Randomized Trial of Atenolol Versus Losartan in Children and Young Adults with Marfan Syndrome

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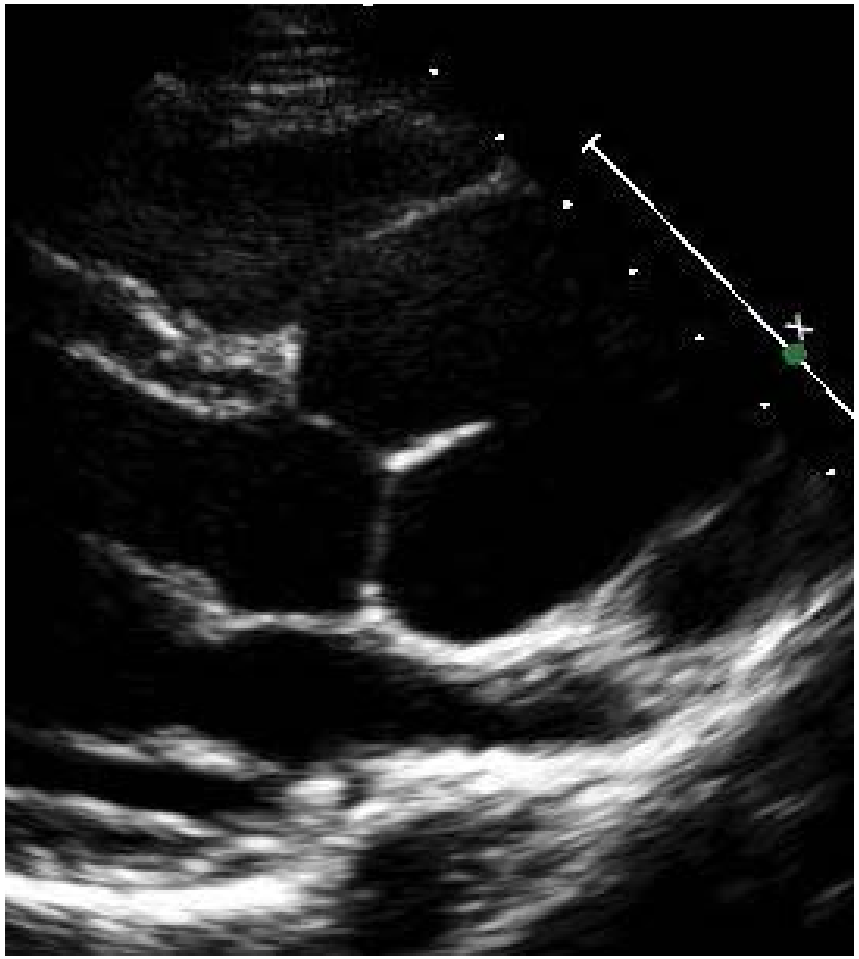
Marfan Syndrome (MFS)



- Autosomal dominant connective tissue disorder; 1 in 5,000
- Caused by mutations in the *FBN1* gene, which encodes fibrillin-1
- Aortic-root dilation and dissection cause premature death

Therapy for Marfan Syndrome

- β-blockers common medical management (Shores et al, NEJM 1994)
- Excessive TGF-β signaling thought to contribute to MFS manifestations
- Losartan may attenuate TGF-β signaling and may be more effective in slowing aortic-root enlargement than β-blockers.

Specific Aim/Primary End Point

- **Purpose: To compare effect of atenolol to that of losartan on aortic-root growth in MFS over 3 years**
- **Hypothesis: Rate of aortic growth will be lower in those receiving losartan than in those receiving atenolol**
- **Primary end point: Rate of change in BSA-adjusted maximum aortic-root diameter z-score (ARz)**

Secondary Endpoints

- Rate of change in aortic-root absolute diameter
- Adverse clinical outcomes:
  - Aortic dissection
  - Aortic-root surgery
  - Death
  - Composite end point
- Adverse events and subject-reported symptoms

Inclusion Criteria

- Age 6 months to 25 years
- Diagnosis of MFS by original Ghent criteria
- ARz > 3.0

Exclusion Criteria

- Prior or impending aortic surgery
- Aortic-root diameter > 5 cm
- Aortic dissection
- Loeys-Dietz or Sphrintzen-Goldberg syndromes
- Therapeutic use of ACE-I, BB, or ARB
- Intolerance or contraindication to BB or ARB

