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Losartan Vs. Atenolol for Prevention of Aortic Dilation in Patients with Marfan Syndrome

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Brief Title: Losartan vs atenolol in Marfan syndrome
Disclosures: The authors declare that there is no conflict of interest

Tweet: No long-term differences in aortic dilation rate or clinical events between Marfan treated with losartan or atenolol

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ABSTRACT

Background: Beta-blockers are the standard treatment in Marfan syndrome (MFS). Recent clinical trials with limited follow-up yielded conflicting results on losartan effectiveness in MFS.

Objectives: The present study aimed to evaluate the benefit of losartan compared to atenolol for the prevention of aortic dilation and complications in Marfan patients over a longer observation period (>5years).

Methods: A total of 128 patients included in the previous LOAT clinical trial (64 in the atenolol and 64 in the losartan group) were followed up over an open-label extension of the study, with the initial treatment maintained.

Results: Mean clinical follow-up was 6.7 ± 1.5yrs. Nine events (14.1%) occurred in the losartan group and 12 (18.8%) in the atenolol group. Survival analysis showed no differences in the combined endpoint of need for aortic surgery, aortic dissection or death ($p = 0.462$). Aortic root diameter increased with no differences between groups: 0.4mm/year (95%CI 0.2–0.5) in the losartan and 0.4mm/year (95%CI 0.3–0.6) in the atenolol group. In the subgroup analyses, no significant differences were observed considering age, baseline aortic root diameter or type of dominant negative vs haploinsufficient FBN1 mutation.

Conclusions: Long-term outcome of Marfan syndrome patients randomly assigned to losartan or atenolol showed no differences in aortic dilation rate or presence of clinical events between treatment groups, Therefore, losartan might be a useful, low-risk alternative to beta-blockers in the long-term management of these patients.

Condensed abstract: 128 Marfan patients were included in an open-label extension of the previous clinical trial to compare atenolol and losartan. With a mean follow-up of 6.7 ± 1.5yrs, no differences in event-free survival or aortic dilation rate were observed between treatment groups. Therefore, although not demonstrated to be superior, losartan might be a useful, low-risk alternative to beta-blockers in the long-term management of Marfan patients.

Keywords: Marfan syndrome, losartan, aortic aneurysm.

Abbreviations:

ARB: angiotensin-II receptor blocker

BSA: body surface area

CI: confidence interval

MFS: Marfan syndrome

MRI: Magnetic resonance imaging

TGF-β: Transforming growth factor beta

SD: standard deviation

Introduction

Marfan syndrome (MFS) is a hereditary connective tissue disorder caused by mutations in the FBN1 gene which encodes for fibrillin-1 protein, an important constituent of the extracellular matrix. Although these patients have a multisystemic disease that involves ocular, skeletal and cardiovascular systems, survival is mainly determined by aortic complications. The current management of aortic involvement in MFS includes regular aortic imaging to evaluate aortic dilation progression, and prophylactic aortic repair when aortic dilation reaches a defined threshold that carries the threat of dissection (1). Current medical treatment aims to delay aortic dilation progression and avoid aortic complications, being beta-blockers the standard treatment for preventing aortic dilation. However, the randomized evidence supporting the use of beta-blockers is limited to a single, small, open-label trial (2) and many patients experience progressive aortic dilation despite such therapy (3,4). Furthermore, aortic dilation in MFS has been related to overexpression of TGF-β (5). Therefore, losartan, an angiotensin-II receptor blocker (ARB) that has previously demonstrated TGF-β antagonism, has been studied. Four large clinical trials with different designs comparing losartan to beta-blockers (6,7); or adding losartan or placebo to baseline treatment(8,9), included Marfan patients with different profiles of age range and aortic dilation. Results at three years of follow-up ranged from reduction to aortic dilation by losartan treatment to no benefit of losartan added to baseline treatment (most of them with baseline beta-blockers). In the LOAT trial(7), similar to The Pediatric Heart Network trial(6), no differences in aortic diameter progression were observed with losartan compared to atenolol treatment. The conflicting results of the published studies raised the question of whether longer intervention would yield different results. Therefore, the aim of the present study was to

evaluate the benefit of losartan compared to atenolol for the prevention of aortic dilation and aortic complications in Marfan patients over a longer period of observation (>5years).

