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Lessons Learned from a Pediatric Clinical Trial: The Pediatric Heart Network Angiotensin Converting Enzyme Inhibition in Mitral Regurgitation Study

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Abstract

Background—Mitral regurgitation is the most common indication for re-operation in children following repair of atrioventricular septal defect (AVSD). We hypothesized that angiotensin converting enzyme (ACE) inhibitor therapy would decrease the severity of mitral regurgitation and limit left ventricular volume overload in children following AVSD repair.

Methods—The Pediatric Heart Network designed a placebo-controlled randomized trial of enalapril in this population. The primary aim was to test the effect of enalapril on the change in left ventricular end-diastolic dimension body surface area-adjusted Z-score. Prior to the launch of the trial, a feasibility study was performed to estimate the number of patients with at least moderate mitral regurgitation following AVSD repair.

Trial Experience—Seventeen months after the start of the study, 349 patients were screened, 8 were trial eligible and only 5 were enrolled. The study was subsequently terminated due to low patient accrual. Several factors led to the problems with patient accrual including: 1) the use of

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criteria to assess disease severity in the feasibility study that were not identical to those used in the trial; 2) failure to achieve equipoise for the study among clinicians and referring physicians; 3) reliance on methodology developed in adult populations with different disease mechanisms; 4) absence of adequate data to define the natural history of the disease process under study. Progress in the treatment of children with cardiovascular disease will depend on the future of multi-center collaborative clinical trials. The lessons learned from this study may contribute to improvements in this research.

Randomized clinical trials have resulted in remarkable advances in cardiovascular care. During the 1990s, results from more cardiovascular clinical trials were published than in the previous three decades combined, ushering in the current era of “evidence-based cardiovascular medicine.” (1) Cardiovascular controlled trials have established novel treatments resulting in major improvements in patient outcomes and have also enhanced our understanding of heart disease and the impact of risk factors and adverse events. Certain populations, however, have been underrepresented in cardiovascular clinical trials, including women, the elderly, minority populations, and children (1–3).

Many barriers impede the design and conduct of randomized clinical trials in children, including the relative rarity of specific diseases, disease heterogeneity, incompletely defined natural history, lack of research infrastructure, ethical issues in pediatric research, and difficulty in identifying valid clinical endpoints. Systematic controlled studies of medications in children with congenital heart disease have thus been limited and most medications are not labeled for pediatric use (4). Therefore, treatment decisions in this population are often based on clinical experience, small observational studies, and extrapolation from adult data, rather than clinical trial evidence. In an attempt to narrow the scientific gap in the pediatric cardiovascular population, the National Heart, Lung, and Blood Institute (NHLBI) established the Pediatric Heart Network (PHN) in 2001(5).

In 2004, the PHN launched a placebo-controlled randomized trial of the angiotensin converting enzyme (ACE) inhibitor enalapril for use in infants and children with mitral regurgitation following atrioventricular septal defect (AVSD) repair. Our failure to complete this trial has led us to reflect on crucial issues that arose in its design and execution. These issues should be of interest to investigators, clinical practitioners, research networks, participating institutions, sponsors, data and safety monitoring boards (DSMBs), and families of the children whom we serve. Our purpose is to encourage discussion so that standards can be developed to better inform future trials in pediatric medicine.

The Pediatric Heart Network Angiotensin Converting Enzyme Inhibition-Mitral Regurgitation Experience

1. Rationale

Mitral regurgitation remains the most common indication for re-operation (about 10% of patients) in children following repair of AVSD. Postoperatively, moderate mitral regurgitation occurs in 15–30% and severe regurgitation occurs in 5–19% of patients (6–10). Residual mitral regurgitation causes volume overload and places a hemodynamic burden on the left ventricle that induces a series of compensatory adjustments, including up-regulation of the renin-angiotensin-aldosterone system (11,12). Although these adjustments may initially restore cardiac output, the disease process is often progressive and compensatory mechanisms fail. Reports are conflicting from trials of ACE inhibitor therapy for the treatment of mitral regurgitation in both the adult and pediatric populations, and use of ACE inhibitors is not recommended for treatment of mitral regurgitation in the current consensus paper from the American College of Cardiology and the American Heart Association (13–17). Despite this, we have observed an escalating trend toward adoption of this therapy in

children, based primarily on data indicating a favorable response to acute ACE inhibitor therapy in children (14,15). We hypothesized that ACE inhibition therapy would decrease the severity of mitral regurgitation, and thus limit left ventricular volume overload in children following AVSD repair.

