Published in final edited form as:
Am Heart J. 2007 October ; 154(4): 624–631. doi:10.1016/j.ahj.2007.06.024.

Rationale and Design of a Randomized Clinical Trial of Beta Blocker Therapy (Atenolol) vs. Angiotensin II Receptor Blocker Therapy (Losartan) in Individuals with Marfan Syndrome

Ronald V. Lacro, MD[a], **Harry C. Dietz, MD**[b], **Lisa M. Wruck, PhD**[c], **Timothy J. Bradley, MD**[d], **Steven D. Colan, MD**[a,c], **Richard B. Devereux, MD**[e], **Gloria L. Klein, MS**[c], **Jennifer S. Li, MD**[f], **L. LuAnn Minich, MD**[g], **Stephen M. Paridon, MD**[h], **Gail D. Pearson, MD, ScD**[i], **Beth F. Printz, MD**[j], **Reed E. Pyeritz, MD, PhD**[k], **Elizabeth Radojewski**[d], **Mary J. Roman, MD**[e], **J. Philip Saul, MD**[l], **Mario P. Stylianou, PhD**[i], and **Lynn Mahony, MD**[m] **Pediatric Heart Network Investigators**

[a]Children's Hospital Boston and Harvard Medical School, Boston, MA

[b]Johns Hopkins University, Baltimore, MD

[c]New England Research Institutes, Watertown, MA

[d]The Hospital for Sick Children, Toronto, Canada

[e]Weill Medical College of Cornell University, New York, NY

[f]Duke University Medical Center, Durham, NC

[g]Primary Children's Medical Center, Salt Lake City, UT

[h]The Children's Hospital of Philadelphia, Philadelphia, PA

[i]National Heart, Lung, and Blood Institute, Bethesda, MD

[j]Columbia University Medical Center, New York, NY

[k]University of Pennsylvania, Philadelphia, PA

[l]Medical University of South Carolina, Charleston, SC

[m]University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Background—Cardiovascular pathology, including aortic root dilation, dissection, and rupture, is the leading cause of mortality in patients with Marfan syndrome (MFS). The maximal aortic root diameter at the sinuses of Valsalva is considered the best predictor of adverse cardiovascular outcome. Although advances in therapy have improved life expectancy, affected individuals continue to suffer cardiovascular morbidity and mortality. Recent studies in a *FBN1*-targeted mouse model of MFS with aortic pathology similar to that seen in humans showed that treatment with losartan normalized aortic root growth and aortic wall architecture.

Address for correspondence/reprints: Ronald V. Lacro, MD, Department of Cardiology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115, Phone: 617-355-8794, FAX: 617-739-3784, E-mail: ron.lacro@cardio.chboston.org.

Methods—The Pediatric Heart Network designed a randomized clinical trial to compare aortic root growth and other short-term cardiovascular outcomes in MFS subjects receiving atenolol or losartan. Individuals 6 months to 25 years of age with a body surface area-adjusted aortic root Z-score > 3.0 will be eligible for inclusion. The primary aim is to compare the effect of atenolol therapy to that of losartan therapy on the rate of aortic root growth over 3 years. Secondary endpoints include progression of aortic regurgitation; incidence of aortic dissection, aortic root surgery, and death; progression of mitral regurgitation; left ventricular size and function; echocardiographically-derived measures of central aortic stiffness; skeletal and somatic growth; and incidence of adverse drug reactions.

Conclusion—This randomized trial should make a substantial contribution to the management of individuals with MFS and expand our understanding of the mechanisms responsible for the aortic manifestations of this disorder.