Methods

The MFS patients included in the previous clinical trial (7) were followed up over an open-label extension of the study, with the initial treatment assigned by randomization being maintained. The follow-up protocol included a minimum of an annual clinical and echocardiographic evaluation. Clinical events (need for aortic surgery based on Guidelines recommendations (1), aortic dissection and/or death) were registered and, after at least 5 years had elapsed from the start of the clinical trial, an MRI study was performed. The study was approved by the Ethics Committees of both hospitals, and all patients (or their guardians) provided their written informed consent.

Participants

The initial inclusion criteria for participation in the LOAT trial were: MFS diagnosis (based on original Ghent criteria), age between 5 and 60 years and maximum aortic root diameter <45mm. Exclusion criteria were: history of aortic dissection or cardiac/aortic surgery, grade III/IV aortic regurgitation, history of angioedema or any other intolerance to angiotensin-converting enzyme inhibitors, ARB or beta-blockers, treatment with other cardiovascular drugs, pregnancy or planned pregnancy, history of asthma, respiratory failure, kidney, or neurological disease. One hundred and forty participants were included in the LOAT trial. In the present study, 12 patients were ruled out: 5 who withdrew consent, 1 for hypertension, 2 for planned pregnancy and 2 for non-compliance within 6 months of the start of the trial (**Figure 1**) and 2 patients in whom Marfan diagnosis was posteriorly ruled out. Thus, 128 patients were included for the extension of the trial (64 losartan group, 64 atenolol).

Treatment

Patients were maintained on the same drug (losartan or atenolol) and at the same dosage as during the clinical trial. Treatment was interrupted if pregnancy was planned (for losartan) or signs of clinical intolerance (hypotension or asthenia) or other side effects associated with the treatment appeared.

MRI study

MRI study was performed with the same protocol as in the LOAT trial. All MRI studies were conducted with 1.5-T systems (Signa Excite GE, Milwaukee, WI, USA) and 3T (Philips Achieva Tx). Imaging of the entire aorta was obtained: steady-state free precession (SSFP) cine acquisitions were obtained in held expiration and with ECG synchronization. Perpendicular cine images were obtained at the level of the sinuses of Valsalva and ascending aorta (at the level of the pulmonary bifurcation) using the double-oblique technique. The three cusp-to-commissure diameters were measured at aortic root level at the end-diastolic frame. The maximum of the three diameters at baseline and at follow-up was considered for analysis. Maximum ascending aortic diameter was also measured. All measurements were indexed by body surface area (BSA) at the time of the MRI study. Measurements were taken by a blinded observer (N.V.) using the QFlow software package, version 5.5 (Medis, Leiden, the Netherlands).

Outcomes

As in the previous LOAT trial, primary endpoints were defined as changes in aortic root and ascending aorta diameter indexed by body surface area (BSA) on MRI with losartan vs. atenolol. Secondary endpoints were clinical events during follow-up including aortic dissection, need for aortic intervention or heart surgery and death.

Statistical analysis

Analyses were made following the modified intention-to-treat principle. Continuous variables were summarized as mean±SD or median and interquartile range. Categorical variables were presented as counts and percentages. Comparison of continuous variables was made by Student's t-test and by chi-square test for categorical variables. When normality was not assumed, non-parametric analyses were made instead. Survival curves were estimated using the Kaplan–Meier method and compared by means of log-rank tests. Statistical significance was considered when P ≤0.05 (two-sided). Analysis were performed using SPSS 19.0 software (IBM, Chicago, IL, USA).

