

September 12-14

**2018**

Les Comtes de Méan  
**Liège, Belgium**

# 6<sup>th</sup> International Meeting on Aortic Diseases

New insights into an old problem **CHU Liège, APF**

[www.chuliege-ima.be](http://www.chuliege-ima.be)

## **The Z-Score--Misleading Clinical Science?**

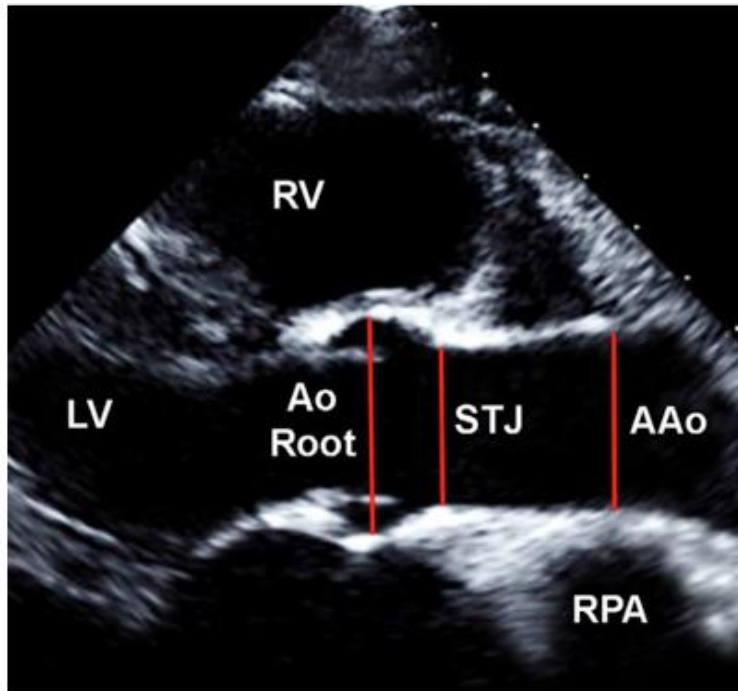
**John A. Elefteriades, MD, PhD (hon)**  
William W.L. Glenn Professor of Surgery  
Director, Aortic Institute at Yale-New Haven  
Yale University School of Medicine  
New Haven, Connecticut, USA



**CHU**  
de Liège

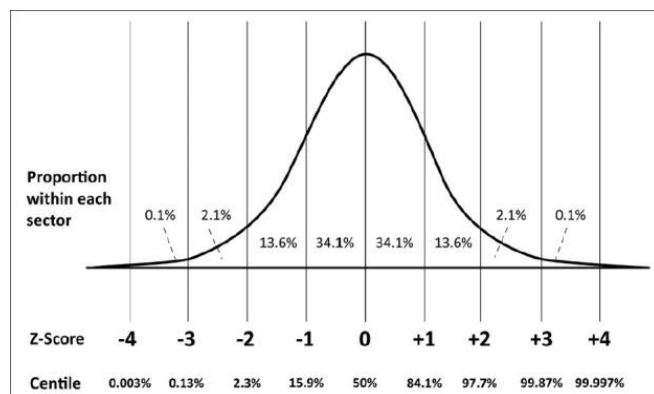


# Measurement modalities



- Re-read all ECHOs for standardization
- 361 ECHOs in children screened
- 27 "normal" children with serial ECHOs
- 26 untreated Marfan children with serial ECHOs