Introduction

The Marfan syndrome (MFS)

MFS is a systemic disorder of connective tissue with autosomal dominant inheritance and a prevalence of approximately 1 per 5,000 population.[1] The cardinal features of this disorder involve the ocular, musculoskeletal, and cardiovascular systems. Cardiovascular pathology, including aortic root dilation, aortic dissection, and myxomatous mitral valve changes, is the leading cause of mortality in MFS. Although early diagnosis and refined medical and surgical management have increased median life expectancy from about 40 to approximately 70 years, individuals with MFS continue to suffer important morbidity.[2]

Up to 90% of individuals with classic MFS will have a cardiovascular “event” during their lifetime, including surgical repair of the aortic root, fatal or non-fatal aortic dissection, or mitral valve surgery.[3,4] In addition, individuals with MFS may have lens dislocation; skeletal involvement including anterior chest deformity, scoliosis, and joint hypermobility; lung disease most commonly manifested by spontaneous pneumothorax; decreased skeletal muscle mass and fat stores; and dural ectasia.[1]

Etiology of Marfan syndrome

MFS is caused by mutations in *FBN1*, the gene encoding fibrillin-1.[5] Over 600 *FBN1* mutations have been reported.[6] Since fibrillin-1 is an important component of the extracellular matrix microfibril,[7,8] this protein was initially thought to play mainly a structural role in connective tissue. Structural abnormalities leading to weakness in connective tissue seemed to explain some clinical findings such as lens dislocation, joint hypermobility, lung bullae, and aortic dissection, but not other features such as bone overgrowth, myxomatous valve changes, and craniofacial abnormalities. Therefore, a more plausible explanation for the changes seen in MFS invokes some combination of altered cellular migration, proliferation, and programmed cell death.

Transforming growth factor β (TGFβ) recently emerged as a potential mediator of these morphogenetic perturbations. The TGFβs are pluripotential cytokines that regulate cell performance and tissue morphogenesis and homeostasis. They are synthesized and secreted as an inactive precursor (the large latent complex) that binds to the extracellular matrix and requires regulated activation to release free TGFβ for biologic activity.[9,10] The latent TGFβ-binding protein component of the large latent complex has been localized to extracellular microfibrils and specifically binds to fibrillin-1.[11,12] The current hypothesis is that abnormal fibrillin causes failure of latent complex sequestration and consequent excessive TGFβ activation,[13] resulting in the MFS phenotype.

In the fibrillin-1 deficient mouse model,[13-16] excessive TGFβ signaling has been associated with progressive aortic root dilation, myxomatous mitral valve changes, and failure of lung alveolar septation. Moreover, the aortic, valve, and lung phenotypes can be attenuated or prevented in these mice by systemic administration of an antibody that specifically antagonizes the activity of TGFβ *in vivo*.[13,14,16] These data support the paradigm that perturbation of matrix sequestration of TGFβ can contribute to the pathogenesis of MFS.

Current Medical Approach to Aortic Root Dilation in MFS

The aortic root diameter at the sinuses of Valsalva is considered the best predictor of adverse cardiovascular outcome.4 The optimal medical therapy for aortic root dilation has been a matter of vigorous debate.17-22 Because several, though not all, studies have shown that therapy with beta-adrenergic blocking drugs (BB) reduces the rate of aortic growth,17-20 many clinicians consider BB to be the standard of care. The presumed mechanisms, decreasing proximal aortic shear stress and heart rate, are plausible based on the pathophysiology; however, treatment with BBs does not prevent attainment of important clinical endpoints including aortic regurgitation, surgery, dissection, and death. In cases where BB therapy is contraindicated or not tolerated, or by clinician preference, calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors are used to reduce the ejection impulse.22 There are no reported randomized trials of these drugs, but ACE inhibitors have the theoretical advantage of inhibiting vascular smooth muscle cell apoptosis based on observations in cultured Marfan aortic media cells.21,23

Pharmacologic trials in mouse models of Marfan syndrome

Numerous studies describe the ability of the angiotensin receptor blocker (ARB), losartan, to achieve clinically-relevant inhibition of TGFβ signaling *in vivo* (reviewed in Habashi16). In several disease states, including chronic renal disease and cardiomyopathy, anti-fibrotic effects of losartan, independent of hemodynamic effects, have been directly linked to TGFβ inhibition.

