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

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

Assessed for Eligibility (n=701)

Eligible, not randomized (n=43, 6%)
- Atenolol (n=303)
  - Withdrew from trial (n=32, 11%)
  - Withdrew from drug, stayed in trial (n=18, 6%)
  - Followed for 3 years (n=268)

Eligible and randomized (n=608, 87%)
- Allocation
  - Follow-up 3 years
    - Withdrew from trial (n=33, 11%)
    - Withdrew from drug, stayed in trial (n=8, 3%)
    - Followed for 3 years (n=267)

Ineligible (n=50, 7%)
- Losartan (n=305)
  - Followed for 3 years (n=267)
## Baseline Characteristics

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

<table>
<thead>
<tr>
<th></th>
<th>Atenolol (mg/kg/d)</th>
<th>Losartan (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.7±1.1</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>Children</td>
<td>2.8±1.0</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>Adults</td>
<td>2.3±1.2</td>
<td>1.2±0.2</td>
</tr>
</tbody>
</table>

Absolute doses for adults (mg/d):
- Atenolol 151±75 mg
- Losartan 85±14 mg
Estimated Rate of Change in ARz

Atenolol: $-0.139 \pm 0.013$ SD units/year
Losartan: $-0.107 \pm 0.013$ SD units/year

P = 0.08
Estimated Rate of Change in Aortic-Root Absolute Diameter

P=0.20

Atenolol: 0.069±0.004 cm/year
Losartan: 0.075±0.004 cm/year
Subgroup Analysis

- All Subjects: 608
  - Adults: 151, P = 0.31
  - Children: 457
  - ARz < 4.5: 387, P = 0.81
  - ARz >= 4.5: 220
  - Past BB Use: 344
  - No Past BB Use: 264, P = 0.11
  - Females: 242, P = 0.40
  - Males: 366

Difference in Slopes:
- Atenolol Beneficial
- Losartan Beneficial
Estimated Change in ARz by Baseline Age

Atenolol, \( P < 0.001 \)

Losartan, \( P = 0.002 \)

Annual Rate of ARz Change

Age (Yrs)

SD units/year ± SE
Freedom from Dissection, Surgery, Death

- Dissection: 0 2
- Surgery: 10 18
- Death: 0 1
- Composite: 10 19

Logrank P=0.10

No. at Risk:

- Atenolol:
  - 303
  - 305
  - 297
  - 298
  - 293
  - 292
  - 290
  - 286
  - 281
  - 166

- Losartan:
  - 300
  - 300
  - 298
  - 295
  - 290
  - 286
  - 280
  - 149
  - 149

Time Post-Randomization, yr

Logrank P=0.10
Freedom from Dissection, Surgery, Death

Outcome | Atenolol | Losartan | logrank P=0.10
--- | --- | --- | ---
Dissection | 0 | 2 | 
Surgery | 10 | 18 | 
Death | 0 | 1 | 
Composite | 10 | 19 | 

No. at Risk

<table>
<thead>
<tr>
<th>Time Post-Randomization, yr</th>
<th>0.0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>303</td>
<td>297</td>
<td>293</td>
<td>292</td>
<td>290</td>
<td>281</td>
<td>166</td>
<td>A</td>
</tr>
<tr>
<td>305</td>
<td>300</td>
<td>298</td>
<td>295</td>
<td>286</td>
<td>280</td>
<td>149</td>
<td>L</td>
</tr>
</tbody>
</table>
### Adverse Events and Reported Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Atenolol</th>
<th>Losartan</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>408</td>
<td>365</td>
<td>0.10</td>
</tr>
<tr>
<td>SAE</td>
<td>40</td>
<td>50</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Possibly/probably related:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>204</td>
<td>163</td>
<td>0.03</td>
</tr>
<tr>
<td>SAE</td>
<td>5</td>
<td>2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

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.
ORIGINAL ARTICLE

Atenolol versus Losartan in Children and Young Adults with Marfan’s Syndrome

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

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Atenolol Rate of ARz Change‡</th>
<th>Dose*</th>
<th>Losartan Rate of ARz Change‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8 mg/kg</td>
<td>-0.143±0.018</td>
<td>1.2 mg/kg</td>
<td>-0.110±0.014</td>
</tr>
<tr>
<td>3.0 mg/kg</td>
<td>-0.133±0.014</td>
<td>1.3 mg/kg</td>
<td>-0.112±0.014</td>
</tr>
<tr>
<td>3.7 mg/kg</td>
<td>-0.127±0.018</td>
<td>1.4 mg/kg</td>
<td>-0.114±0.017</td>
</tr>
</tbody>
</table>

*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

A

Resting heart rate beats/minute

P = 0.008

Atenolol dose, mg/kg/day

B

Resting heart rate beats/minute

P = 0.99

Losartan dose, mg/kg/day
Average 24-hr HR vs. Dose in Children at 3 Years

C

Average 24-hr heart rate beats/min

P=0.004

Atenolol dose, mg/kg/day

D

Average 24-hr heart rate beats/min

P=0.48

Losartan dose, mg/kg/day
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