Results

One hundred and twenty-eight patients were included in the study, 64 from the losartan group and 64 from the atenolol group. Baseline characteristics are described in **Table 1**. No differences were observed related to age, sex, body surface area or aortic dimensions. A total of 109 (85%) patients had FBN1 gene analysis, of whom a pathogenic mutation was found in 89 (82%): 50 (56%) being classified as dominant negative, 26 (29%) as haploinsufficient and 13 (15%) as unclassifiable. In the losartan group, 54 patients (84.4%) continued with losartan throughout follow-up; of the rest, 4 discontinued medical treatment, 5 changed to β-blockers and 1 received a combination of atenolol plus losartan (owing to hypertension). Forty-eight patients (75.0%) in the atenolol group continued with atenolol throughout follow-up; 12 of the remaining patients discontinued medical treatment and 4 changed to losartan.

Mean clinical follow-up was 6.7±1.5years (median: 7.2 years, IQR 6.3 to 7.8years). Nine events occurred in the losartan group (7 elective ascending aorta surgery, 1 elective descending aorta surgery and 1 type A aortic dissection) and 12 in the atenolol group (9 elective ascending aorta surgery, 2 type A aortic dissection and 1 type B aortic dissection). Aortic root diameter

prior to type A dissections were 43, 47, and 49 mm. Three of the four aortic dissections resulted in death (1 type B). Survival analysis showed no differences in the combined endpoint of aortic surgery, aortic dissection or death (p = 0.462) or for the combined endpoint of acute aortic syndrome or death (p = 0.305). Survival curves are shown in the **Central Illustration**.

Sixty-one patients from the losartan group and 58 from the atenolol group had follow-up MRI, either at a minimum of 5 years of follow-up or before the event. Mean MRI follow-up was 5.9 ± 2.0years. Aortic root diameter increased in both groups: 0.4mm/year (95%CI 0.2–0.5) in the losartan and 0.4mm/year (95%CI 0.3–0.6) in the atenolol groups. However, no statistically-significant differences in aortic dilation progression were observed between groups: -0.0 mm/year (95%CI -0.25-0.17, p = 0.754). Furthermore, no statistically significant differences were observed when evaluating aortic root diameters indexed by body surface area or ascending aorta diameters (**Table 2**). Similar results were found when only patients who continued with the same treatment as during the trial were considered (**Online Table 1**).

In the subgroup analyses, no significant beneficial effect of losartan was observed on aortic root diameter regardless of sex, age group, baseline aortic root diameter or type of dominant negative vs haploinsufficient FBN1 mutation (**Figure 2**).

Discussion

This is the longest study to date comparing clinical evolution and aortic dilation in Marfan patients treated with atenolol vs losartan. This study found no differences in clinical events over a long period of treatment (median: 7.2 years) nor in aortic dilation progression assessed by MRI (median: 6.7 years). Furthermore, no differences were observed in the subgroup analysis by sex, age, baseline aortic diameters or type of FBN1 mutation.