We designed the ACE Inhibition in Mitral Regurgitation (ACEi in MR) trial to evaluate the efficacy and safety of the ACE inhibitor enalapril for the treatment of significant mitral regurgitation in children (ClinicalTrials.gov ID: NCT00113698; Figure 1). Children who had residual mitral (left atrioventricular valve) regurgitation after repair of an AVSD were selected as the study population for two reasons: 1) the regurgitant orifice in AVSD responds dynamically to left ventricular size, and, therefore, might respond to medical therapy; and 2) this is a reasonably homogeneous group with a relatively high incidence of at least moderate mitral regurgitation post-operatively.

2. Study Design

Prior to the trial, we performed a feasibility study. Each network center undertook a chart review of the assessment of mitral regurgitation in patients following AVSD repair according to local echocardiography reports from 2003–2004. The degree of mitral regurgitation was collected at each center from the reports determined by subjective assessment of the color Doppler width or area (e.g. none, trivial, mild, moderate, or severe). The image data were not re-reviewed and data on left ventricular size were not collected for the purposes of the feasibility study. A total of 1,005 reports covering a 5-year period from 07/01/1997-06/30/2002 were reviewed, and 195 patients were identified as having at least moderate mitral regurgitation based on subjective assessment following AVSD repair. Based on these reports, we estimated the incidence of at least moderate mitral regurgitation to be 20% in post-operative AVSD patients followed at PHN centers.

The primary aim of the trial (Drug Phase) was to test the effect of enalapril therapy on the six-month change in left ventricular end-diastolic dimension (LVEDD) body surface area (BSA)-adjusted Z-score. Secondary aims included assessment of the effects of enalapril on changes in echocardiographic measures of left ventricular geometry and hemodynamics (ejection fraction, regurgitant fraction, fiber stress, sphericity index, and BSA-adjusted Z-scores for mass and end-diastolic and end-systolic dimensions and volumes), the change in level of neurohormonal activation evaluated by measurement of B-type natriuretic peptide, and the incidence of adverse effects.

Two groups of patients who had undergone repair of an AVSD were targeted for the study. Inclusion and exclusion criteria are shown in Table 1. Group 1 patients were to be evaluated at the time of AVSD repair. Eligible patients ≥ 5 years of age were to be enrolled and observed for six months in an Observational Phase to allow the heart to adapt to the surgical intervention, and thus to allow the effects of ACE inhibition to be assessed independently of the acute results of the surgery. Group 2 patients were those who had had their surgery performed either prior to the study launch or at non-PHN institutions but referred to a PHN center, so that they could not be enrolled into the Observational Phase. At ≥ 6 months after surgery, subjects in both groups with at least moderate mitral regurgitation were to be randomized to receive enalapril or placebo for six months.

We defined moderate mitral regurgitation on the study echocardiogram used to assess trial eligibility as: 1) either a proximal regurgitant jet area $\geq 6 \text{ mm}^2/\text{m}^2$ or a regurgitant fraction $\geq 30\%$ (extrapolating from data on adults with mitral regurgitation), and 2) left ventricular volume overload as shown by the presence of a LVEDD BSA-adjusted Z score of ≥ 2.0 (18). An echocardiography core laboratory centrally assessed all study echocardiograms.

We assumed a standard deviation of 0.75 for the change in LVEDD BSA-adjusted Z-score in conjunction with a two-sided 0.05 Type I error rate, 85% power, a minimum clinically significant group difference in mean Z-score change of 0.5, and one interim look at the data. These assumptions resulted in a total required sample size of 82 subjects. A loss to follow-up rate of 10% was assumed to occur over the six months. Thus, the total required sample size was 92 subjects (46 per group) for the Drug Phase.