To test the hypothesis that angiotensin II type 1 (AT1) blockade decreases aortic damage, Dietz and colleagues[16] randomized cohorts of 2-month-old mice with a fibrillin-1 mutation found in a patient with classic MFS to receive placebo, propranolol, or losartan. Echocardiography was used to monitor the aortic root. After 6 months, the rate of aortic growth in losartan-treated animals was indistinguishable from that seen in wild-type controls ($p=0.55$). Aortic growth in propranolol-treated mice was significantly less than that in the placebo group ($p<0.001$), but greater than that in losartan-treated mice ($p<0.02$). Aortic wall architecture showed progressive deterioration in untreated and propranolol-treated mice, but the aortic wall architecture in losartan-treated mice could not be distinguished from that in wild-type littermates. Losartan also improved non-cardiovascular manifestations of MFS, including distal airspace pathology. Furthermore, improvements in the losartan-treated mice correlated with reduced TGFβ signaling. Since blood pressure and heart rate were decreased similarly in BB- and losartan-treated mice, the protection afforded by ARBs goes beyond alteration of hemodynamics to modification of the underlying pathology, presumably through antagonism of TGFβ.

Rationale for this trial

Despite the major advances in the medical and surgical management of MFS, morbidity persists. Existing medical therapies do not target the pathogenic basis for MFS; these therapies simply aim to reduce hemodynamic stress on predisposed tissue. ARB therapy has the theoretical advantage of modifying the abnormal tissue directly by antagonism of TGFβ. The compelling results of losartan therapy in mice prompted a desire to translate these results systematically to humans. Neither the safety nor efficacy of administration of

losartan in humans with MFS can be evaluated in the absence of a randomized clinical trial. This multi-center, randomized clinical trial will compare outcomes in individuals with MFS randomized to either atenolol or losartan.

Study Design and Methods

Study overview

This trial is designed to test the hypothesis that ARB therapy with known TGFβ antagonism will reduce the rates of aortic root diameter growth and progression of aortic regurgitation compared to BB therapy. We will enroll 604 children and young adults who will be randomly assigned to receive BB (atenolol) or ARB (losartan) for 36 months. This study was designed by the NHLBI-funded Pediatric Heart Network (PHN)[24] and will be conducted at 14 Clinical Centers. A flow chart of the study design is shown in the Figure.

Patient selection

Inclusion criteria

1. Diagnosis of MFS according to Ghent criteria[25]
2. Age 6 months to 25 years
3. Body surface area (BSA)-adjusted aortic root Z-score > 3.0 (sinuses of Valsalva) AND
4. Informed consent and assent of participant, parent(s), or legal guardian as applicable

Exclusion criteria

1. Prior aortic surgery
2. Aortic root dimension at the sinuses of Valsalva > 5 cm
3. Planned aortic surgery within 6 months of enrollment
4. Aortic dissection
5. Clinical or molecular diagnosis of other connective tissue disorders that have overlap with MFS (Shprintzen-Goldberg syndrome26 or Loeys-Dietz syndrome14)
6. Therapeutic (e.g., for systemic hypertension, arrhythmia, ventricular dysfunction, or valve regurgitation) rather than prophylactic use of ACE inhibitor, BB, or calcium channel blocker
7. History of angioedema while taking an ACE inhibitor or BB
8. Intolerance to ARB that resulted in termination of therapy
9. Intolerance to BB that resulted in termination of therapy
10. Renal dysfunction (creatinine >upper limit of age-related normal values)
11. Asthma
12. Diabetes mellitus
13. Pregnancy or planned pregnancy within 36 months of enrollment OR
14. Inability to complete study procedures including history of poor acoustic windows (inability to obtain accurate measurement of aortic root)

The decision to restrict the study subjects to a younger population derives from the likelihood that older individuals with MFS who have not yet required surgery are biased toward milder variants of the disorder and are less likely to demonstrate a treatment effect within the 3-year time-frame of this study. A similar rationale led to the requirement for a BSA-adjusted aortic root Z-score > 3.0 at the time of enrollment.

Randomization and stratification

Eligible subjects will be randomly assigned in a 1:1 ratio to receive atenolol or losartan using randomly permuted blocks within strata defined by attainment of maximum height (defined here as 16 years of age for males and 15 years for females27) and BSA-adjusted aortic root Z-score at baseline (<4.5 SD / ≥4.5 SD). Dynamic allocation within center will be used to ensure equal numbers of subjects in each treatment arm at each center.