Beta-blockers have become standard in the prevention of aortic dilation and dissection in patients with MFS since the report by Shores et al(2). However, their benefit is debatable and two meta-analyses also reached opposing conclusions(10,11). More recently, four prospective randomized trials: The COMPARE trial (8), Pediatric Heart Network(6), SARTAN(9) and LOAT(7) were the first to examine the use of ARBs in human Marfan patients, following the publication of the landmark work by Habashi et al. (12), in a mouse model, and the remarkably positive results of a small, non-randomized trial on the effects of losartan in a small sub-set of children with a severe phenotype of the disease (3). The designs of these recent trials were diverse: the COMPARE and SARTAN trials assessed the benefit of adding losartan to baseline therapy, compared to adding placebo, and the Pediatric Heart Network and LOAT trials compared the administration of losartan vs atenolol. The COMPARE was open-label, the Pediatric Heart Network was single-blinded and the SARTAN and LOAT double-blinded, randomized trials. Evaluation of the primary outcome, the rate of aortic root enlargement, was evaluated by echocardiography in the largest trials: the Pediatric Heart Network and SARTAN, and by MRI in the COMPARE and LOAT trials. While COMPARE included only adult patients, 28% and 40% in the SARTAN and LOAT trials, respectively, were <18 years of age. By contrast, 75% in the Pediatric Heart Network were <16 years and mean Z-score of included patients ranged from 3.2 to 4.0. Clinical events were similar between treatment groups and only the COMPARE showed a slight reduction in aortic root growth rate at 3 years in the group treated with losartan (0.77+1.36 vs. 1.35+1.55 mm, P <0.014). No relationship was found between blood pressure changes during treatment and aortic root growth rate changes. Recently, a meta-analysis was published of all prospective randomized clinical trials studying the effect of losartan on aortic dilation (13). The results indicate that losartan treatment slows the rate of

aortic dilation; however, no benefits on clinical outcomes were observed in the losartan group compared with the non-losartan group (most under beta-blocker treatment). This result, however, should be interpreted with caution: as previously exposed, the design of the six studies differed significantly, and the meta-analysis included redundant information of subgroup analyzes of the COMPARE trial. Furthermore, the relatively low dose of losartan administered in human trials compared to the mouse model could be an explanation for the lack of consistent positive results in human. However, one of the questions that remains to be answered is whether a longer intervention would yield to different results. This question is partly addressed in the current study, where most patients maintained the baseline randomized treatment and its doses, and after a 6-year treatment, we found no difference between losartan and atenolol treatment groups in the aortic root dilation rate or clinical events. In addition, we found no differences in losartan efficacy depending on the type of FBN1-mutation, thus not replicating the results from Franken et al. (14), which demonstrated a more marked reduction of aortic dilation rate with the addition of losartan in haploinsufficient Marfan patients.

Limitations

Although the initial trial was double-blinded, the extension was open-label. However, experts who measured aorta size by MRI were blinded to the medical treatment and clinical information. A further limitation was the absence of a control group with placebo, not possible for ethical reasons since beta-blockers are accepted as the standard treatment. The final sample size of the study was not large; however, with the use of MRI for aortic diameter measurements, it sufficed to detect clinically-significant differences of 2 mm in 6 years in the aortic root dilation rate between treatment groups (97% statistical power to detect a difference ≥0.4mm/year). In the current study, 85% of patients underwent FBN1 gene analysis, 82% of whom had pathogenic

mutations. The proportion of negative FBN1 in our study (18%) was similar to other clinical trials: 15% in the MARFANSARTAN, 16.2% in the COMPARE and 11.7% in the PHN.

Conclusions

The results showed no differences in long-term treatment with losartan compared to atenolol in aortic root and ascending aorta dilation rate or the frequency of clinical events in MFS patients. Although losartan has not proven superior to atenolol in monotherapy in MFS patients, it might be a useful, low-risk alternative to beta-blockers in the long-term management of these patients.

Clinical Perspectives

Competency in Patient Care: In patients with Marfan syndrome, the angiotensin-II receptor blocker, losartan, is a reasonable alternative to beta-adrenergic inhibition with atenolol for prevention of aortic dilation and associated complications.

Translational Outlook: Further studies are needed to evaluate the utility of combined treatment with both drugs in this situation.

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Figure Legends

Central Illustration: Losartan vs atenolol in Marfan syndrome. Comparison of survival curves between treatment groups for the composite endpoint of aortic dissection or death (A), aortic dissection, aortic surgery or death (B).

Figure 1: Flow diagram for inclusion and follow-up of patients. MFS: Marfan syndrome; MRI: magnetic resonance imaging.