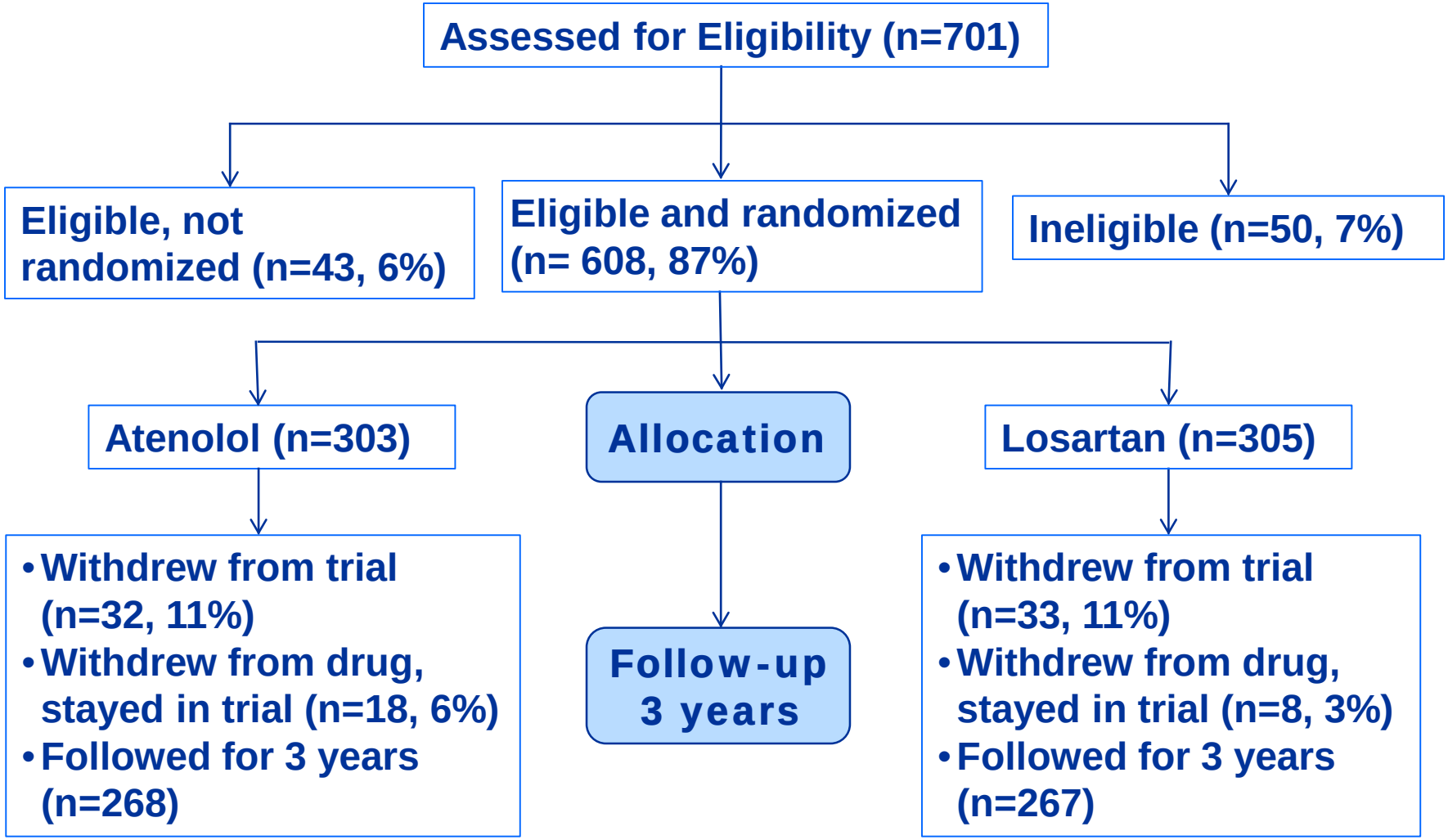
Study Design

- Randomization to atenolol or losartan stratified
  - Growing children vs. adult (♂≥16 yr, ♀≥15 yr)
  - Baseline ARz <4.5 vs. ≥4.5
- Dynamic allocation within each of 21 centers
- Atenolol
  - Maximum dose of 4 mg/kg/day (max 250 mg)
  - Goal of ≥20% decrease in mean heart rate by 24-hr recording
- Losartan
  - Maximum dose of 1.4 mg/kg/day (max 100 mg), as recommended by FDA

Statistical Analysis

- Primary analysis: intention-to-treat
- Primary end point:
  - Parametric curves longitudinal regression
  - Baseline-adjusted rates of change compared using test of treatment-by-time interaction
  - Final critical P value < 0.0453 (3 interim analyses)