Study treatments

All subjects on prophylactic therapy with BB, ARB, ACE inhibitor, or calcium channel blocker before enrollment will be weaned off medication over a 14-day period. Following this, a drug washout period of 14–21 days will occur before baseline assessment and randomization.

After the baseline clinical evaluation, subjects will enter the uptitration period, during which they will receive atenolol or losartan. Study drugs will be administered in either liquid or pill form depending on the subject's ability to swallow pills. The goal of the uptitration period is to reach the effective dose (defined below) that will be continued throughout the maintenance phase. Each uptitration cycle will last 21 – 28 days.

The average starting dose of atenolol will be 0.5 mg/kg and the dose will be increased in each subsequent cycle by ~1 mg/kg to a maximum daily dose of 4 mg/kg, not to exceed 250 mg. The mean heart rate measured using a 24-hour ambulatory electrocardiogram (24-hour ECG) will guide uptitration. The goal of treatment with atenolol will be a ≥ 20% decrease in the mean heart rate, which reflects adequate beta blockade.[28,29]

The average starting dose of losartan will be 0.4 mg/kg and the daily dose will be increased as tolerated by ~0.4 mg/kg in each subsequent cycle to a maximum daily dose of between 1.0 and 1.4 mg/kg, not to exceed 100 mg.

Masking of treatment group assignment

The primary endpoint and many of the secondary endpoints will be measured in the Echocardiography Core Laboratory by personnel masked to treatment group assignment. However, given the difference in heart rate response between the two therapies and the differences in uptitration (to heart rate response for atenolol but not for losartan), study personnel supervising uptitration will be aware of the subject's treatment assignment. No one else including subjects, their families, and primary care providers will be informed of the subject's treatment assignment.

Study measurements and subject follow-up

The following data will be obtained at baseline and at 6, 12, 24, and 36 months after randomization:

- Review of medical history
- Height, weight, upper-to-lower segment ratio, and blood pressure
- Echocardiographic images

- 24-hour ECG
- Questionnaire regarding adverse drug reactions.

After the maintenance dose is established, subjects will be contacted quarterly to assess for adverse effects. Date of aortic dissection, aortic surgery, and death will be recorded, if applicable.

Trial outcomes

The *primary outcome* is the rate of change in the BSA-adjusted aortic root (sinuses of Valsalva) Z-score. Aortic root size and growth rate are considered the best predictors of the risk of aortic dissection and remain the most commonly used measures to determine the timing of surgery in both adults and children.[4,30-32] Echocardiograms will be performed by echocardiographers trained for this protocol, and interpreted centrally to minimize bias and inter-observer error. Secondary outcomes are listed in the Table.

Statistical Considerations

Longitudinal data from two participating centers were used to estimate rate of change and covariance structure of the primary outcome. Data for potentially eligible patients were also collected from participating clinical centers to characterize the expected study population. Estimates from these analyses were used to calculate target sample size.

The potential decrease in Z-score change rate is greater in those who have not attained maximum height (“children,” defined here as less than 16 years of age27) than in those who have (“adults”); therefore, the minimum clinically significant difference (MCSD) between the treatment groups was assessed separately for adults and children.

The MCSD for children was chosen with the goal of reaching adulthood (16 years) with minimal aortic root dilation, defined as BSA-adjusted aortic root Z-score of 2 standard deviations (SD). For adults, the MCSD was defined as an effect that would delay surgery by 10 years, assuming that surgery is performed when aortic root dimension exceeds 5 cm. Preliminary results and other data[2] led to estimated MCSD's of 0.25 and 0.08 SD/year for children and adults, respectively. In the preliminary analysis dataset, 67% of the subjects were children, so the overall MCSD was calculated as the weighted average, 0.194 SD/year.

After 20% inflation to account for subject dropout, three interim analyses, and potential crossover, a total of 604 subjects will be required to detect the MCSD with 85% power at significance level 0.05. Because the power to detect the overall MCSD is much greater in children than in adults, the power of the primary analysis will be compromised if a large proportion of adults are enrolled in the trial. Therefore, adult enrollment will be capped at 33%.