Figure 2: Comparison of the effect of losartan compared to atenolol on aortic root dilatation rate in subgroups of Marfan patients. Mean differences in mm/year are indicated by solid squares. Horizontal lines represent 95% confidence intervals and in parentheses is reported the number. CI: confidence interval.

Table 1. Baseline characteristics according to study group

	Losartan n=64	Atenolol n=64	p
General features			
Mean age (years)	25.6±13.8	23.8±13.6	0.464
Sex (Female)	41 (64.1%)	34 (53.1%)	0.282
Weight (Kg)	61.5±21.0	64.8±20.6	0.374
Height (cm)	171.7±16.7	175.0±18.8	0.290
Body surface area (m^2)	1.71±0.4	1.78±0.4	0.313
Presence of causal FBN1 mutation (% of tested)	45 (83.3%)	44 (80.0%)	
Dominant negative	25 (55.6%)	25 (56.8%)	
Haploinsufficient	13 (28.9%)	13 (29.5%)	
No causal FBN1 mutation (% of tested)	9 (16.7%)	11 (20.0%)	0.966
Not tested (% total)	10 (15.6%)	9 (14.1%)	0.804
Blood pressure (mmHg)			
Systolic	119.9±17.9	119.5±14.5	0.908
Diastolic	73.8±11.5	73.5±8.3	0.879
Mean arterial pressure	89.1±12.6	88.8±9.0	0.881
Aortic dimensions by MRI			
Aortic root			
Diameter (mm)	35.7±5.9	30.9±13.4	0.869
Diameter/BSA (mm/m^2)	21.3±4.1	20.3±3.4	0.166
Z-score	3.2±2.3	3.2±2.3	0.846

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Z-score ≤3 (%)	29 (45.3%)	27 (42.2%)	0.856
Ascending aorta			
Diameter (mm)	26.2±4.8	26.7±5.9	0.632
Diameter/BSA (mm/m^2)	15.6±2.8	15.1±2.5	0.264

Plus-minus values are mean±SD

BSA= body surface area; MRI: magnetic resonance imaging

Table 2. Aortic dilation outcome over the extended study period.

Aortic dilation rate by MRI	n	Losartan Mean (95% CI)	n	Atenolol Mean (95% CI)	Inter -group difference Mean (95% CI)	p
Aortic root						
Diameter (mm/yr)	61	0.4±0.6 (0.2 to 0.5)	58	0.4±0.5 (0.3 to 0.6)	0.0 (−0.25 to 0.17)	0.754
Diameter/BSA (mm/m^2/yr)	61	−0.1±0.4 (−0.2 to 0.0)	58	−0.1±0.4 (−0.2 to 0.0)	0.0 (−0.2 to 0.1)	0.803
Z-score (per year)	61	−0.1±0.4 (−0.2 to −0.0)	57	−0.2±0.4 (−0.3 to 0.1)	0.1 (−0.1 to 0.2)	0.236
Ascending aorta						
Diameter (mm/yr)	61	0.2±0.4 (0.1 to 0.3)	58	0.1±0.6 (0.0 to 0.3)	0.1 (−0.1 to 0.2)	0.551
	61		58	−0.2±0.4 (−0.3 to	0.0 (−0.1 to 0.2)	0.745
Diameter/BSA (mm/m^2/yr)		−0.2±0.4 (−0.3 to −0.1)		−0.1)		