# “Aortic Z-Score” Basics



**How many standard deviations  
above or below the mean.  
Depends on the BSA.  
Does not take age into account.**

- $Z = \frac{(x - \mu)}{\sigma}$

$\sigma$

**x = observed measurement**

**$\mu$  = expected measurement (population mean)**

**$\sigma$  = population standard deviation**

---

**Calculations now done on-line.**

**Boston Children's Hospital is most popular.**

**Methodological details are secret.**

# Z-Score used extensively in aortic outcomes studies

## *The* NEW ENGLAND JOURNAL *of* MEDICINE

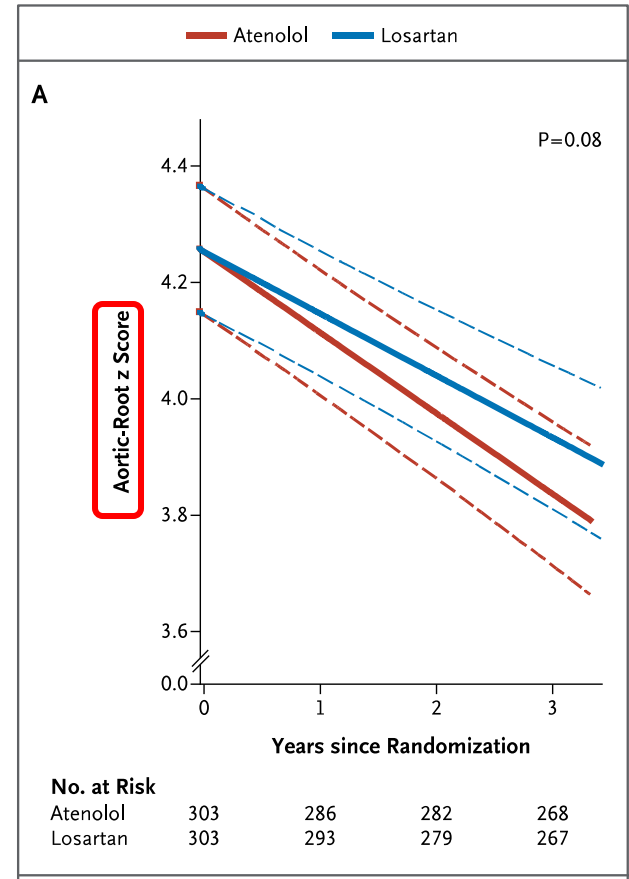
ESTABLISHED IN 1812

NOVEMBER 27, 2014

VOL. 371 NO. 22

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

R.V. Lacro, H.C. Dietz, L.A. Sleeper, A.T. Yetman, T.J. Bradley, S.D. Colan, G.D. Pearson, E.S. Selamet Tierney, J.C. Levine, A.M. Atz, D.W. Benson, A.C. Braverman, S. Chen, J. De Backer, B.D. Gelb, P.D. Grossfeld, G.L. Klein, W.W. Lai, A. Liou, B.L. Loeys, L.W. Markham, A.K. Olson, S.M. Paridon, V.L. Pemberton, M.E. Pierpont, R.E. Pyeritz, E. Radojewski, M.J. Roman, A.M. Sharkey, M.P. Stylianou, S. Burns Wechsler, L.T. Young, and L. Mahony, for the Pediatric Heart Network Investigators\*



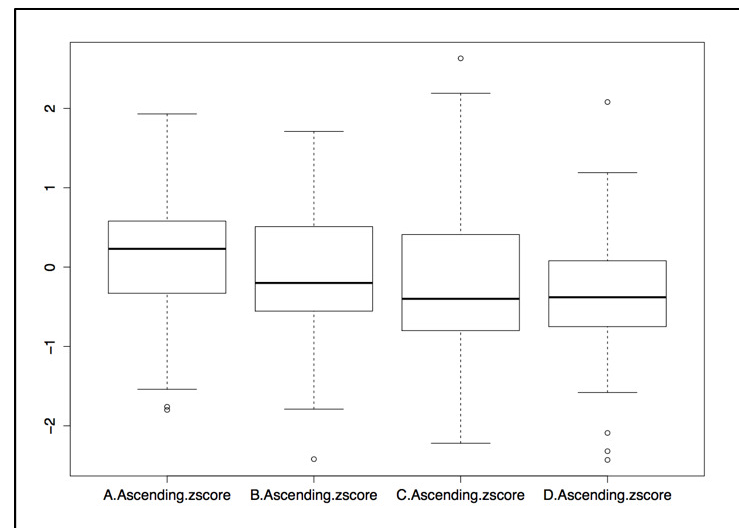
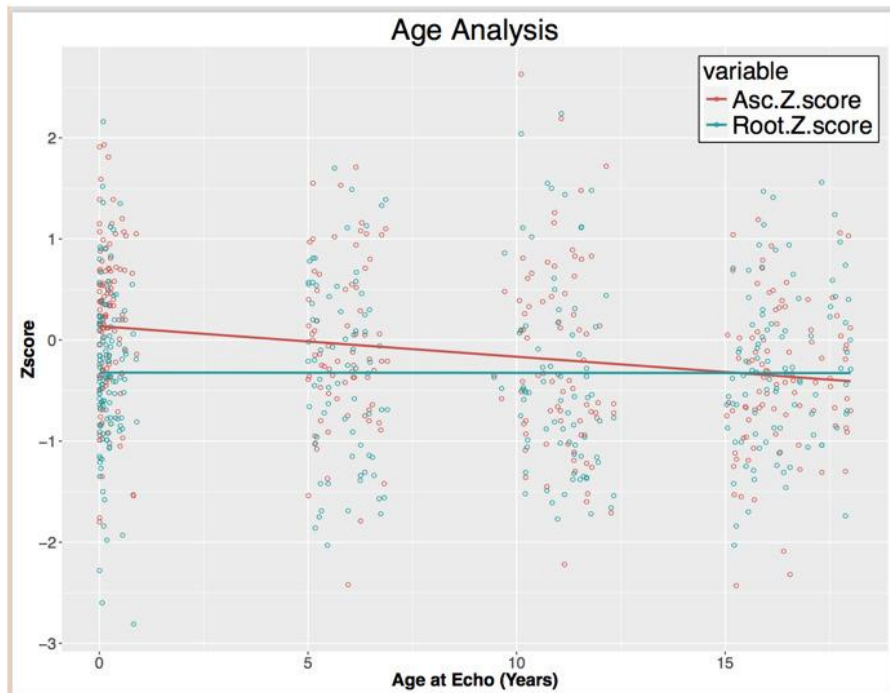