Primary analyses will be performed on an intention-to-treat basis. The primary outcome of rate of change in BSA-adjusted aortic root Z-score will be modeled using the parametric curves longitudinal model[33] with treatment efficacy assessed by a likelihood ratio test of whether the treatment group by time interaction effect is zero. If significant dropout occurs, the reasons for dropout will be evaluated. If the data appear to be missing at random, all available data will be included in analysis and multiple imputation methods will be used to impute values for missing data.

Secondary analyses will compare treatment groups: 1) with covariate-adjusted analysis; 2) according to treatment actually received; and 3) after exclusion of any randomized subjects found subsequently to have been trial ineligible at the time of enrollment.

Four interaction analyses are planned to estimate the effect of the following characteristics on treatment effect:

- Attainment of maximum height at baseline: subjects with no change in height after the baseline visit vs. subjects with increased height after the baseline visit
- Age at baseline as a continuous variable
- Baseline BSA-adjusted aortic root Z-score (<4.5 vs. ≥ 4.5)
- Prior use of BB (yes vs. no)

To monitor the trial for large treatment differences, three formal interim analyses are planned, timed to occur when one-third, one-half, and three-quarters of post-baseline measurements are expected to be available. An O'Brien-Fleming stopping boundary, with a Lan-DeMets adjustment, will be used for this purpose.[34,35] A Data and Safety Monitoring Board (DSMB) and an independent medical monitor have been established by NHLBI to monitor this trial for safety.

Trial organization and Timeline

The PHN Marfan Study Subcommittee and PHN Steering Committee, together with the NHLBI, will be responsible for all aspects of this study. The protocol has been approved by an independent Protocol Review Committee and DSMB, and by the Institutional Review Board at each Clinical Center and at the Data Coordinating Center. This study will be conducted under an Investigational New Drug Application with the Federal Drug Administration. The trial is registered at ClinicalTrials.gov (NCT00429364). Infants, children, and young adults will be recruited for this trial from among patients at the Clinical Centers over a period of approximately 36 months, with data accrual to continue for an additional 3 years. Enrollment began in February 2007; as of June 15, 2007, 66 subjects had been enrolled. All centers will follow the same study procedures.

Discussion

Choice of primary outcome

The major clinical cardiovascular endpoints for individuals with MFS are aortic root surgery, aortic dissection, and death. It is fortunate that aortic dissection and death are rare in children and young adults with MFS, but this also means that a trial designed to assess differences in these events would require an impractical number of patients and years. The decision to intervene surgically is a function of aortic root size or growth rate, and is relatively standardized. Therefore, a primary endpoint related to change in aortic root size was considered to be clinically relevant as well as feasible. In addition, aortic root size and growth rate were favorably affected by losartan treatment in the mouse model.

Importance of knowledge to be gained

The results of this trial will make an important contribution to the management of individuals with MFS by determining whether the rates of aortic growth and progression of aortic regurgitation are lower in those subjects receiving ARB therapy when compared to those receiving BB therapy, and by determining the effect of these two drugs on the secondary endpoints. Without this trial we will not be able to assess the efficacy or the safety of losartan administration in humans with MFS across a broad range of genotypes and severities.

Limitations

Although the study will be a prospective, randomized trial, it will not be possible to mask all of the subjects or their care providers to the study drug assignment. Valid treatment comparisons can be made without masking, as long as care is taken to avoid treatment-related biases in outcome assessment. This will be achieved because the physicians at the Echocardiography Core Laboratory evaluating the primary endpoint and many secondary endpoints will be masked to treatment assignment. In addition, every effort will be made to prevent the study subjects and their families from learning their treatment assignment.

The lack of a placebo arm is another potential limitation. During protocol development, several designs and drugs were considered, including designs with a placebo arm. After extensive discussion, and because BB therapy is considered by many to be the standard of care for patients with MFS, a majority of the trial subcommittee members concluded that a placebo arm would not be acceptable to many patients, families, study investigators, and primary cardiologists. Without a placebo arm, our study will not be able to evaluate the efficacy of each of the therapies independently, only the efficacy of one therapy relative to the other.

