TRIAL OF BETA BLOCKER THERAPY (ATENOLOL) VS. ANGIOTENSIN II RECEPTOR BLOCKER THERAPY (LOSARTAN) IN INDIVIDUALS WITH MARFAN SYNDROME
PUBLIC USE DATASET

ABOUT THE STUDY

The NHLBI Marfan Study was conducted by the Pediatric Heart Network (PHN) at 20 centers in North America and 1 center in Belgium from January 2007 through February 2011. Inclusion criteria were an age of 6 months to 25 years, a diagnosis of Marfan's syndrome according to the original Ghent criteria, and a z-score for the maximum aortic-root diameter indexed to body-surface area greater than 3.0. Exclusion criteria were previous or impending aortic surgery; an aortic-root diameter greater than 5 cm; a history of aortic dissection; a diagnosis of the Loeys–Dietz syndrome or the Shprintzen–Goldberg syndrome; therapeutic rather than prophylactic use of an angiotensin-converting–enzyme inhibitor, beta-blocker, or calcium-channel blocker; prior adverse effects related to treatment with ARB or beta-blocker therapy or a contraindication to such treatment; and an inability to complete study procedures.

Participants were assigned to atenolol or losartan in a 1:1 ratio, stratified according to age (young adults [defined as male participants 16 to 25 years of age and female participants 15 to 25 years of age] vs. children [male participants younger than 16 years of age and female participants younger than 15 years of age]) and a baseline aortic-root z-score of less than 4.5 versus a z-score of 4.5 or greater. 608 participants were enrolled; 303 participants were randomly assigned to atenolol and 305 to losartan. Study visits occurred at baseline and at 6, 12, 24, and 36 months after randomization. Echocardiograms were obtained at each study visit and were interpreted in a core laboratory.

The aims of the study were:

Primary aim:

- To compare the effect of BB therapy to that of ARB therapy on the rates of aortic growth and progression of aortic regurgitation.
- Primary outcome:
    - Rate of change in aortic root (sinuses of Valsalva) BSA-adjusted Z-score
- Secondary outcomes:
    - Rate of change in aortic root (sinuses of Valsalva) absolute dimension
    - Rate of change in ascending aorta absolute dimension and BSA-adjusted Z-score
    - Rate of change in aortic annulus absolute dimension and BSA-adjusted Z-score
    - Rate of change of aortic regurgitation, measured as change in vena contracta area indexed for BSA

Secondary aim 1:

- To compare the effect of BB therapy to that of ARB therapy on the incidence of the following cardiovascular events: aortic dissection, aortic root surgery, and death.
- Outcomes:
    - Aortic dissection, aortic root surgery, or death at 36 months after randomization
    - Time to first occurrence of aortic dissection, aortic root surgery, or death up to 36

months after randomization

Secondary aim 2:

- To compare the effect of BB therapy to that of ARB therapy on the progression of mitral regurgitation.
- Outcome:
    - Rate of change of mitral regurgitation, measured as change in vena contracta area indexed for BSA

Secondary aim 3:

- To compare the effect of BB therapy to that of ARB therapy on left ventricular size and function.
- Outcomes:
    - Rate of change of left ventricular mass, volume, mass to volume ratio, and ejection fraction by two-dimensional echocardiography
    - Rate of change of left ventricular end-diastolic and end-systolic dimensions, diastolic septal and posterior wall thickness, left ventricular mass and shortening fraction by M-mode

Secondary aim 4:

- To compare the effect of BB therapy to that of ARB therapy on echocardiographically-derived measures of central aortic stiffness.
- Outcome:
    - Rate of change of ascending aortic elastic modulus and stiffness index

Secondary aim 5:

- To compare the effect of BB therapy to that of ARB therapy on skeletal and somatic growth.
- Outcomes:
    - Rate of change in Z-scores for weight, height, body mass index (BMI), and upper-to-lower segment ratio corrected for age in subjects as determined by availability of Z-scores
    - Rate of change in weight and BMI with covariate adjustment for age in all subjects

Secondary aim 6:

- To compare the effect of BB therapy to that of ARB therapy on the incidence of drug side effects.
- Outcome:
    - Incidence of adverse events and patient-reported symptoms.

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The study design has been described in great detail in Lacro et al. (*Am Heart J* 2007), Lacro et al. (*NEJM* 2014), and in the study protocol (all available to users with approved logins). Table 1 provides key subject characteristics. Additional information can be found in the published articles on specialized topics (see posted Bibliography at http://pediatricheartnetwork.com/ResourcesPublications/Publications.aspx#73556-marfan-trial).