All participating centers received Institutional Review Board approval. A DSMB appointed by the NHLBI monitored the conduct of the study. Written informed consent was obtained from the parent or guardian of each patient participating in either phase of the study. Assent from the subject was obtained when age appropriate.

3. Enrollment

The Observational Phase of the ACEi in MR trial began June 1, 2004 and the start date for randomization in the Drug Phase was six months later, on December 1, 2004. Recruitment in the Drug Phase was estimated to require two years. Two groups of patients were screened for eligibility—those who completed the Observational Phase (Group 1) and those who were already ≥ 6 months postoperative from their repair (Group 2). By April 2005, 257 patients from both groups were screened, but only one patient had been randomized in the Drug Phase. With the goal of increasing study enrollment, the protocol was amended to broaden the Drug Phase eligibility criteria by 1) extending the upper age limit for eligibility from 5 to 18 years, and 2) lowering the LVEDD BSA Z score eligibility criterion from 2.0 to 1.5 to be more inclusive of borderline left ventricular dilation. In addition, community outreach and advertising to referring cardiologists and advocacy groups were implemented. An additional 92 patients were subsequently screened for a total of 349 patients screened by November 2005 (Figure 2).

In total, only eight patients were ultimately trial eligible and five were enrolled, all from Group 2 (i.e., subjects who were ≥ 6 months postoperative). The PHN ACEi in MR Subcommittee and the PHN Steering Committee reviewed these patient accrual numbers and recommended that the Drug Phase of this study be halted because the recruitment rate was much lower than expected. The DSMB of the PHN met on November 4, 2005 and concurred with the recommendation which was accepted by NHLBI.

4. Cost

PHN clinical sites receive an infrastructure budget that supports personnel and administrative costs for all studies. For each study, the sites also receive reimbursement for expenses related to screening, enrollment, and follow-up of subjects. For this study, the sites received \$150 per patient for screening, \$2,150 per patient for the Observational Phase, and \$10,120 per patient for the Drug Phase. Based on 196 patients screened (but not enrolled in the Observational Phase), 153 patients in the Observational Phase, and five patients in the Drug Phase (as of November 4, 2005), a total of \$408,950 was paid to the PHN centers for patient-related costs for the entire study, but only \$50,600 was spent on patients enrolled in the trial. This represents just 2% of the total patient care budget for the PHN for the study period. The personnel, administrative, and data-related costs for the clinical sites, the Data Coordinating Center, and core laboratory are difficult to estimate because they are spread across multiple studies, but it is unlikely that these represented more than another \$100,000 for the Drug Phase. The total expenditure was able to be limited because of careful tracking and early recognition of inadequate enrollment despite multiple adjustments to the protocol and the agreement of the research team to terminate the drug arm of the study.

Factors Leading to Under Accrual

In this NHLBI-funded randomized trial of ACE inhibition to treat mitral regurgitation, we enrolled only 5% of the intended study sample and spent substantial effort before enrollment was suspended. It was disheartening that, despite screening 349 subjects, only eight were eligible, and only five of the planned 92 participants were randomized. This experience, however, is not atypical: more than 80 percent of all clinical trials fall short of their accrual goals (19,20). As a result, trials are stopped, timelines are extended, or the studies accrue inadequate sample sizes, resulting in confidence intervals that are so wide or power so low that they are uninterpretable. As randomized trials involving patients with congenital heart disease are more commonly undertaken, it is worthwhile to analyze why this trial failed.

We believe that several factors likely led to this outcome.