The study may not detect an effect that is smaller than that for which the study is powered and may be underpowered for subgroup analyses and some secondary endpoints. In particular, the study will be underpowered to determine whether atenolol or losartan is superior in preventing or delaying aortic dissection, surgery, and death because these events are expected to be rare in our study population. Thus, the primary endpoint is a surrogate rather than a true clinical endpoint, but is a predictor of more serious MFS outcomes. Finally, the study results may not be generalizable to individuals with MFS who have BSA-adjusted aortic root Z-scores ≤ 3.0 or to those individuals with variants of MFS who do not meet the Ghent diagnostic criteria for MFS.

Conclusions

The appeal of a trial of losartan therapy in patients with MFS reflects its rational derivation from disease pathogenesis, its novel mechanism of action, and its performance in validated mouse models of MFS. One of the primary goals of the Pediatric Heart Network is to promote evidence-based clinical care. Given the widespread publicity and excitement regarding the performance of losartan in animal models and the lack of practical barriers for its widespread clinical application, we sought to take advantage of a unique but time-limited opportunity to assess the utility of this therapy with a randomized study design while clinical equipoise is still maintained. This trial should make a substantial contribution to the management of individuals with MFS and will expand our understanding of the mechanisms responsible for the aortic manifestations of this disorder.

Acknowledgments

We are grateful to Josephine Grima Ph.D. and other staff at the National Marfan Foundation for their support during development of this trial.

This work was supported by U01 HL068285 (Lacro); U01 HL068270 (Wruck, Mahony, Colan, Klein), U01 HL068269 (Li), U01 HL068292 (Minich), U01 HL068290 (Printz, Devereux, Roman), U01 HL068288 (Bradley), U01 HL068281 (Saul), and U01 HL068279 (Paridon, Pyeritz) from the National Heart, Lung, and Blood Institute, NIH/DHHS; the Howard Hughes Medical Institute (Dietz); the National Marfan Foundation (Dietz); and the Smilow Center for Marfan Syndrome Research (Dietz).

Appendix

National Heart, Lung, and Blood Institute

Gail Pearson, Rae-Ellen Kavey, Mario Stylianou, Judith Massicot-Fisher, Marsha Mathis, Victoria Pemberton

Network Chair

Lynn Mahony, University of Texas Southwestern Medical Center

Data Coordinating Center

New England Research Institutes, Lynn Sleeper (PI), Steven D. Colan, Lisa Wruck, Gloria Klein, David F. Teitel

Clinical Site Investigators

Children's Hospital Boston, Jane Newburger (PI), Ronald V. Lacro (study co-chair), Martha King; *Johns Hopkins University School of Medicine*, Harry C. Dietz (study co-chair), Jennifer Leadroot, Gretchen Oswald; *Children's Hospital of New York*, Daphne Hsu (PI), Beth Printz, Mary Roman, Richard Devereux, Rosalind Korsin; *Children's Hospital of Philadelphia*, Victoria Vetter (PI), Steven Paridon, Reed E. Pyeritz, Kathy Lee; *Cincinnati Children's Medical Center*, D. Woodrow Benson (PI), Larry W. Markham, Lois Bogenschutz, Teresa Barnard; *Duke University*, Page A. W. Anderson (PI), Jennifer S. Li, Stephanie Wechsler, Charlie Sang, Jr, Wesley Covitz, Ming Xu, Lori Jo Sutton, Kari Crawford; *Medical University of South Carolina*, J. Philip Saul (PI), Geoff Forbus, Teresa Atz; *Primary Children's Medical Center, Salt Lake City, Utah*, LuAnn Minich (PI), Anji Yetman, Susan Sorenson, Marian Sharrow; *Hospital for Sick Children, Toronto*, Brian McCrindle (PI), Timothy Bradley, Elizabeth Radojewski; *Baylor College of Medicine*, Jeffrey Towbin, Andres Menesses-Diaz; *Ghent University*, Bart Loeys, Julie De Backer, Virginie Szymczak; *Mount Sinai School of Medicine*, Bruce Gelb, Kerrie Lee; *Stanford University School of Medicine*, David Liang, Sunny Pellone; *Washington University School of Medicine*, Angela Sharkey, Alan Braverman, Melissa Callahan