Screening, Randomization, and Follow-up



Baseline Characteristics

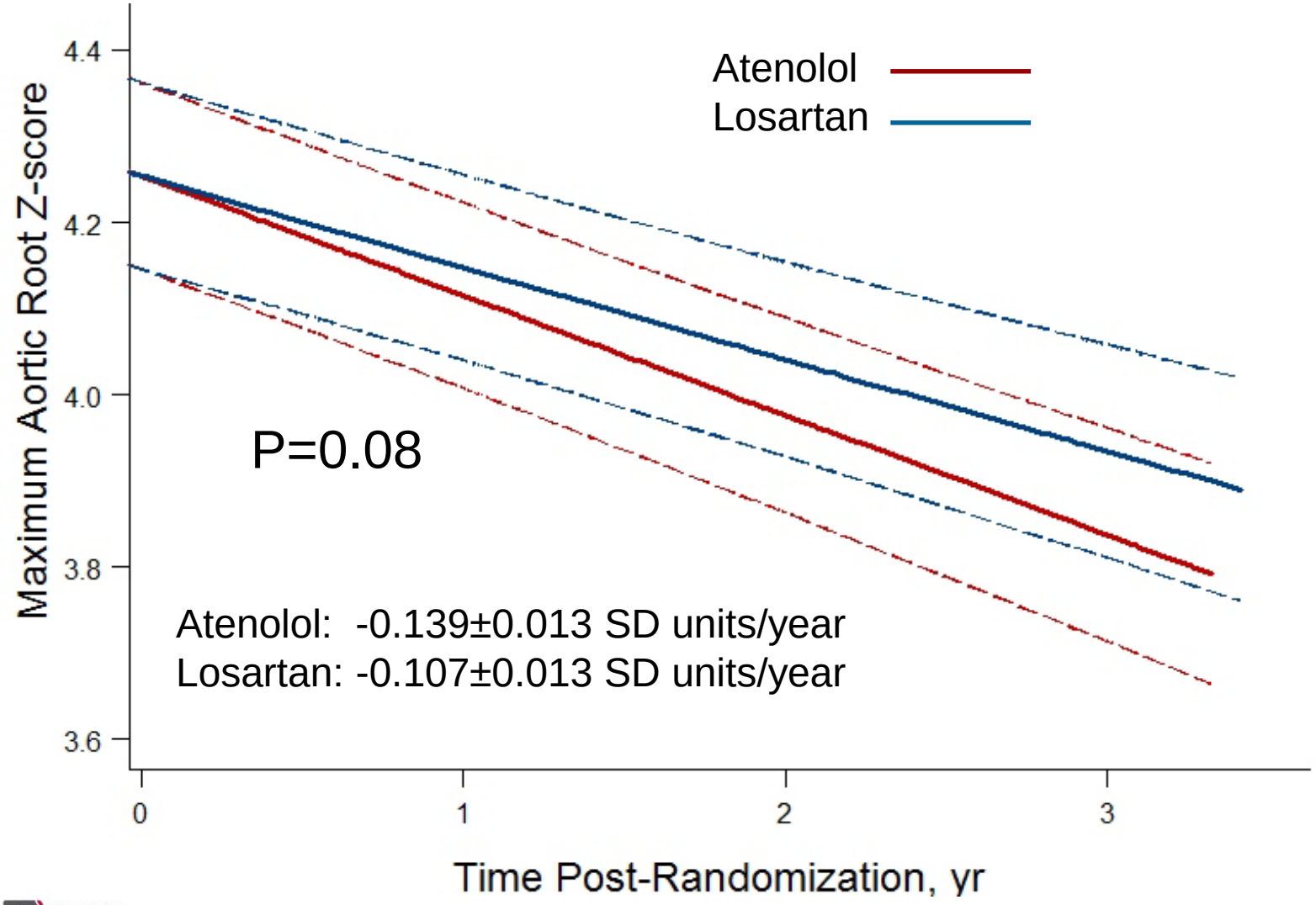
Characteristic	Atenolol (n=303)	Losartan (n=305)
Age at randomization, yr	11.5±6.5	11.0±6.2
Adult (♂≥16 yr, ♀≥15 yr)	76 (25%)	75 (25%)
Male	180 (59%)	186 (61%)
Max. aortic-root diameter, cm	3.4±0.7	3.4±0.7
Max. aortic-root diameter z-score	4.0 (3.5, 4.8)	4.0 (3.3, 5.0)
Prior use of beta-blocker	173 (57%)	171 (56%)

Prescribed Doses of Study Medications

	Atenolol (mg/kg/d)	Losartan (mg/kg/d)
All	2.7±1.1	1.3±0.2
Children	2.8±1.0	1.3±0.2
Adults	2.3±1.2	1.2±0.2