1. The available sample size was estimated from a retrospective chart review at participating centers using criteria that differed from trial entry criteria

Our feasibility study involved chart review of the *subjective* assessment of mitral regurgitation according to echocardiogram reports from the year prior to the design phase; the incidence of at least moderate mitral regurgitation was estimated to be 20%. In contrast, our trial entry criteria required quantitative measurements to operationalize the definition of moderate to severe mitral regurgitation instead of the qualitative grading assessment used in the chart review. Some echocardiographic measurements specified in the entry criteria, e.g. regurgitant fraction and proximal regurgitant jet area, were not routinely available in the retrospective feasibility study. Other echocardiographic measurements used in the trial entry criteria, such as the degree of left ventricular dilation secondary to mitral regurgitation detectable within six months of surgery, were not collected in the feasibility study. If we had conducted the feasibility study using the defined trial eligibility criteria, we might have been alerted to the inadequate sample size available for this trial.

2. Clinical equipoise could not be established at the centers

The ethics of clinical research require equipoise--a state of uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial (21). We, as PHN investigators, had clinical equipoise with each arm in the drug trial based on conflicting data reported from trials of ACE inhibitor therapy for the treatment of mitral regurgitation in both the adult and pediatric populations (12–16). Equipoise, however, could not be uniformly established among our colleagues at the participating centers. A total of 47 patients screened for the trial with at least mild to moderate mitral regurgitation noted in the chart were already on ACE inhibitors or had ACE inhibitor use planned by their primary cardiologists. These physicians may have felt compelled to use medical therapy because they believed that such therapy might delay the need for repeat mitral valve surgery despite the lack of evidence showing benefit of ACE inhibitors in this setting. Others may have used ACE inhibitors because they were not fully informed of the study and used the medicine routinely in their patients after AVSD surgery.

This culture of off-label use of drugs in pediatrics is historically based, since most drugs prior to recent years have not been labeled for use in children. Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease remains common. A recent study analyzed data from 31,432 children in the Pediatric Health Information System database hospitalized during 2005 with cardiovascular disease, and showed that 78% received ≥ 1 cardiovascular medication off-label and 31% received ≥ 3 cardiovascular medications off-label (4). The practice of off-label use without adequate information on drug efficacy and safety places children at risk for adverse events and

ineffective therapy. In nine reports evaluating pediatric drug-related adverse events, off-label prescriptions were involved in 23–60% (3). These data highlight the need for further study to determine which treatments are effective and should be used more frequently and which are unsafe or ineffective in children hospitalized with cardiovascular disease. In launching this trial, we did not fully appreciate how daunting it could be to change the culture among pediatric cardiologists from experiential practice to evidence-based medicine.

3. Quantitative eligibility criteria for the trial had not been verified in children

Of 349 patients screened, only eight met the study definition of at least moderate mitral regurgitation, left ventricular dilation, and had no exclusion criteria. Many quantitative methods are used to estimate the severity of mitral regurgitation including: area of the regurgitant jet, size of the regurgitant orifice, regurgitant fraction, and effective regurgitant orifice area by proximal isovelocity surface area (18,22,23). For inclusion in this trial, we defined at least moderate mitral regurgitation to require either a proximal regurgitant jet area $\geq 6 \text{ mm}^2/\text{m}^2$ or a regurgitant fraction $\geq 30\%$ with evidence of left ventricular dilation demonstrated by a LVEDD BSA-adjusted Z-score ≥ 2 (later 1.5). Our definition was of necessity adapted from published guidelines in adults (18). A number of the techniques recommended in adult guidelines have not been evaluated in children with AVSD. We relied on the presence of left ventricular dilation in conjunction with either a regurgitant jet or a regurgitant fraction consistent with at least moderate regurgitation. Regurgitant jet area rather than jet width was selected because the regurgitant orifice in AVSD is nearly always non-circular. The selection of the specific criteria for the proximal regurgitant jet area was based on adjustment of the published adult criteria for BSA. The selection of these two criteria combined a quantitative measure of the severity of mitral regurgitation with evidence of left ventricular enlargement. We included left ventricular dilation as an entry criterion based on the data that left ventricular volume overload resulting from the mitral regurgitation is the primary cause of the clinically important outcomes that therapy is intended to avert (10,11).