Echocardiography Core Laboratory

Children's Hospital Boston: Steven D. Colan (Director), Seda Selamet Tierney

Protocol Review Committee

Michael Artman, Chair; Judith Massicot-Fisher, Executive Secretary; Erle Austin, H. Scott Baldwin, Timothy Feltes, Julie Johnson, Thomas Klitzner, Jeffrey Krischer, G. Paul Matherne, Kenneth G. Zahka

Data and Safety Monitoring Board

John Kugler, Chair; Rae-Ellen Kavey, Executive Secretary; David J. Driscoll, Mark Galantowicz, Sally A. Hunsberger, Thomas J. Knight, Holly Taylor, Catherine L. Webb

References

1. Judge DP, Dietz HC. Marfan's syndrome. Lancet 2005;366:1965–76. [PubMed: 16325700]

2. Silverman DI, Burton KJ, Gray J, Bosner MS, Kouchoukos NT, Roman MJ, et al. Life expectancy in the Marfan syndrome. Am J Cardiol 1995;75:157–60. [PubMed: 7810492]
3. Pyeritz RE. Marfan syndrome: current and future clinical and genetic management of cardiovascular manifestations. Semin Thorac Cardiovasc Surg 1993;5:11–16. [PubMed: 8424997]
4. Gott VL, Greene PS, Alejo DE, Cameron DE, Naftel DC, Miller DC, et al. Replacement of the aortic root in patients with Marfan's syndrome. N Engl J Med 1999;340:1307–13. [PubMed: 10219065]
5. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature 1991;352:337–39. [PubMed: 1852208]
6. Collod-Beroud G, Beroud C, Ades L, Black C, Boxer M, Brock DJ, et al. Marfan Database (third edition): new mutations and new routines for the software. Nucleic Acids Res 1998;26:229–3. [PubMed: 9399842]
7. Visconti RP, Barth JL, Keeley FW, Little CD. Codistribution analysis of elastin and related fibrillar proteins in early vertebrate development. Matrix Biol 2003;22:109–21. [PubMed: 12782138]
8. Sakai LY, Keene DR, Glanville RW, Bachinger HP. Purification and partial characterization of fibrillin, a cysteine-rich structural component of connective tissue microfibrils. J Biol Chem 1991;266:14763–70. [PubMed: 1860873]
9. Munger JS, Harpel JG, Gleizes PE, Mazzieri R, Nunes I, Rifkin DB. Latent transforming growth factor-beta: structural features and mechanisms of activation. Kidney Int 1997;51:1376–82. [PubMed: 9150447]
10. Bonewald LF. Regulation and regulatory activities of transforming growth factor beta. Crit Rev Eukaryot Gene Expr 1999;9:33–44. [PubMed: 10200910]
11. Isogai Z, Ono RN, Ushiro S, Keene DR, Chen Y, Mazzieri R, et al. Latent transforming growth factor beta-binding protein 1 interacts with fibrillin and is a microfibril-associated protein. J Biol Chem 2003;278:2750–57. [PubMed: 12429738]
12. Dallas SL, Keene DR, Bruder SP, Saharinen J, Sakai LY, Mundy GR, et al. Role of the latent transforming growth factor beta binding protein 1 in fibrillin-containing microfibrils in bone cells in vitro and in vivo. J Bone Miner Res 2000;15:68–81. [PubMed: 10646116]
13. Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, et al. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. Nat Genet 2003;33:407–11. [PubMed: 12598898]
14. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275–81. [PubMed: 15731757]
15. Ng CM, Cheng A, Myers LA, Martinez-Murillo F, Jie C, Bedja D, et al. TGF-beta-dependent pathogenesis of mitral valve prolapse in a mouse model of Marfan syndrome. J Clin Invest 2004;114:1586–92. [PubMed: 15546004]
16. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 2006;312:117–21. [PubMed: 16601194]
17. 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. [PubMed: 8152445]
18. Rossi-Foulkes R, Roman MJ, Rosen SE, Kramer-Fox R, Ehlers KH, O'Loughlin JE, et al. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. Am J Cardiol 1999;83:1364–68. [PubMed: 10235096]
19. Salim MA, Alpert BS, Ward JC, Pyeritz RE. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. Am J Cardiol 1994;74:629–33. [PubMed: 7915491]
20. Selamet Tierney ES, Feingold B, Printz BF, Park SC, Graham D, Kleinman CS, et al. Beta-blocker therapy does not alter the rate of aortic root dilation in pediatric patients with Marfan syndrome. J Pediatr 2007;150:77–82. [PubMed: 17188619]

