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Lessons from the trials

COMPARE and Pediatric Heart Network Investigator trials: Losartan finally validated in humans with Marfan, but much work remains!

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ABSTRACT

A landmark study by Habashi et al¹ in 2006 documented for the first time both the prevention and reversal of structural changes in the aorta associated with Marfan syndrome, via pharmacological means. This study, carried out in a rat model, concluded that such results were due to an inhibitor effect by the drug losartan on TGB- β 1 (Figure 1).

Habashi's paper prompted some physicians, in the absence of human trials, to begin the clinical off-label use of losartan on Marfan patients, arguing that this was justified due to the drug's excellent safety profile. This has caused some controversy.

Two significant randomized human trials of losartan in Marfan patients have since been conducted, which contribute different but valuable elements to the debate; the COMPARE trial demonstrated a significantly lower increase in aortic root diameter among study subjects receiving losartan compared with a placebo group after 3 years, although no significant differences were observed in aortic diameter beyond the root itself. A more recently concluded trial by Lacro et al² from the Paediatric Heart Network, comparing losartan with atenolol (and no placebo group), appeared to show no comparative benefit with respect to the rate of aortic dilatation over three years among the losartan users compared with study patients given atenolol, with both groups of patients experiencing a similar decrease in the rate of dilatation over the 3 year follow-up.

Both studies suggest a positive impact of losartan on aortic dilation in humans with Marfan, but they also highlight a number of important questions that remain unanswered. Further trials are clearly needed in order to assess optimal dosing and to guide timing of therapy, and also to further assess the potential and comparative effectiveness of both losartan and β -blockers, individually and in combination, as therapeutic treatments for aortic protection of different groups of patients with Marfan syndrome.

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[http://dx.doi.org/
10.5339/gcsp.2014.51](http://dx.doi.org/10.5339/gcsp.2014.51)

Submitted: 22 October 2014
Accepted: 11 December 2014
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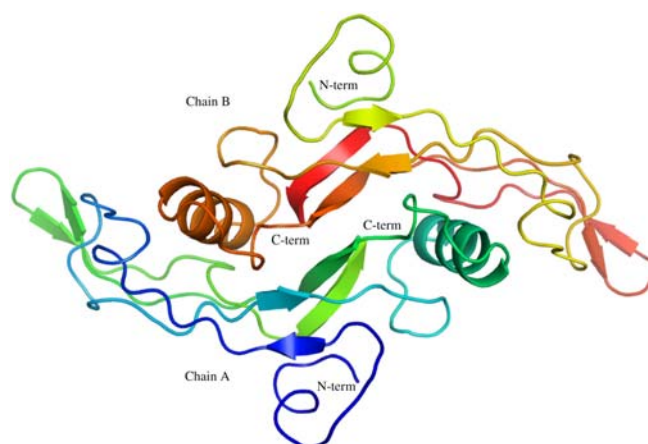


Figure 1. Homo dimer of TGF- β 1. Courtesy of Poornima Rao, QCRC.

BACKGROUND

The landmark paper by Habashi and colleagues, published in *Science* almost 8 years ago, produced a good deal of excitement in both the clinical and scientific communities. The authors reported for the first time ever a reversal of the structural changes to the aorta in Marfan syndrome using an angiotensin receptor blocker (ARB) commonly used for the treatment of hypertension and heart failure (Figure 2 & 3). The only limitation was that these results were observed in an animal model of Marfan syndrome, and not tested further in humans at the time.

Interestingly, in the same study, the use of ACEI and clinically used β -blockers proved ineffective in reversing or slowing the disease. The authors offered a convincing mechanistic explanation to their findings, concluding that losartan inhibits TGF- β 1, which has been implicated in causing medio-necrosis and dilatation of the aorta in Marfan syndrome³ (Figure 4 & 5).

These findings stimulated the clinical use of ARB losartan in Marfan patients and in patients with thoracic aortic aneurysms, even before experimental validation in Humans. The justification given was that losartan is already in clinical use for the treatment of hypertension and heart failure, and that it has been shown to have an excellent safety profile. Such off-label use of the drug in the absence of a randomized clinical trial was criticized by many workers in the field. The recent publication of the COMPARE Trial, and the trial by Lacro and colleagues, are a welcome addition to the literature as they begin to address this issue directly.