Results are annual change expressed as mean±SD (95% CI). p represents t-test. BSA: body surface area.
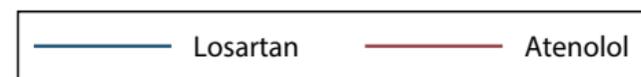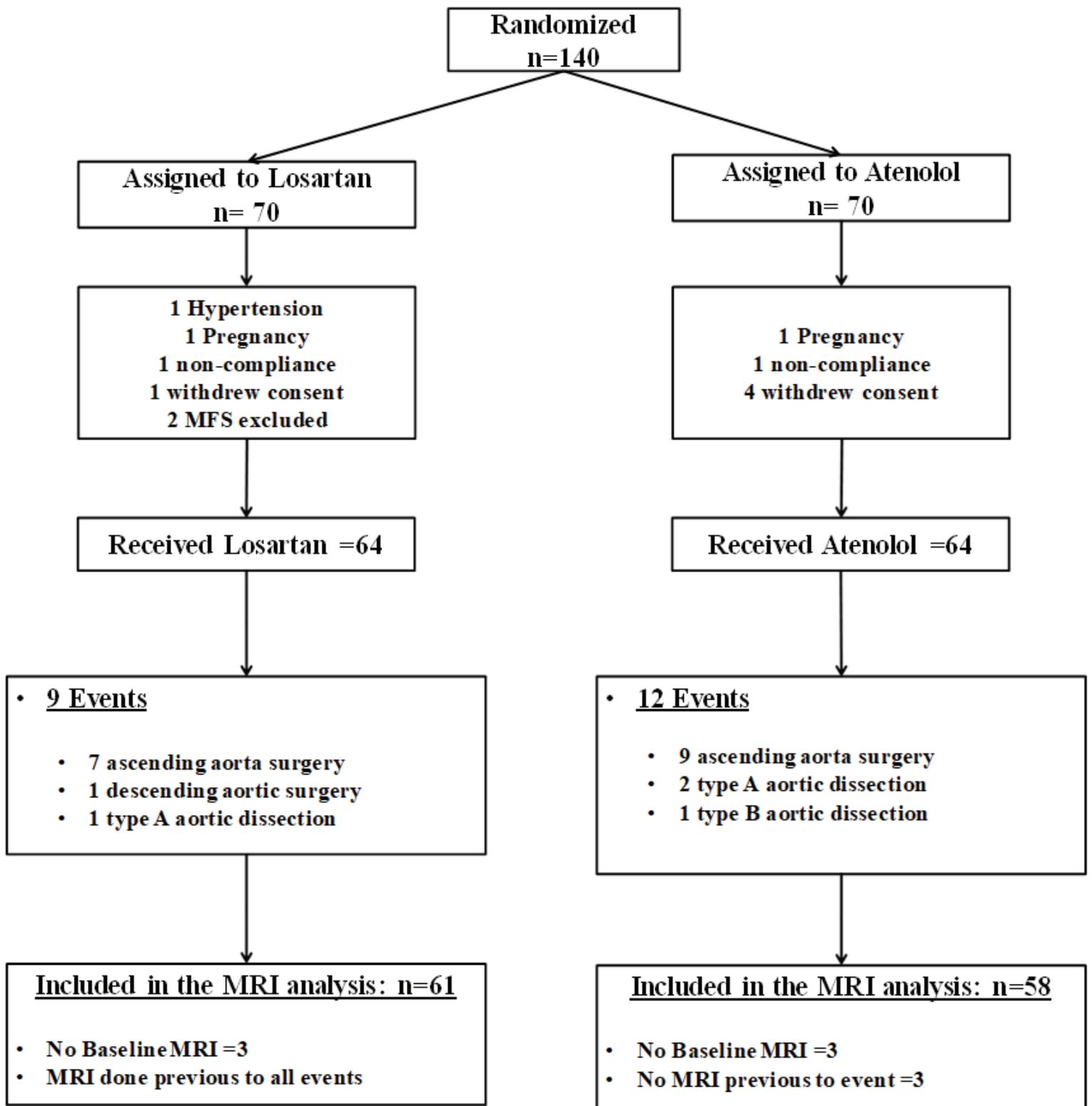
A — Aortic dissection or death