Absolute doses for adults (mg/d):
Atenolol 151±75 mg
Losartan 85±14 mg

Estimated Rate of Change in ARz



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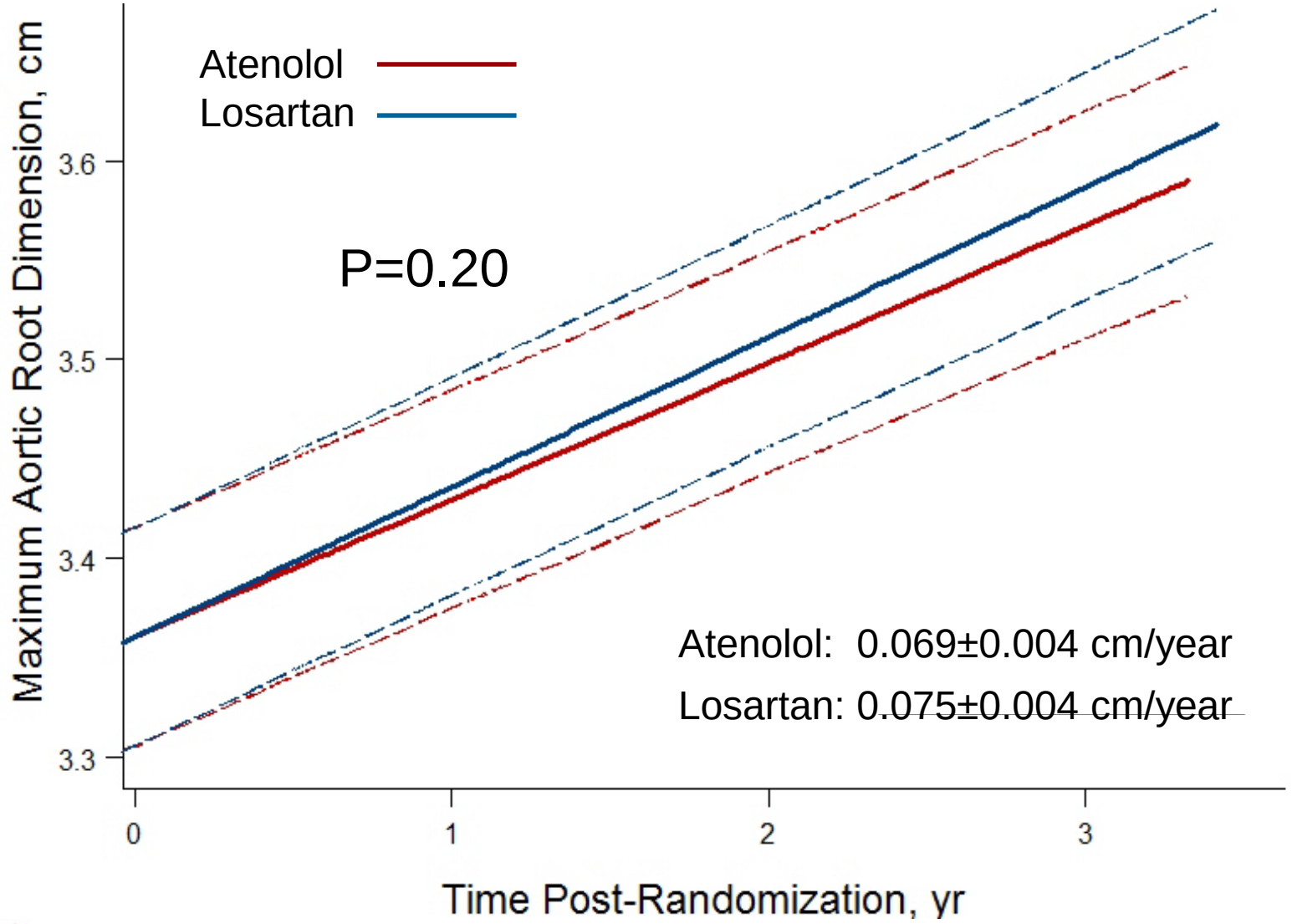
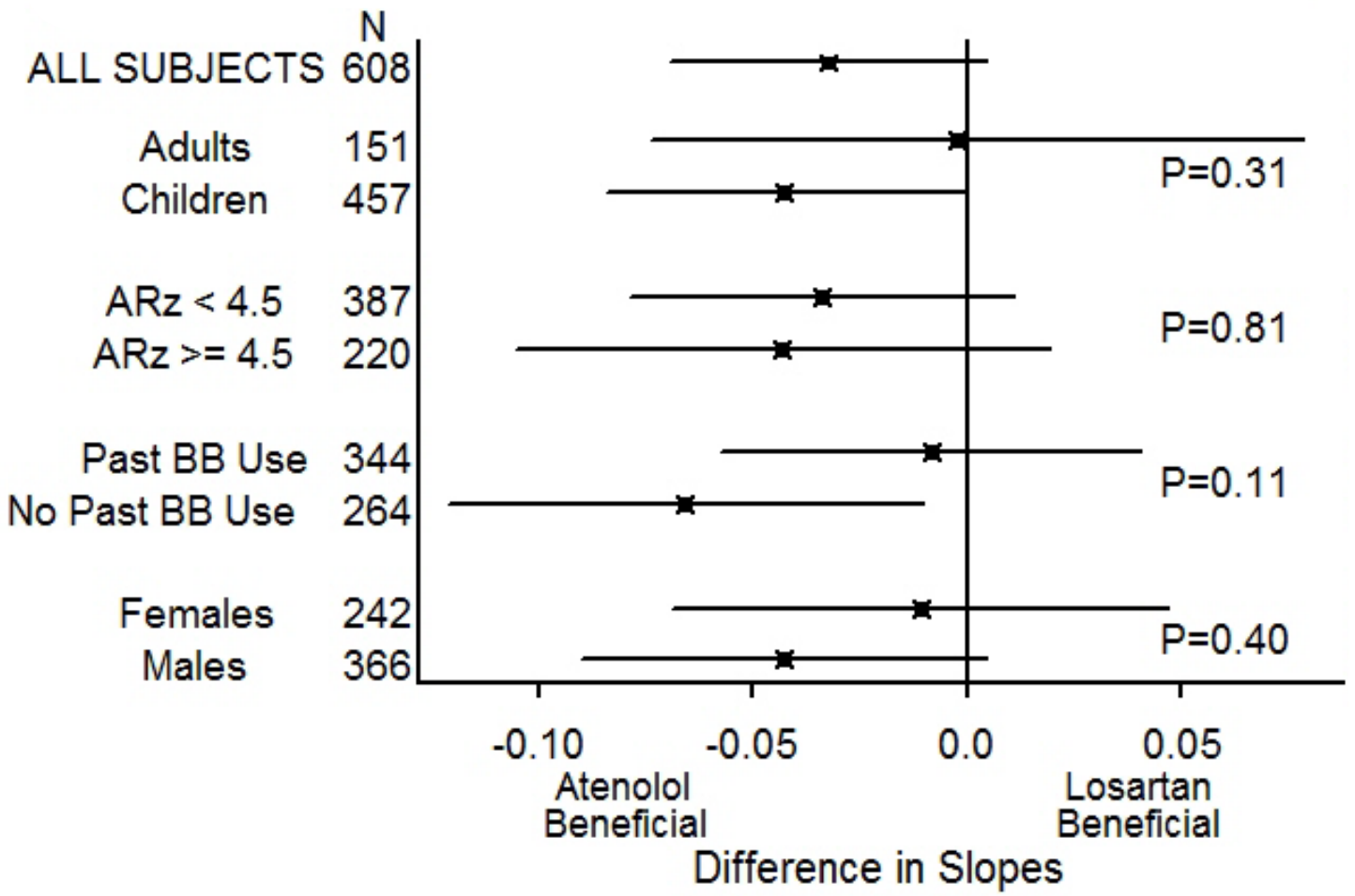
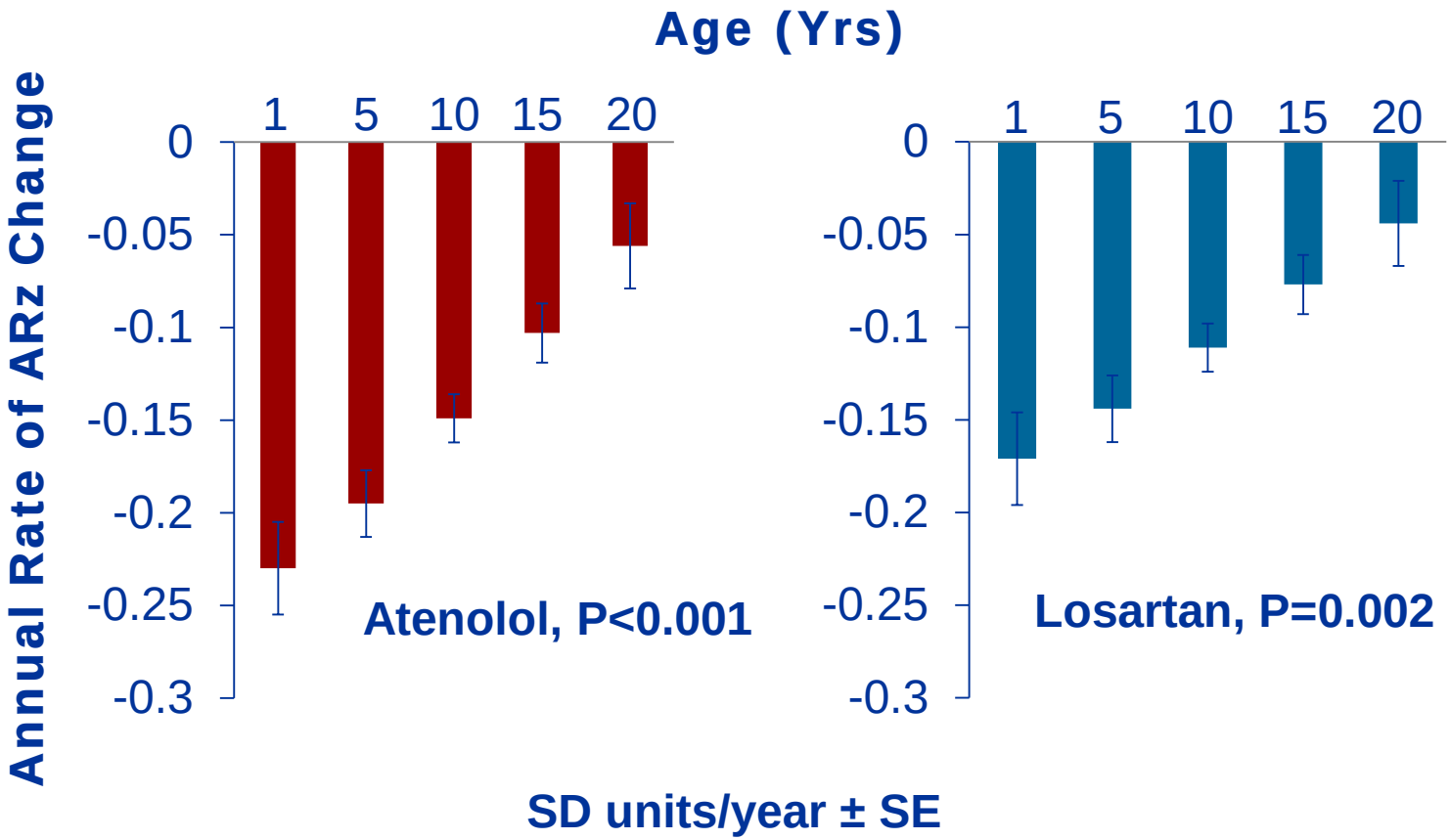
Estimated Rate of Change in Aortic-Root Absolute Diameter