Table 1. Key Marfan Study Analytic Cohort (N=608) Characteristics

Characteristic	Atenolol (N = 303)	Losartan (N = 305)
Age — yr	11.5±6.5	11.0±6.2
Young adult — no. (%)†	76 (25)	75 (25)
Male sex — no. (%)	180 (59)	186 (61)
Race — no. (%)‡		
White	266 (88)	260 (85)
Black	21 (7)	25 (8)
Asian	6 (2)	10 (3)
Other	10 (3)	10 (3)
Hispanic — no./total no. (%)‡	36/302 (12)	46/305 (15)
Presence of causal *FBN1* mutation — no. (%)		
Yes	93 (31)	88 (29)
No	9 (3)	15 (5)
Unknown	201 (66)	202 (66)
Family history of Marfan's syndrome — no./total no. (%)	180/295 (61)	181/290 (62)
Echocardiography findings§		
Maximum aortic-root diameter — cm	3.4±0.7	3.4±0.7
Maximum aortic-root-diameter z score		
Median	4.0	4.0
Interquartile range	3.5-4.8	3.3-5.0
≥4.5 — no./total no. (%)	106/303 (35)	114/304 (38)
Medical history — no. (%)		
Cardiac surgery	6 (2)	6 (2)
Cardiovascular disorder¶	39 (13)	36 (12)
Prior use of beta-blocker	173 (57)	171 (56)
Endocrine disorder‖	7 (2)	0
Neurodevelopmental disorder**	56 (18)	61 (20)
Psychiatric disorder††	23 (8)	16 (5)

* Data are adapted from Lacro et al. Plus–minus values are means ±SD. The demographic and clinical characteristics did not differ significantly between the two treatment groups (P>0.20 for all comparisons), with the exception of a history of an endocrine disorder (P = 0.007).
† Young adults were defined as male participants who were 16 to 25 years of age and female participants who were 15 to 25 years of age.
‡ Race or ethnic group was reported by the participant or a family member at the time of enrollment.
§ Data are based on readings at a central echocardiographic laboratory. Echocardiographic data were missing for one participant in the losartan group because of an unreadable echocardiogram.
¶ Cardiovascular disorder was defined by exercise intolerance; syncope; arrhythmia, hypertension, or hypotension requiring therapy; chest pain; shortness of breath; or other cardiovascular conditions.
‖ Endocrine disorder was defined by either the use of hormone therapy to limit growth or delayed puberty.
** Neurodevelopmental disorder was defined as attention deficit–hyperactivity disorder requiring therapy, developmental delay requiring therapy, learning disability requiring services, or other neurodevelopmental conditions.
†† Psychiatric disorder was defined as depression requiring therapy, anxiety, or other psychiatric conditions.

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DATA AND DOCUMENTATION

The following datasets and descriptor files are available for download. A login and password (request access via http://www.pediatricheartnetwork.org) are required for download capability. The lock date used for creation of the public dataset was March 26, 2014. Privacy protection of these data is described in Appendix A.

1. Study data collection forms
2. SAS version 9.4 datasets
3. Excel datasets (with variable formats applied) – These data have a .csv extension, which means that the file may also be opened either in Excel, OR in a text editor, appearing as a comma-delimited file.
4. Codebooks for each dataset – These contain variable names, labels, and descriptive statistics for each variable on the data collection forms. Key created variables are included as well.
5. The files *formats.sas7bcat* and *marformats64.sas7bcat* – Include this file in your program using:
   ```
   options fmtsearch = (fmtlib.formats);
   ```
   where fmtlib is specified using a libname statement as the path name.
6. Code list D forms A110, A114, and A200

STUDY RESOURCES

Resources posted on the pediatricheartnetwork.org website include:

- Marfan Study bibliography (see **http://pediatricheartnetwork.com/ResourcesPublications/Publications.aspx#73556-marfan-trial**)
- Marfan Study protocol (with login access)

DATA USE POLICY

- REQUIRED ACKNOWLEDGEMENTS: All presentations and publications using these data must include the following statement: *"The NIH/NHLBI Pediatric Heart Network Marfan Study dataset was used in preparation of this work. Data were downloaded from http://pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets.aspx on mm/dd/yyyy"."*
- PAPER, ABSTRACT, and PRESENTATION TITLES: Titles may, at the authors' discretion, mention the PHN database but should not imply that the work is from the PHN. An example of an acceptable phrase would be, "an analysis of the Pediatric Heart Network public database." Whether or not the title makes mention of the PHN, acknowledgement should be made as described in bullet 1.

- All users are requested to send a copy of published abstracts and articles to the PHN Data Coordinating Center at New England Research Institutes (PHNpubs@neriscience.com) within one month of publication. This will allow the PHN and the NHLBI to document the continued impact of this study on the field.