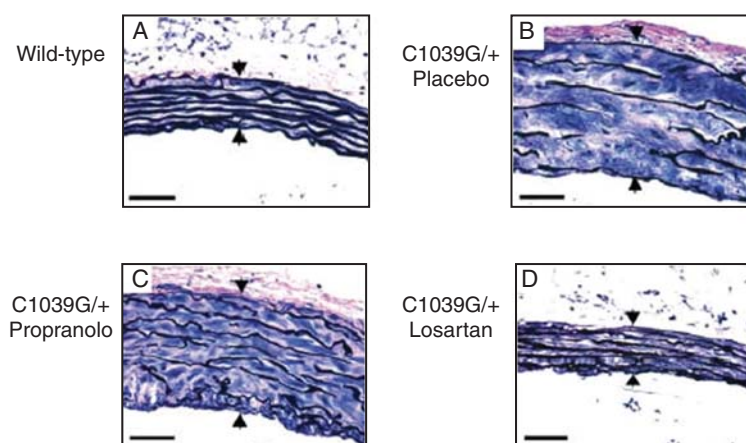


Figure 2. Pre-natal treatment of Marfan syndrome with losartan and propranolol. Propranolol (C) shows no beneficial effect compared to placebo (B), whilst losartan shows significant benefit (D). Adapted from Habashi, Judge, Diaz et al, *Science*, 2006 April 7;312(5770): 117–121.

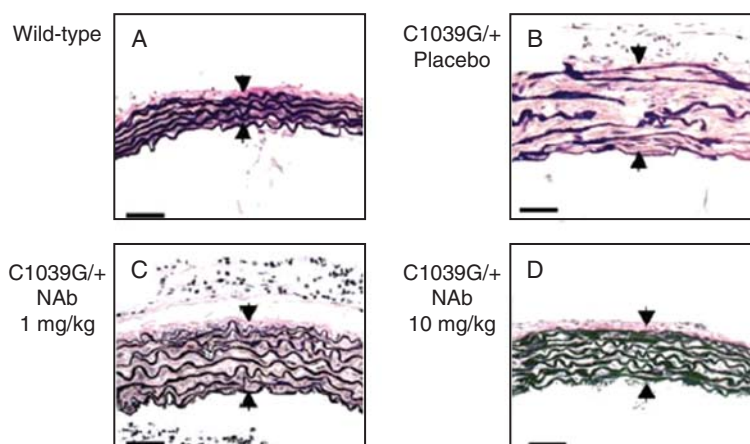


Figure 3. Post-natal treatment of Marfan syndrome with TGF- β neutralizing antibody. Significant reversal of the condition demonstrated at 10 mg/kg (D). Adapted from Habashi, Judge, Diaz et al, *Science*, 2006 April 7;312(5770): 117–121.

STUDY DESIGN: COMPARE AND LACRO

Compare

The COMPARE (COzzar in Marfan PATients Reduces aortic Enlargement) trial is an open label, multi-center randomized trial with blinded assessment of end points. Adult patients aged 18 years or more, who were diagnosed with MFS using the Ghent criteria⁴, were included in the trial. Exclusion criteria included aortic root diameter of >50 mm, a history of aortic dissection or the presence of more than one vascular prosthesis.

A total of 233 eligible patients were identified from specialized Marfan units in four Dutch university hospitals and from the Dutch national database of adults with congenital heart disease⁵ (CONCOR), and randomly assigned to receive losartan ($n = 116$) or to a control group receiving no additional drugs ($n = 117$). All previously prescribed drugs were continued. The losartan group additionally received 100 mg per day of losartan (starting with 50 mg per day for the first 14 days).

The primary end point was rate of dilatation of the aorta at 6 predefined points from the root to the bifurcation, measured by MRI or CT after 3 years of follow-up. Secondary end points were (1) total aortic