B — Aortic surgery, aortic dissection or death
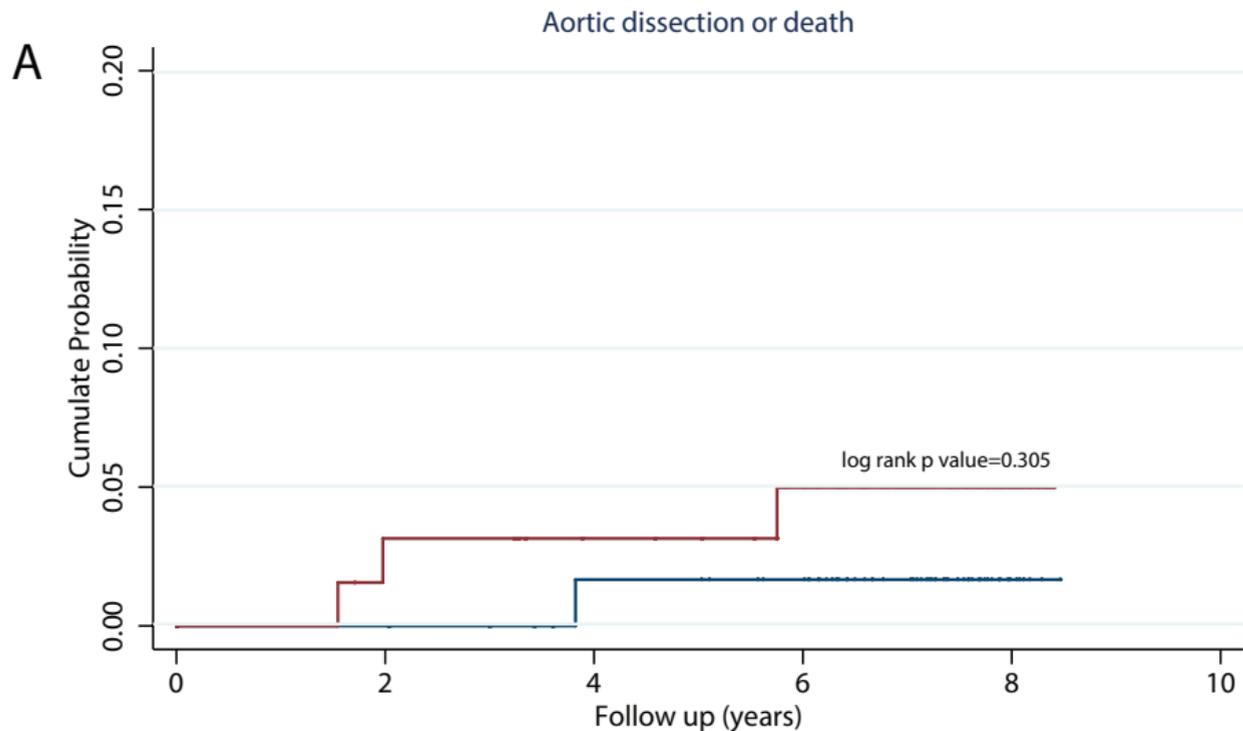
Number at risk

Losartan	64	64	59	55	7	0
Atenolol	64	61	57	51	8	0

Characteristic	Mean (95%CI)
Age <18yrs (45)	0.12 (-0.22, 0.45)
Age ≥ 18yrs (74)	-0.04 (-0.21, 0.13)
Male (51)	-0.09 (-0.47, 0.29)
Female (69)	0.05 (-0.20, 0.30)
Baseline aortic root ≤ 37mm (68)	0.03 (-0.24, 0.31)
Baseline aortic root > 37mm (52)	-0.03 (-0.35, 0.29)
Haploinsufficient (25)	0.15 (-0.30, 0.59)
Dominant negative (49)	-0.26 (-0.59, 0.07)

