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

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Presented at the American Heart Association Scientific Sessions 2014

November 18th, 2014
Characteristics of Losartan Trial:

- Randomized trial of Losartan vs. Atenolol in treatment of aortic root dilatation
- Children and young adults with Marfan disease.
- Well-balanced baseline characteristics of two groups.
- End-points:
  - Aortic growth (absolute)
  - Change in aortic root z-score.
  - Composite end-point: Dissection, Operation, Death

Findings:

- No difference in aortic growth
- No difference in aortic root z-score change
- No difference in composite end-point
- No difference in sub-group analyses (age, gender, z-score, prior β-blocker use)

“Negative” Trial
Could the trial be a false negative?

- Patient number **sufficient**
- Duration of follow-up **adequate** (3 years)
- Losartan dose **generous**
  - Some evidence of diverging curves favoring Losartan (composite end-point only).

**Unlikely false negative**

**Clinical trial did not live up to promise of early animal and clinical testing**

Two analyses that might have unmasked a possible Losartan contribution

• **Histologic analysis** in operated aortas in both groups (18 Losartan, 10 β-blocker)—see if histology normalized, as in Marfan mouse study.

• **Genetic confirmation** of positivity for *FBN1* mutation
  – only 44% had genetic testing
  – of those with genetic testing, only 71% were positive

Did patients without “real” Marfan’s disease “contaminate” the groups, thus masking a positive Losartan effect?
Was Losartan compared against a “Straw Man”?

• This could well be, as the evidence for a positive effect of β-blockers on aortic root aneurysms is weak.
  – Classic Shores study has limitations.
  – Other studies equivocal at best.


If really comparing against “Straw Man” placebo, then thrust of trial that Losartan is of no benefit at all.
However, Rx Quiver not completely empty

1560 patients at Aortic Institute at Yale

STATINS!