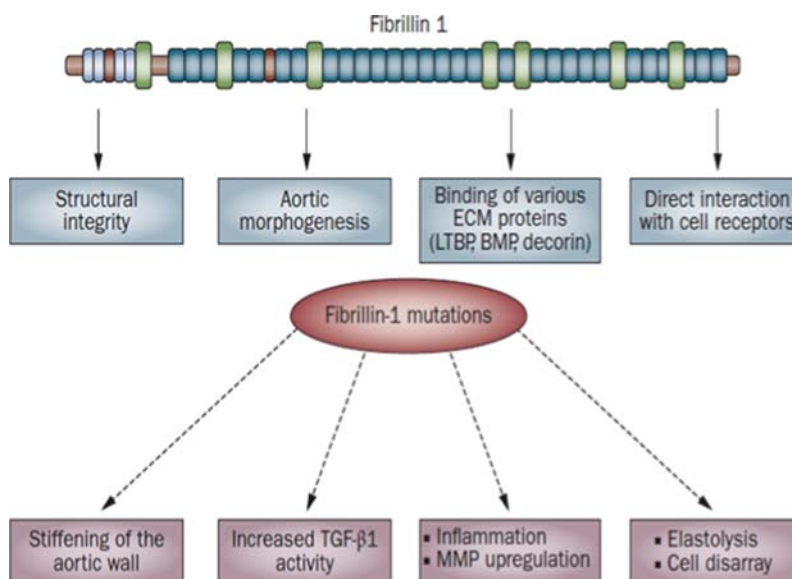


Figure 4. Structural and functional effects of normal and mutant fibrillin-1 in regulation of aortic wall homeostasis. From Elhamamsi & Yacoub, *Nat Rev Cardiology* 6, 771–786 (2009).

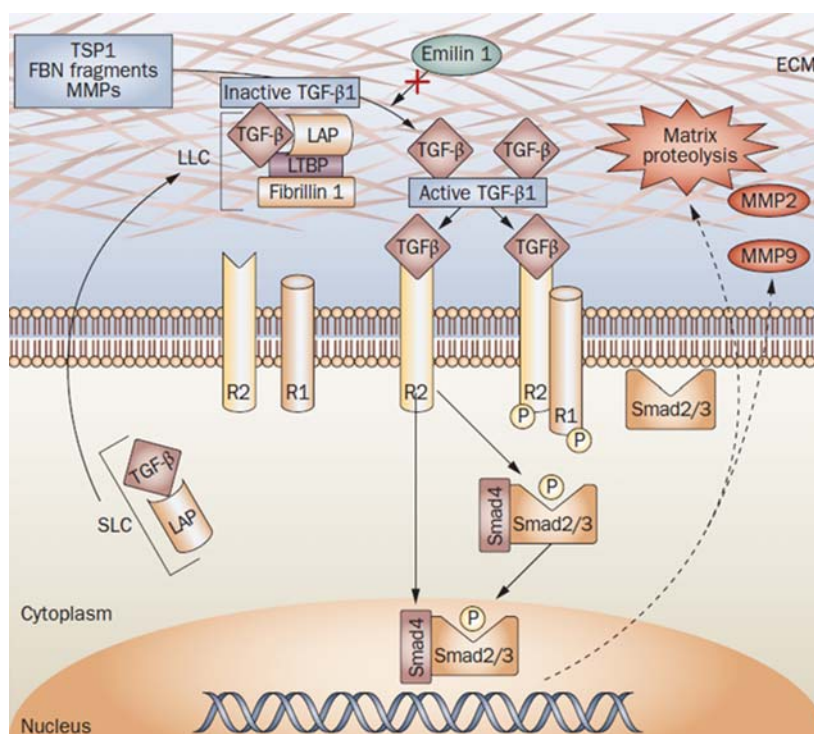


Figure 5. The role of TGF-β1 in TAA formation. From Elhamamsi & Yacoub, Nat Rev Cardiology 6, 771–786 (2009).

volume expansion rate, and (2) a combined end point of cardiovascular mortality, aortic dissection, or prophylactic aortic surgery.

Lacro

The Pediatric Heart Network team enrolled a total of 608 patients, aged between 6 months and 25 years, diagnosed with MFS according to Ghent criteria, and with a z-score of maximum aortic root diameter indexed to body surface area greater than 3. Exclusion criteria were similar to COMPARE.

Study participants were assigned to blocks stratified by age and z-score, and then randomly permuted to a losartan or an atenolol group (ratio 1:1). The atenolol group was given an initial dose of 0.5 mg per kg, increased on the basis of a haemodynamic response to a maximum of 4 mg per kg. The losartan group received an initial dose of 0.4 mg per kilo, adjusted on the basis of body weight up to a maximum of 1.4 mg per kg.

The primary outcome was the rate of aortic root enlargement, expressed as a change in the z-score. Secondary end points included the rate of change in absolute diameter of the aortic root, changes in aortic regurgitation, time to aortic dissection, death, prophylactic surgery, somatic growth and adverse events.

RESULTS

Compare

At 3 years, the rate of increase in aortic root diameter was found to be significantly lower in the losartan group, at 0.77 ± 1.36 versus $1.35 \text{ mm} \pm 1.55$ in the control group (Figure 6). The rate of increase was not related to reduction in blood pressure.