IS THE Z-SCORE AN ACCURATE,  
RELIABLE INDICATOR ON WHICH  
WE CAN BASE CLINICAL  
OUTCOMES STUDIES?

THREE IMPORTANT QUESTIONS:

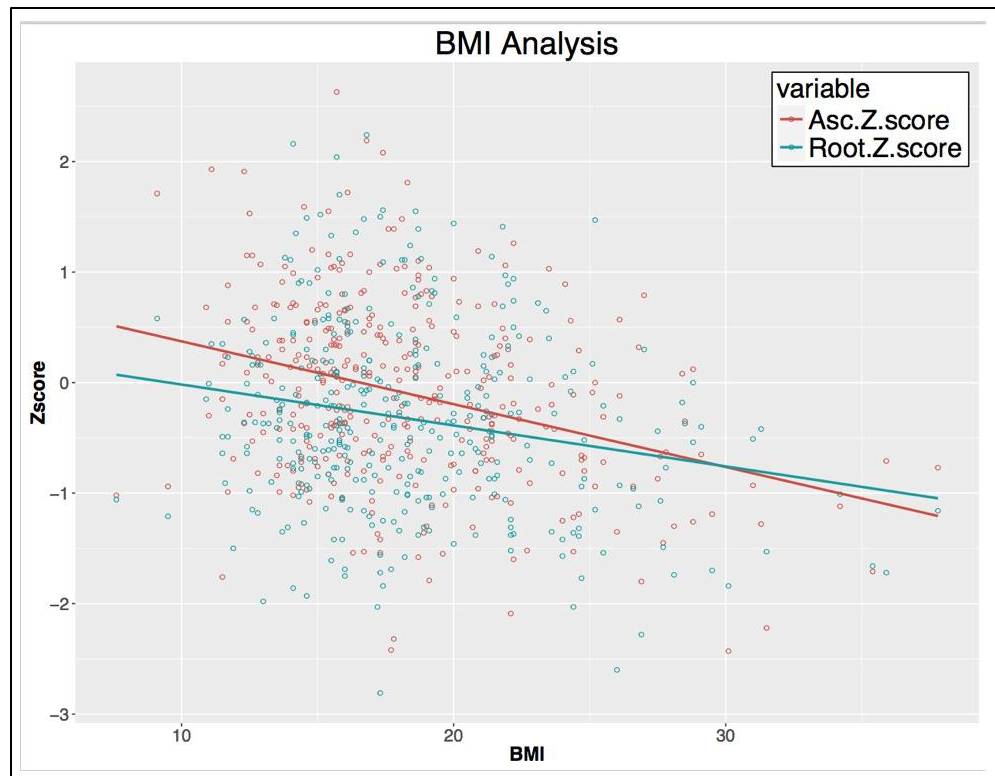
- Does z-score decrease naturally with age in “normal children”?
- Does z-score decrease as the BMI of the growing child increases?
- Does z-score decrease naturally in untreated Marfan children?