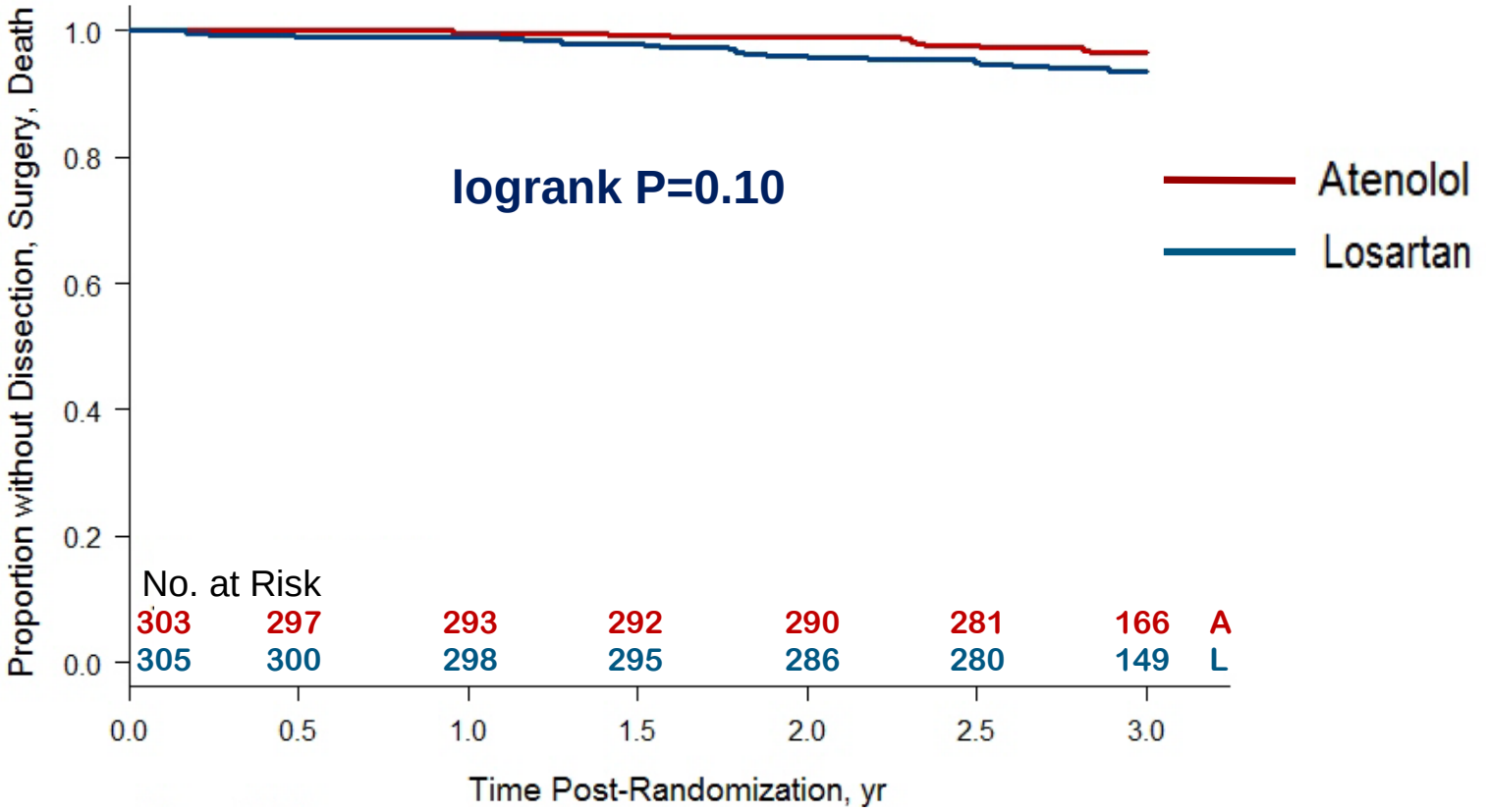
Subgroup Analysis



Estimated Change in ARz by Baseline Age



Freedom from Dissection, Surgery, Death



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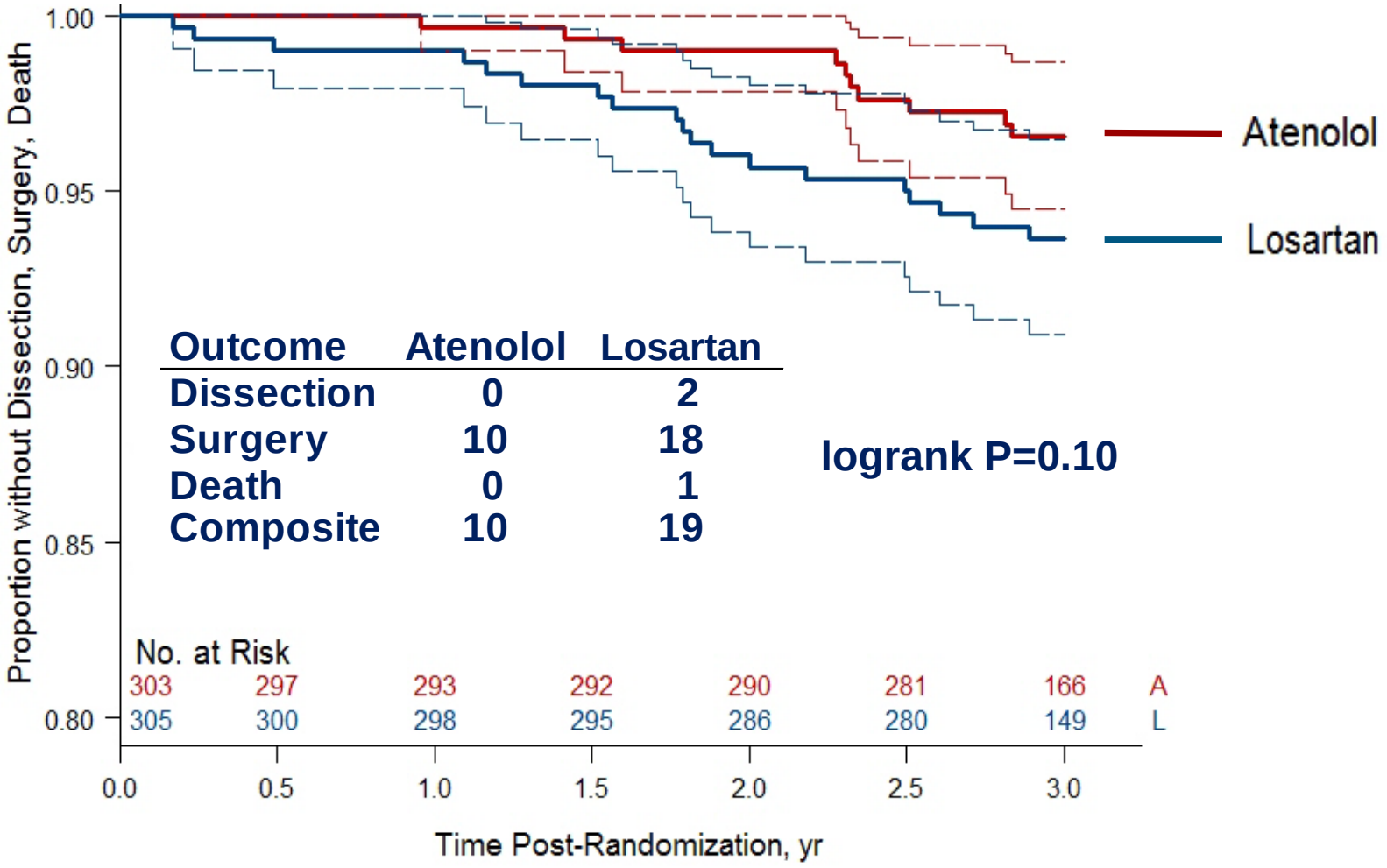