In contrast, the three-year follow-up showed that there were no significant differences in aortic diameter at the other pre-specified points (other than the aortic root), and no significant difference in the combined end point of cardiovascular death, aortic dissection or prophylactic aortic surgery.

Importantly, the beneficial effect of aortic root dilatation in the additional losartan group appeared to be consistent in all the sub-groups examined⁶ (Figure 7).

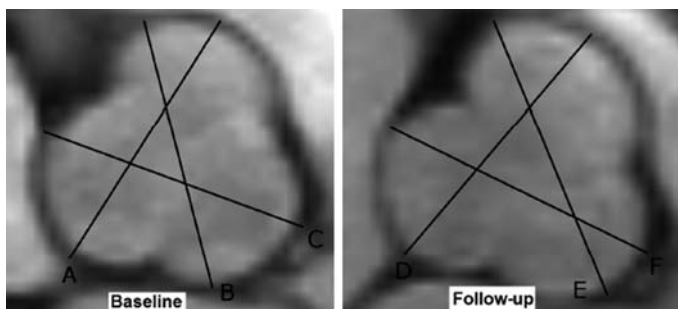


Figure 6. MRI showing the aortic root in short axis of a COMPARE patient with Marfan syndrome at baseline and after 3 years of follow-up. From Groenick M, Hartog A, Mulder B et al. *European Heart Journal*, 10.1093/euroheartj/eht 334.

Lacro

At 3 years, both groups (atenolol and losartan) showed a comparable decrease in the rate of aortic root dilatation relative to body surface area (-0.139 ± 0.013 and -0.107 ± 0.013 standard deviation units per year respectively for atenolol and losartan). However, in terms of absolute diameter and z-score of the aortic annulus (but not the ascending aorta), there was a small but significant difference in favor of the atenolol group. Similarly to the COMPARE Trial, secondary end points showed no significant variance between the two groups (Figure 8).

DISCUSSION

The COMPARE and Lacro trials were the first prospective randomized trials to examine the use of ARBs in human Marfan patients, following on from the landmark work published by Habashi and colleagues on