Does z-score decrease naturally with age in “normal children”? **YES!**



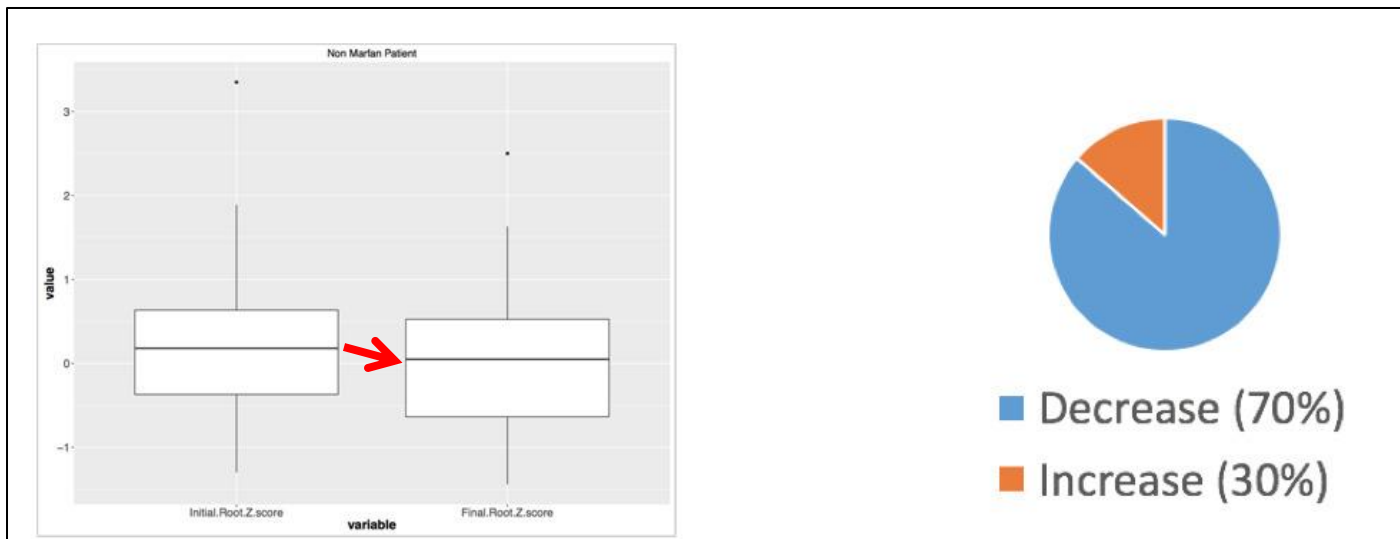


Does z-score decrease as the BMI of the growing child increases? **YES!**





Does z-score decrease naturally in untreated Marfan children? **YES!**







Does z-score decrease naturally with age in “normal children”? **YES!**  
Does z-score decrease as the BMI of the growing child increases? **YES!**  
Does z-score decrease naturally in untreated Marfan children? **YES!**

SO, DOES A DECREASING Z-SCORE IN A DRUG TRIAL OF AORTIC ANEURYSM RX HAVE ANY REAL MEANING? **APPARENTLY NOT**



THIS IS ONE REASON  
WE VOICED A WORD  
OF CAUTION ON ONE  
TRIAL CLAIMING TO  
HAVE DEMONSTRATED  
A DRUG EFFECT



***Take the Z-score in aortic outcomes studies with a huge grain of salt!***

## Atenolol versus Losartan in Marfan's Syndrome

**TO THE EDITOR:** Lacro et al. (Nov. 27 issue)<sup>1</sup> report no benefit of losartan, an angiotensin-receptor blocker (ARB), over the beta-blocker atenolol in respect to the rate of aortic-root dilatation in Marfan's syndrome. A possible interpretation of this study might be that ARBs are as effective as beta-blockers in the treatment of patients with Marfan's syndrome.<sup>2</sup> However, such an interpretation assumes that beta-blockers are an effective treatment option.

Beta-blockers are presently considered to be first-line therapy in patients with Marfan's syndrome. However, their benefit is debatable and not supported by robust evidence. Several observational studies and only one clinical trial<sup>3</sup> have evaluated the effectiveness of beta-blockers in patients with Marfan's syndrome, and the results have been conflicting. Two meta-analyses also reached opposing conclusions<sup>4,5</sup> (Table 1). Remarkably, no study showed a benefit of beta-blockers in preventing clinical end points (e.g., death or dissection).

As a reflection of these uncertainties, the 2010 guidelines of the American College of Cardiology Foundation and the American Heart Association recommend the use of beta-blockers, whereas the 2014 guidelines of the European

Society of Cardiology do not. If beta-blockers are not truly effective, then the study by Lacro et al. has really shown that ARBs are as effective as a placebo.

Bulat A. Ziganshin, M.D.

Sandip K. Mukherjee, M.D.

John A. Elefteriades, M.D.

Aortic Institute at Yale—New Haven Hospital  
New Haven, CT  
john.elefteriades@yale.edu

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

1. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med* 2014;371:2061-71.

2. Bowen JM, Connolly HM. Of Marfan's syndrome, mice, and medications. *N Engl J Med* 2014;371:2127-8.

3. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335-41.

4. Gersony DR, McCloughlin MA, Jin Z, Gersony WM. The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: a meta-analysis. *Int J Cardiol* 2007;114:303-8.

5. Gao L, Mao Q, Wen D, Zhang L, Zhou X, Hui R. The effect of beta-blocker therapy on progressive aortic dilatation in children and adolescents with Marfan's syndrome: a meta-analysis. *Acta Paediatr* 2011;100(9):e101-e105.

DOI: 10.1056/NEJMc1500128