Of the 349 screened patients with initial local echocardiograms available for analysis (Figure 2), 40% (139/349) were judged to have greater than mild mitral regurgitation and 18% were judged to have moderate to severe mitral regurgitation by the site investigators using qualitative assessment on the local echocardiogram. Of these, however, only 54 patients had no other exclusion criteria (including ACE inhibitor use) based on the local echocardiogram, and received a study echo to assess quantitative criteria (Figure 2). Subsequently, only eight met the study definition of at least moderate mitral regurgitation (regurgitant fraction $\geq 30\%$ or proximal regurgitant jet area/BSA $\geq 6 \text{ mm}^2/\text{m}^2$) with left ventricular dilation [defined as LVEDDz ≥ 2 (later 1.5)] in the absence of any newly identified clinical exclusion criteria. For three patients the degree of mitral regurgitation was indeterminate. Analysis of the 42 remaining patients showed that none had a regurgitant fraction $> 30\%$ or an LVEDD z-score ≥ 2 (later 1.5), and 81% had a proximal regurgitant jet area/BSA $> 6 \text{ mm}^2/\text{m}^2$. Thus, most patients were excluded from trial entry because of the absence of left ventricular dilation. We therefore attempted to broaden this requirement by decreasing the LVEDDz requirement to ≥ 1.5 , but ultimately this decrease had little effect on enrollment.

The lack of left ventricular dilation may be related to the possibility that a six month period of time was not long enough to observe left ventricular remodeling. Another possibility is that young children following AVSD surgery may have restrictive left ventricular physiology that inhibits dilation with short-term volume overload. Alternatively, we cannot exclude the possibility that the proximal regurgitant jet area value of $6 \text{ mm}^2/\text{m}^2$ overestimated the actual degree of mitral regurgitation since the left ventricle did not dilate.

Neither this method of quantitative assessment of mitral regurgitation nor echocardiographic estimation of regurgitant fraction has been validated in children after repair of AVSD.

In this study, we presumed that left ventricular dilation would be a mechanistic consequence of significant mitral regurgitation, but in fact we failed to detect ventricular dilation in a significant number of subjects who met adult quantitative criteria for at least moderate mitral regurgitation. Since the pathophysiologic consequences of mitral regurgitation are mediated through left ventricular volume overload, it would be difficult to justify a clinical trial of medical therapy for mitral regurgitation in children who have no evidence of left ventricular volume overload. Prior to initiating this trial, there were insufficient natural history data to define the frequency and timing of onset of ventricular dilation as a consequence of mitral regurgitation after repair of AVSD, and this lack of natural history data continues to be a barrier to the design and execution of trials of this kind.

Conclusion

Despite our detailed planning and execution of a feasibility analysis, the slow enrollment rate and ultimate failure of this trial were due to several identifiable factors:

1. Use of criteria to assess disease severity in the feasibility study that were not identical to those used in the trial.
2. Failure to achieve equipoise for the study among clinicians and referring physicians.
3. Reliance on methodology developed in adult populations with different disease mechanisms.
4. Absence of adequate data to define the natural history of the disease process under study.

The PHN's sustainable infrastructure, which supports multiple simultaneous studies, meant that we did not have to dismantle an entire clinical trial structure, and thus were able to minimize the financial losses associated with closing this trial.

Given evidence indicating different toxicities and benefits for drugs in children compared with adults (25,26), pediatric clinical trials are necessary to appropriately assess therapeutic agents. When there is limited market value in conducting such trials, the NIH becomes one of the few organizations willing to sponsor such randomized trials. Progress in the treatment of children with cardiovascular disease will depend on the future of these multi-center collaborative clinical trials. Studies which better define the natural history of pediatric cardiovascular conditions will facilitate the conduct of randomized clinical trials involving these conditions (27–29). We have used the lessons learned from this study to better plan subsequent studies within the PHN. This includes the ongoing randomized clinical trial of atenolol versus losartan in individuals with Marfan syndrome for which the criteria used in the feasibility phase were identical to those being used in the actual trial (30). We hope that the issues discussed and the lessons learned from this study will facilitate improved research for children.