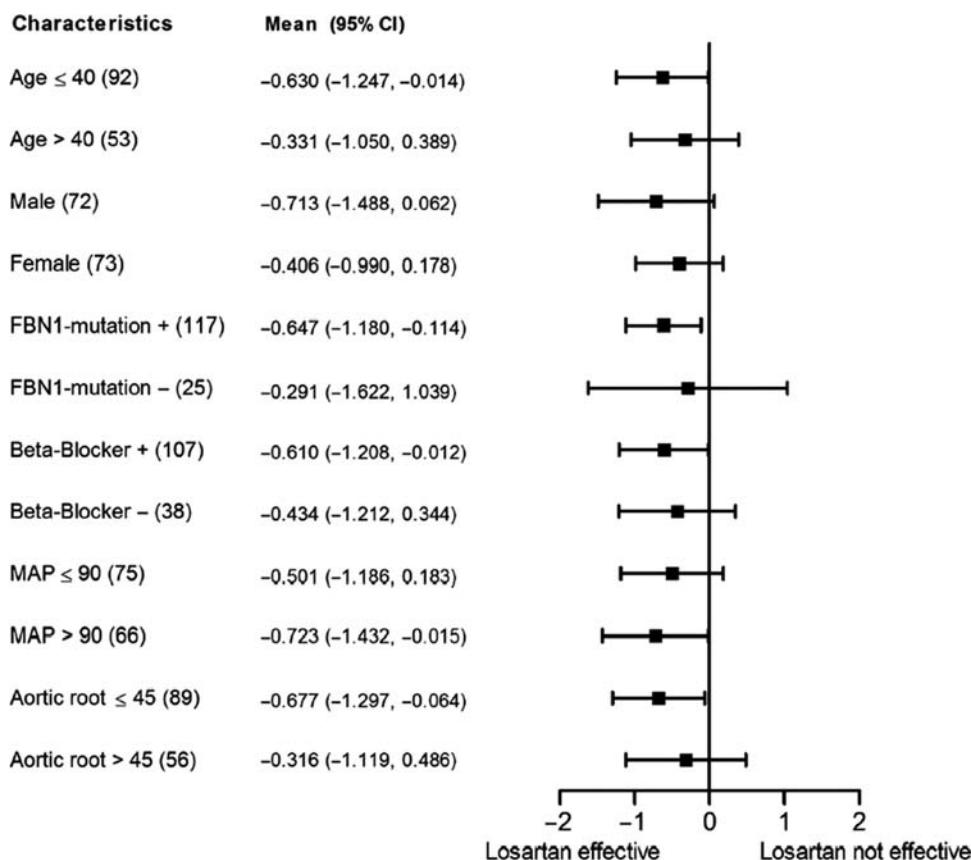


Figure 7. Effects of Losartan treatment on aortic root dilatation rate in sub-groups of Marfan patients. From Groenick M, Hartog A, Mulder B et al. *European Heart Journal*, 10.1093/euroheartj/eht 334.

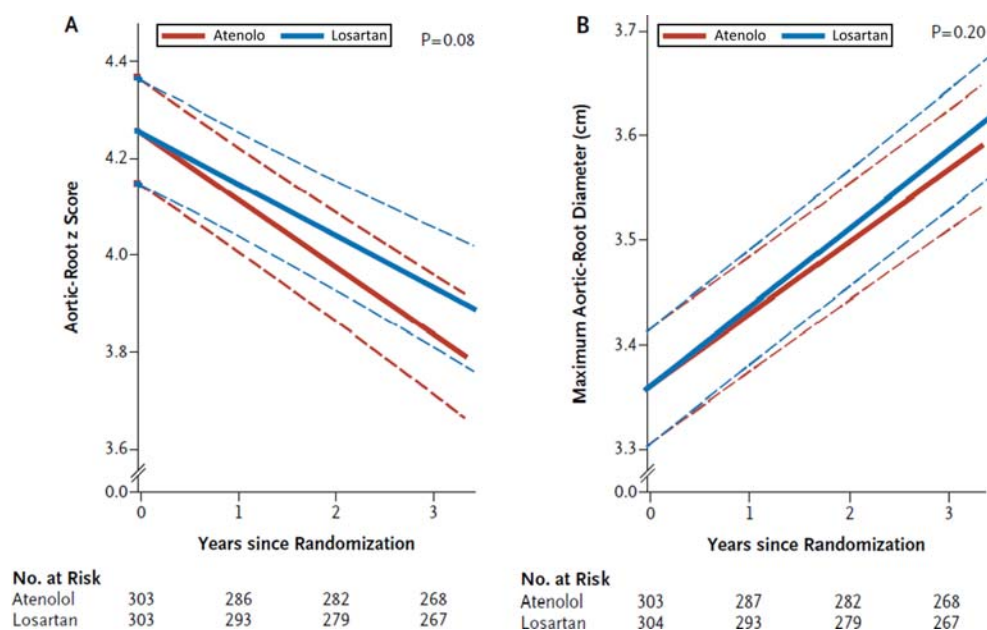


Figure 8. Changes in aortic root z-score and aortic root diameter according to treatment group. From Lacro RV, Dietz HC, Sleeper LA et al, Atenol versus Losartan in Children and Young Adults with Marfan Syndrome, NEJM, 2014 November 27; 371(22): 2061–71.

the rat model, and the remarkably positive results reported from a small, non-randomized trial on the effects of losartan in a small sub-set of children who had a severe phenotype of the disease⁷ (Figure 9).

Although both COMPARE and Lacro suggest a positive effect of losartan in reducing the rate of aortic root enlargement in MFS patients, a number of important questions remain to be answered, particularly in light of the fact that the Lacro trial unexpectedly suggested no significant differences between patients in their cohort treated with losartan or atenolol.

A number of possible explanations may underlie the Lacro results:

1. We are aware that the dosage of atenolol prescribed by investigators in this trial was adjusted for physiological effect (to reduce mean heart rate by 20% or more), and was higher than for most other studies. At the same time, the dosage of losartan prescribed followed current FDA guidelines