- The login and password provided to each user are valid for 6 months. If a user decides to complete analyses leading to more than one presentation or publication in that time period, it is requested that they notify the PHN Data Coordinating Center at New England Research Institutes of their additional analysis topics, solely for the purposes of tracking.

- The login and password to access the public dataset is provided to a single user. If a colleague would like to access the public dataset for a different analysis topic, a separate request for login and password should be submitted via the www.pediatricheartnetwork.org website.

- As an approved user, you agree that you will not attempt to establish the identities of research participants through use of this dataset.

- As an approved user, you agree to not place these data in other public locations.

TIPS ON USING THESE DATA

1. Identification numbers for study subjects and study sites have been re-assigned for privacy protection.
    - *random_id*: Subject ID ranging from 144501 to 145871
    - *site_id*: Site ID ranging from 1 to 100 [only available for randomized subjects]; there were 21 sites

2. Prior to analysis, original variables must have any special values (typically negative numbers, see Appendix B) set to missing. Created variables (labelled as <created> in the codebooks) already contain a SAS missing value if the measurement is unavailable.

3. The study data are contained in multiple individual forms. These forms may be used jointly by merging on *random_id,* in combination with VISIT (0=Baseline; 1=Month 6; 2=Month 12; 3=Month 24; 4=Month 36; 5=Dose adjustment; OR on core lab echo forms: BSLN, MN06, MN12, MN24, and MN36).

4. The data contain 1370 screening records and 608 randomized subjects.

5. The amfs_randomized dataset contains randomization data, not associated with a study form.

6. The created_variables dataset contains key created variables from the study, including change in aortic root z-score and dimension, clinical outcomes, history of beta blocker use (1 subject was confirmed to have taken a BB of unknown dose/duration), study drug compliance, and major eligibility violations (which were excluded in secondary analysis).

7. The family_id dataset contains information on subjects who were close relatives of each other (parent/child/sibling). The 608 randomized subjects came from 549 families. 494 of these families had 1 randomized subject, 51 families had 2, and 4 families had 3.

8. The variable echopurp on forms 302, 303, and 304 distinguishes between the regular echo reads and the repeat QC echo reads. To exclude the repeat QC reads, delete observations with echopurp=2.

9. For the main results, echos were reclassified if they were close to or not close to 3 years of follow-up. The SAS code to use for this is:

```
*OMIT 3 YR ECHO THAT IS VERY LATE- DONE AT 4.80 YRS;
if random_id=144842 and compress(visit)="MN36" then delete;
*OMIT 3 YR ECHO THAT IS VERY LATE- DONE AT 4.01 YRS;
if random_id=144574 and compress(visit)="MN36" then delete;
*OMIT 3 YR ECHO THAT IS >3.75 YRS- DONE AT 3.85 YRS;
if random_id=145758 and compress(visit)="MN36" then delete;

*RECLASSIFY 3 WITHDRAWAL ECHOS TO BE USED AS NEXT STUDY VISIT VALUE;
if random_id=144678 and visit=”WD” then visit='MN36';  *2.7 yrs;
if random_id=145734 and visit=”WD” then visit='MN36';  *2.28 yrs;
if random_id=144515 and visit=”WD” then visit='MN36';  *2.53 yrs;
```

ADDITIONAL ASSISTANCE

If you have questions about the study dataset that this documentation and the above resources (protocol, articles) have not answered, please email the PHN Mailbox at PHNmailbox@neriscience.com.

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APPENDIX A

Implementation of Privacy Protection Rules for Public Use of the PHN Marfan Study Dataset

Variables that could lead to subject identification were eliminated in the public dataset. Steps included:

1. Removal of original study ID number (replaced with *random_id*, a random consecutive numbering ranging from 144501 to 145871), and removal of the name of the person completing the forms, and echo IDs. Of note, no subject names, addresses, or medical record numbers were ever contained in the original study dataset.

2. All dates in the original datasets were removed, and replaced with subject age on that date, in years with at most two decimal places.

3. Free (write-in) text variables were generally removed from the public datasets. When included as clinically relevant, they were first scanned for any identifying information (e.g., dates) and deleted accordingly.

4. Race categories with small sample size were recoded into an “other” category.

5. A small number of outlier heights and weights were set to missing.

APPENDIX B

Special Value Codes

-9 = missing

-8 = don't know/indeterminate

-7 = refused to answer

-6 = not recorded

-5 = measurement could not be reliably recorded or is not interpretable (study technically inadequate)

-4 = illegible

-2 = programmed skipped field based on results of or response to a previous question

-1 = not applicable/structure not present