Outcome	Atenolol	Losartan
Dissection	0	2
Surgery	10	18
Death	0	1
Composite	10	19

logrank P=0.10

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Adverse Events and Reported Symptoms

	Atenolol	Losartan	P value*
All:			
AE	408	365	0.10
SAE	40	50	0.31
Possibly/probably related:			
AE	204	163	0.03
SAE	5	2	0.25

Subject-reported symptoms: Bothersome symptoms were rare at baseline and during maintenance.

*Poisson regression

Limitations

- Not generalizable to individuals with ARz ≤ 3.0
- No placebo arm
- Limited information on optimal dose of losartan
- Limited statistical power to detect subgroup findings and treatment differences in relatively low clinical event rates
- Personnel supervising uptitration were aware of treatment assignment, but core lab readers were masked

Conclusions

- We found no significant difference in the rate of aortic-root dilation between the two treatment groups over 3 years.
- The treatment effect did not differ according to pre-specified subgroups.
- The dose of atenolol used in this study was higher than that in many other studies.
- Both drugs were well-tolerated.
- Losartan and atenolol may be more effective at reducing ARz in younger subjects.

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ORIGINAL ARTICLE

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Thank You

- Patients and families
- Study coordinators
- Referring physicians
- The Marfan Foundation
- NHLBI
- FDA Office of Orphan Products Development
- Merck & Co, Inc.
- Teva Canada Limited

Backup Slides Follow

Blood Pressure (BP) and Heart Rate

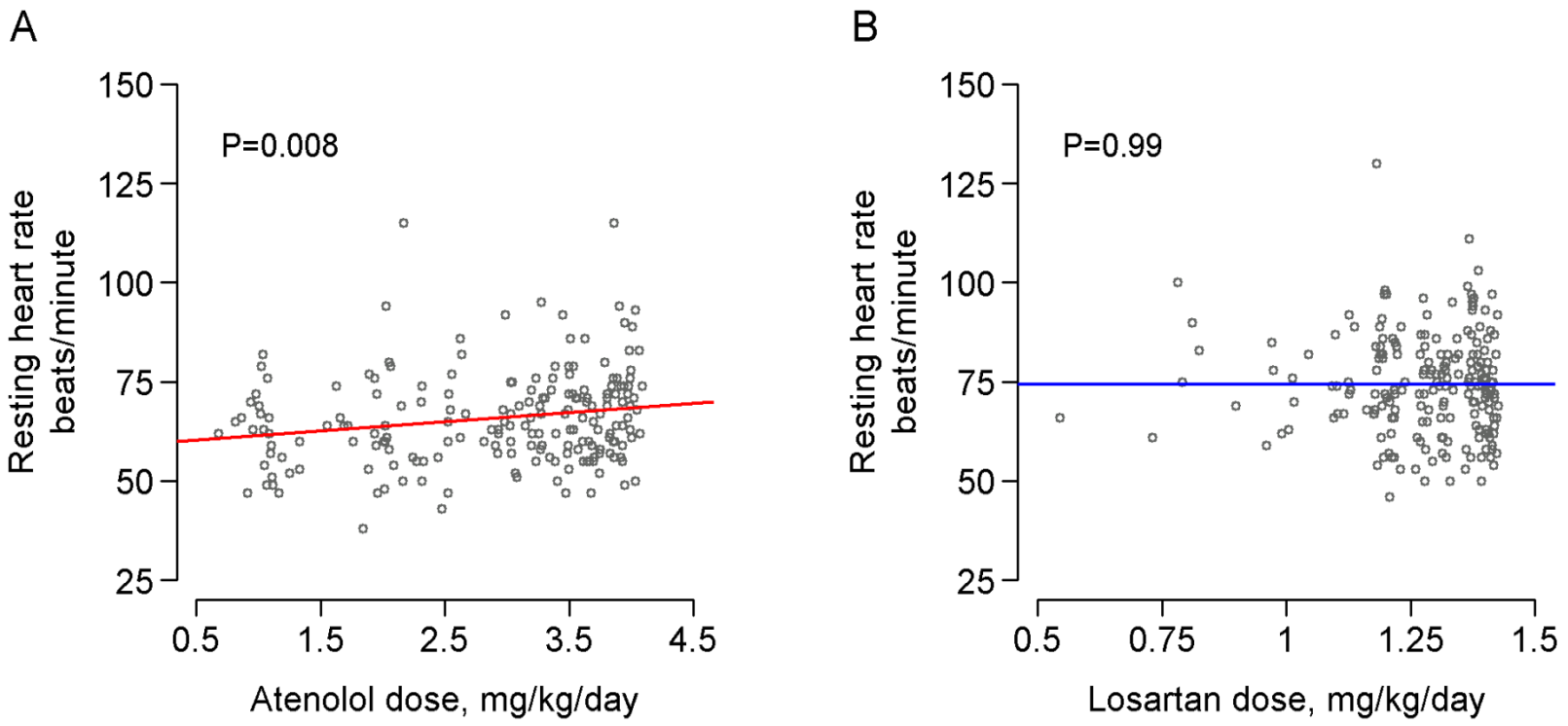
- Baseline BP and heart rate not different between groups
- At 3 years, mean diastolic BP lower in atenolol group (54±8 vs. 56±8 mm Hg, P=0.04), but no difference in systolic BP (95±12 vs. 96±13 mm Hg, P=0.44) or mean BP (68±10 vs. 69±9 mm Hg, P=0.13)
- Resting and average 24-hr heart rates significantly lower in atenolol group