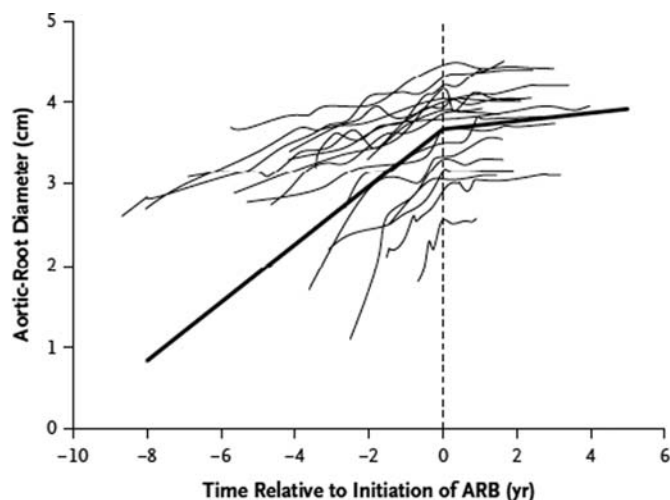


Figure 9. Change in Aortic Root diameter, standardized according to the time of initiation of therapy with an Angiotensin II-Receptor Blocker (ARB). From Brooke B, Habashi J, Judge D, Patel N, Loeys B, Dietz H, Angiotensin II Blockade and Aortic Root Dilatation in Marfan Syndrome, N Engl J Med, 2008;358:2787–95.

at the time, and was as a result in a much narrower range. Given a current paucity of data on appropriate dosing and selection of β -blockers in relation to Marfan, it is possible that the atenolol dose used in this trial was more effective than the investigators anticipated. Equally, we currently lack an understanding of the optimal dosage for losartan for MFS, so it is difficult to compare effectiveness of the two strategies. It is possible that a higher dose of losartan (or another ARB) might have shown a much greater effect on aortic growth rate.

2. There was a small but significant difference in diastolic blood pressure (lower in the atenolol group), which could in itself have contributed to lowering the growth rate in aortic diameter in that group, compared with the losartan cohort. Thus we may not be comparing the effect of the two drugs directly in the findings.
3. The z-scores of patients included in the Lacro trial also suggested advanced aortic disease, whilst in Habashi's mouse models losartan was given at an early stage. Again it might be the case that with advancing disease, the aorta becomes more resistant to TGF- β suppression, thus reducing the measured effect of losartan vs atenolol in this particular study, compared with a trial potentially carried out at an earlier stage of disease.

A final, more general observation from the Lacro trial is that a greater decrease in aortic root z-scores over time was recorded in younger patients vs older ones. This suggests greater benefit, with either therapy, if intervention is started early in the course of the disease. The lack of a placebo group in this particular trial means that it was not possible to evaluate the magnitude of this benefit, but other studies of β -blockers vs placebos in Marfan patients would tend to support this assertion.

The authors of both trials point to a number of limitations in relation to trial design, the end points measured, the exclusion criteria and the statistical power of their work in relation to sub-group analysis. However, both studies make a first important contribution towards a better understanding of the important role that ARBs like losartan might play in improving outlook and outcomes for people living with Marfan syndrome.

Losartan has, in our view, confirmed its validity as a useful and low-risk option in the management of patients with MFS. However, considerable gaps in our knowledge and understanding remain, which will require significant additional research in order to maximize its potential. Only through further trials and analysis will this promise be properly evaluated, understood and harnessed for the benefit of patients.

WHAT WE HAVE LEARNED

β -blockers continue to be the standard therapy used by most centers to reduce the rate of aortic root enlargement in patients with Marfan syndrome. However, the results of the COMPARE and Lacro trials will contribute greatly to the debate about the use of losartan and other ARBs as an alternative therapeutic choice.

Clearly, additional research is needed on optimizing timing, selection and dosage for different patient groups, but both trials support the view that losartan offers, at the very least, a safe and valid option for MFS patients unable to take β -blockers. It may even be a superior option across the board. Again, combination therapies involving β -blockers and ARBs together may offer yet another beneficial pathway for patients, which should be seriously investigated through new trials.

A recent NEJM editorial by Bowen and Connolly⁸ eloquently sums up the opportunity ahead: "The promise in translational medicine" they conclude "is that knowledge gained through basic research will result in treatments that change the natural history of the disease [Marfan syndrome] so that its clinical manifestations are attenuated or even prevented". Habashi's work gave us a tantalizing glimpse of this as a potential future. Whether losartan eventually provides us with the magic bullet to make this a reality remains to be seen. The suggestion at the present time, however, is that it could at least play an important role in the overall jigsaw.

The authors of the COMPARE and Lacro trials should be congratulated for providing a stimulus, which we hope will lead to further analysis, and further trials in the near future. Every breakthrough in this area provides hope of improved outcomes, and of a better quality of life for people living with Marfan, and possibly with thoracic aortic Aneurysms as well, whether syndromic (e.g. Loeys Dietz syndrome⁹) or otherwise.

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