21. Yetman AT, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. Am J Cardiol 2005;95:1125–27. [PubMed: 15842990]
22. Dean JC. Management of Marfan syndrome. Heart 2002;88:97–103. [PubMed: 12067963]
23. Nagashima H, Sakomura Y, Aoka Y, Uto K, Kameyama K, Ogawa M, et al. Angiotensin II type 2 receptor mediates vascular smooth muscle cell apoptosis in cystic medial degeneration associated with Marfan's syndrome. Circulation 2001;104:I282–I287. [PubMed: 11568070]
24. Mahony L, Sleeper LA, Anderson PA, Gersony WM, McCrindle BW, Minich LL, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27:191–98. [PubMed: 16261271]
25. de Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62:417–26. [PubMed: 8723076]
26. Greally, MT. GeneReviews at GeneTests: Medical Genetics Information Resource (database online). University of Washington; Seattle: 1997-2006. Shprintzen-Goldberg syndrome. 1-13-20063-29-2006
27. Erkula G, Jones KB, Sponseller PD, Dietz HC, Pyeritz RE. Growth and maturation in Marfan syndrome. Am J Med Genet 2002;109:100–15. [PubMed: 11977157]
28. Amery A, De Plaen JF, Lijnen P, McAinsh J, Reybrouck T. Relationship between blood level of atenolol and pharmacologic effect. Clin Pharmacol Ther 1977;21:691–99. [PubMed: 324694]
29. Tuininga YS, Crijns HJ, Brouwer J, van den Berg MP, Man i V, Mulder G, et al. Evaluation of importance of central effects of atenolol and metoprolol measured by heart rate variability during mental performance tasks, physical exercise, and daily life in stable postinfarct patients. Circulation 1995;92:3415–23. [PubMed: 8521562]
30. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg 2002;73:17–27. [PubMed: 11834007]
31. Nollen GJ, Groenink M, Tijssen JG, Van Der Wall EE, Mulder BJ. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. Eur Heart J 2004;25:1146–52. [PubMed: 15231373]
32. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, et al. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg 2006;81:169–77. [PubMed: 16368358]
33. Fitzmaurice, GM.; Laird, NM.; Ware, JH. Applied Longitudinal Analysis. Hoboken NJ: John Wiley & Sons, Inc.; 2004.
34. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549–56. [PubMed: 497341]
35. Lan KKG, Demets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659–63.

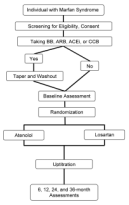

Figure.

Flow diagram for the trial. BB: beta blocker; ARB: angiotensin II receptor blocker; ACEi: angiotensin converting enzyme inhibitor; CCB: calcium channel blocker

Table

Outcome Variables

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
- 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
- Rate of change of mitral regurgitation, measured as change in vena contracta area indexed for BSA
- Rate of change in Z-scores for left ventricular mass, volume, mass to volume ratio, and ejection fraction by two-dimensional echocardiography
- Rate of change in Z-scores for left ventricular end-diastolic and end-systolic dimensions, diastolic septal and posterior wall thickness, left ventricular mass and shortening fraction by M-mode
- Rate of change of aortic root and ascending aortic elastic modulus and stiffness index
- Rate of change in Z-scores for weight, height, BMI 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
- Incidence of adverse drug reactions reported during routine surveillance

BSA: body surface area; BMI: body mass index