00	3 (1.0%)	1 (0.3%)	0.37	10 (3%)	12 (4%)	0.83

* Subject-reported symptoms were based on a detailed questionnaire administered at each study visit. Bothersome is at least 3 measured on a 1 to 4 scale where 4 is most bothersome.

†Two weeks after washout period and before study drug initiation

‡ Fisher exact test: comparisons with P values < 0.1 are shown in bold.

¶ Palpitations (cardiac arrhythmia) and dysgeusia are included for completeness, but only have allowable scores of 1 and 2 for bothersome.

§ Fainting with loss of consciousness is included for completeness, but only has allowable scores of 3 and 4 for bothersome.

‖Other represents the maximum bothersome score of the other adverse drug reactions per subject per visit.