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References

1. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA* 2001;286:708–713. [PubMed: 11495621]
2. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682–1688. [PubMed: 12153370]
3. Shah SS, Hall M, Goodman D, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med* 2007;161:282–290. [PubMed: 17339510]
4. Pasquali SK, Hall M, Slonim AD, et al. Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. *Circ Cardiovasc Qual Outcomes* 2008;1:74–83. [PubMed: 20031793]
5. Mahony L, Sleeper LA, Anderson PA, 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;27:191–8. [PubMed: 16261271]
6. Hanley FL, Fenton KN, Jonas RA, et al. Surgical repair of complete atrioventricular canal defects in infancy. Twenty-year trends. *J Thorac Cardiovasc Surg* 1993;106(3):387–94. discussion 394–7. [PubMed: 7689672]
7. Moran AM, Daebritz S, Keane JF, et al. Surgical management of mitral regurgitation after repair of endocardial cushion defects: early and midterm results. *Circulation* 2000;102(19 Suppl 3):III 160–5.
8. Crawford FA Jr, Stroud MR. Surgical repair of complete atrioventricular septal defect. *Ann Thorac Surg* 2001;72(5):1621–8. discussion 1628–9. [PubMed: 11722055]
9. Michielon G, Stellin G, Rizzoli G, et al. Repair of complete common atrioventricular canal defects in patients younger than four months of age. *Circulation* 1997;96(9 Suppl):II-316–22.
10. Ten Harkel AD, Cromme-Dijkhuis AH, Heinerman BC, et al. Development of left atrioventricular valve regurgitation after correction of atrioventricular septal defect. *Ann Thorac Surg* 2005;79(2):607–12. [PubMed: 15680844]
11. Pisacane C, Pacileo G, Santoro G, et al. New insights in the pathophysiology of mitral and aortic regurgitation in pediatric age: role of angiotensin-converting enzyme inhibitor therapy. *Ital Heart J* 2001;2(2):100–6. [PubMed: 11256536]
12. Gaasch WH, Aurigemma GP. Inhibition of the renin-angiotensin system and the left ventricular adaptation to mitral regurgitation. *J Am Coll Cardiol* 2002;39(8):1380–3. [PubMed: 11955859]
13. Wisenbaugh T, Sinovich V, Dullabh A, et al. Six month pilot study of captopril for mildly symptomatic, severe isolated mitral and isolated aortic regurgitation. *J of Heart Valve Dis* 1994;3(2):197–204. [PubMed: 8012639]
14. Calabro R, Pisacane C, Pacileo G, et al. Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation. *Am Heart J* 1999;138(5 Pt 1):955–61. [PubMed: 10539829]
15. Gupta DK, Kapoor A, Garg N, et al. Beneficial effects of nicorandil versus enalapril in chronic rheumatic severe mitral regurgitation: six months follow up echocardiographic study. *J Heart Valve Dis* 2001;10(2):158–65. [PubMed: 11297201]
16. Seguchi M, Nakazawa M, Momma K. Effect of enalapril on infants and children with congestive heart failure. *Cardiol Young* 1992;2(1):14–19.
17. Bonow RO, Carabello B, de Leon AC, et al. ACC/AHA Guidelines for the Management of Patients with valvular heart disease. Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Heart Valve Dis* 1998;7(6):672–707. [PubMed: 9870202]
18. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for the evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777–802.
19. Rendell JM, Licht RW. Under-recruitment of patients for clinical trials: an illustrative example of a failed study. *Acta Psychiatr Scand* 2007;115:337–339. [PubMed: 17430410]