Losartan better   Atenolol better
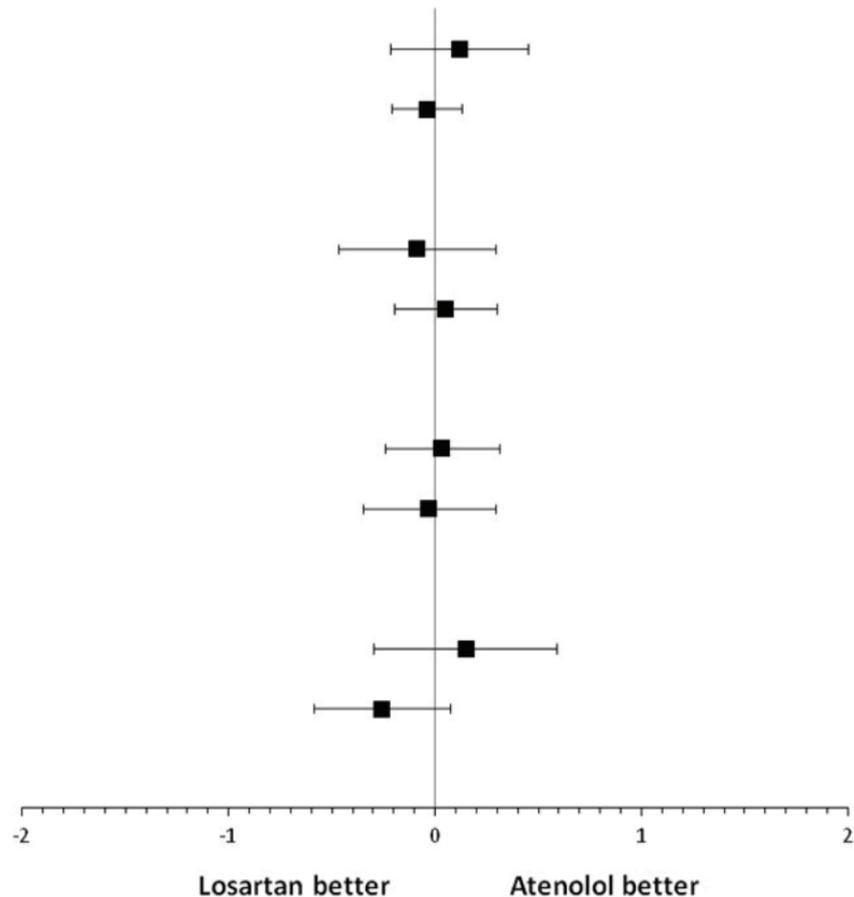
SUPPLEMENTAL MATERIAL

Supplemental table 1. Aortic dilation outcome over the extended study period in patients

with no change in treatment

Aortic dilation rate by MRI	n	Losartan Mean (95% CI)	n	Atenolol Mean (95% CI)	Inter -group difference Mean (95% CI)	p
Aortic root						
Diameter (mm/yr)	52	0.4±0.7 (0.2 to 0.6)	44	0.3±0.5 (0.2 to 0.5)	0.1±0.1(−0.2 to 0.3)	0.606
Diameter/BSA (mm/m^2 /yr)	52	−0.2±0.4 (−0.3 to −0.1)	44	−0.1±0.4 (−0.2 to 0.0)	0.0±0.1 (−0.2 to 0.1)	0.600
Z-score (per year)	52	−0.2±0.4 (−0.3 to 0.0)	43	−0.2±0.4 (−0.4 to −0.1)	0.1±0.1 (−0.1 to 0.3)	0.247
Ascending aorta						
Diameter (mm/yr)	52	0.2±0.4 (0.1 to 0.3)	44	0.1±0.7 (−0.1 to 0.3)	0.1±0.1 (−0.1 to 0.4)	0.207
Diameter/BSA (mm/m^2 /yr)	52	−0.2±0.4 (−0.3 to −0.1)	44	−0.2±0.4 (−0.3 to 0.0)	0.0±0.1 (−0.2 to 0.2)	0.998

Results are annual change expressed as mean±SD (95% CI). p represents t-test. BSA: body surface area.