Association of Dose with Change in ARz

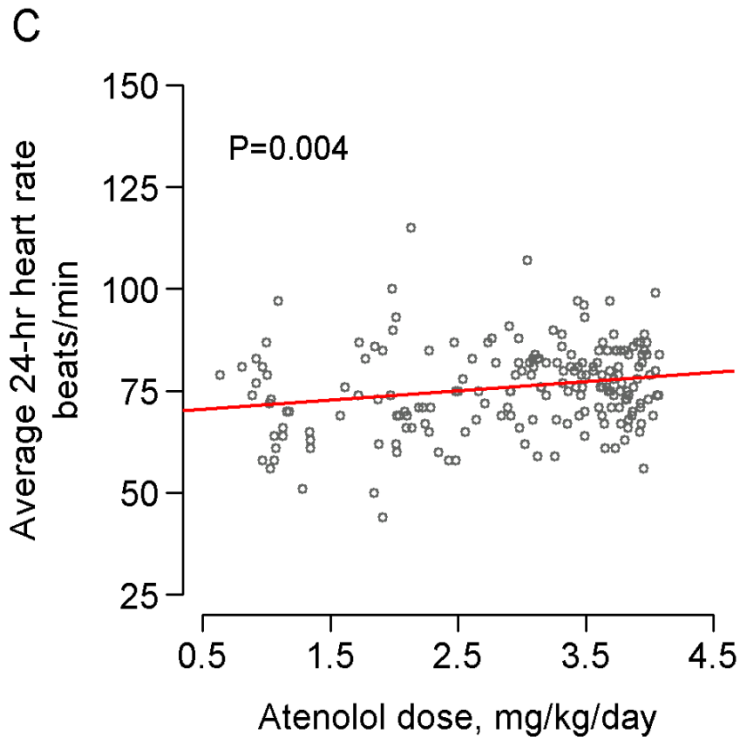
Atenolol		Losartan	
Dose*	Rate of ARz Change‡	Dose*	Rate of ARz Change‡
1.8 mg/kg	-0.143±0.018	1.2 mg/kg	-0.110±0.014
3.0 mg/kg	-0.133±0.014	1.3 mg/kg	-0.112±0.014
3.7 mg/kg	-0.127±0.018	1.4 mg/kg	-0.114±0.017

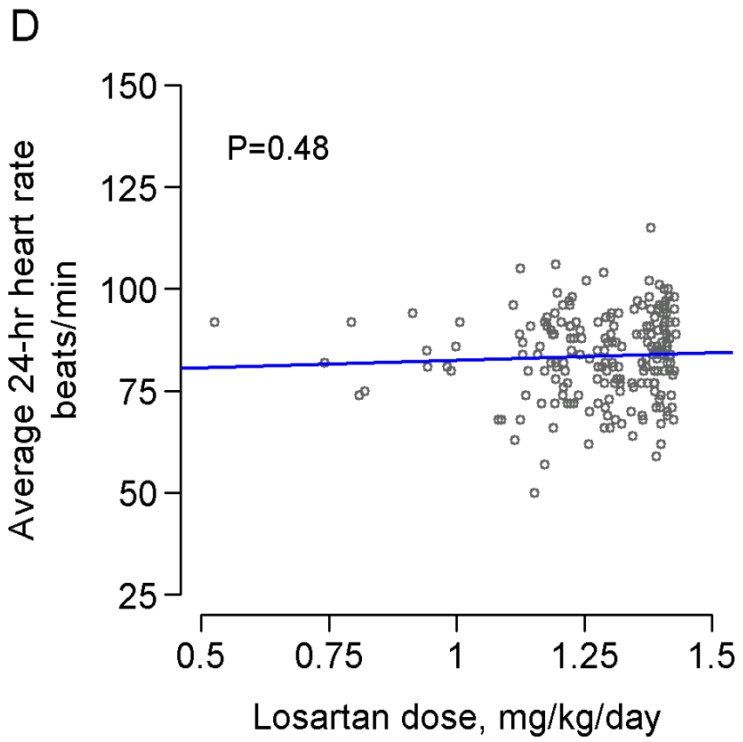
*Doses are quartiles of prescribed maintenance dose.
‡SD units/year ± SE
P=0.51 for atenolol, P=0.78 for losartan

Resting HR vs. Dose in Children at 3 Yrs



Average 24-hr HR vs. Dose in Children at 3 Years





Rate of Change in Aortic-Annulus Z-Score & Absolute Diameter

- Change in Z-score (SD units/yr)
  - -0.279±0.018 for atenolol
  - -0.175±0.018 for losartan
  - P<0.001
- Change in Absolute Diameter (cm/yr)
  - 0.015±0.003 for atenolol
  - 0.030±0.003 for losartan
  - P=0.002