20. Gajewski BJ, Simon SD, Carlson SE. Predicting accrual in clinical trials with Bayesian posterior predictive distributions *Statist. Med.* 2007;10.1002/sim
21. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;16;317(3):141–5.
22. Alharthi MS, Mookadam F, Tajik AJ. Echocardiographic quantitation of mitral regurgitation. *Expert Review of Cardiovascular Therapy* 2008;6 (8):1151–1160. [PubMed: 18793117]
23. Patel AR, Mochizuki Y, Yao J, et al. Mitral regurgitation: comprehensive assessment by echocardiography. *Echocardiography* 2000;17(3):275–83. [PubMed: 10978995]
24. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Safety* 2006;5:703–718.
25. Roberts R, Rodriguez W, Murphy D, et al. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA* 2003;290:905–911. [PubMed: 12928467]
26. Benjamin DK Jr, Smith PB, Murphy MD, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA* 2006;296:1266–1273. [PubMed: 16968851]
27. McCrindle BW, Zak V, Sleeper LA, et al. Laboratory measures of exercise capacity and ventricular characteristics and function are weakly associated with functional health status after Fontan procedure. *Circulation* 2010;5;121(1):34–42.
28. Williams IA, Sleeper LA, Colan SD, et al. Functional state following the Fontan procedure. *Cardiol Young* 2009;15:1–11.
29. Anderson PA, Sleeper LA, Mahony L, et al. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. *J Am Coll Cardiol* 2008;8;52(2):85–98.
30. Lacro RV, Dietz HC, Wruck LM, et al. 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. *American Heart Journal* 2007;154:624–31. [PubMed: 17892982]

Figure 1.
ACE inhibition in Mitral Regurgitation Trial

Figure 2.
Patient Flow Diagram

Table 1

Inclusion and Exclusion Criteria

Observational Phase	Inclusion Criteria	No longer requires intensive care =28 days after repair of an AVSD (including primum atrial septal defect, transitional AVSD, and complete AVSD) Age =5 years Complete transthoracic echocardiogram =28 days after repair Informed consent of legal guardian
	Exclusion Criteria	Tetralogy of Fallot and total or partial anomalous venous connection Associated mitral stenosis with a mean diastolic gradient of >10mm Hg Other sources of LV volume overload, (e.g. >mild aortic regurgitation defined as a regurgitant jet/annulus ratio >20%, or significant left-to right shunt, defined as an echocardiographically determined Qp/Qs =1.5 Associated obstructive LV outflow lesions that are more than trivial, defined as a LV outflow peak instantaneous gradient of >20 mm Hg Significant residual coarctation, defined as an arm/leg systolic pressure difference of >20 mm Hg Associated hypertrophic obstructive cardiomyopathy
Drug Phase	Inclusion Criteria	=6 months postoperative from repair of an AVSD (primum atrial septal defect, transitional AVSD, and complete AVSD) Age = 5 years At least moderate mitral regurgitation, defined as both LV end-diastolic dimension BSA-adjusted Z-score =2.0 AND Either a proximal regurgitant jet area =6 mm ² /m ² or a regurgitant fraction =30% Asymptomatic or minimally symptomatic, defined by Ross or NYHA heart failure class I or II Atrioventricular synchrony (paced or intrinsic) Girls of child bearing potential must either abstain from sexual activity or provide assurance of birth control Informed consent of legal guardian and assent when appropriate
	Exclusion Criteria	Tetralogy of Fallot, total or partial anomalous venous connection, and obstructed pulmonary venous return. Reoperation for mitral regurgitation after the initial repair of an AVSD LV dysfunction, defined as an ejection fraction <55% Treatment with an ACE inhibitor within 6 months of randomization Associated mitral stenosis with a mean diastolic gradient of >10 mm Hg Other sources of LV volume overload, including >mild aortic regurgitation with a regurgitant jet/annulus ratio >20%, or significant left-to right shunt, defined as an echocardiographically-determined Qp/Qs=1.5 Systemic hypertension, defined as sustained systolic or diastolic blood pressure =95 th % ile for age Associated obstructive LV outflow with a LV outflow peak instantaneous gradient of >20 mm Hg Significant residual coarctation with a arm/leg systolic pressure difference of >20 mm Hg Associated hypertrophic obstructive cardiomyopathy History of chronic renal or hepatic dysfunction or persistent neutropenia Severe mitral regurgitation that is expected to need surgery = 6 months Residual postoperative lesions that are expected to require additional surgery = 6 months Need for ACE inhibitor therapy expected within 6 months in the opinion of the attending cardiologist History of intolerance to ACE inhibitors Pregnancy or intent to become pregnant