

Medical Treatment in Marfan Syndrome

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Why do we have to treat?



Flo Hyman (1954 -1986)

Captain of the American Women's
Olympic Volleyball team

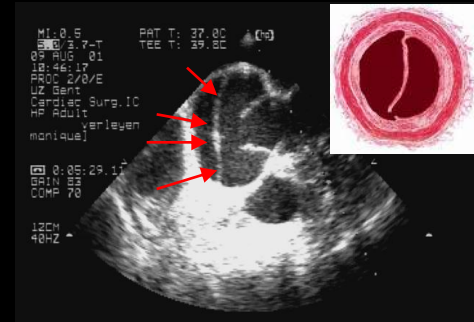
Died during a match in Japan at age

32 > Acute aortic dissection

Post mortem diagnosis of MFS

**70 - 100 % of overall mortality in
MFS is due to cardiovascular
complications**

>> aortic dissection



→ To avoid aortic dissection

Is treatment useful?

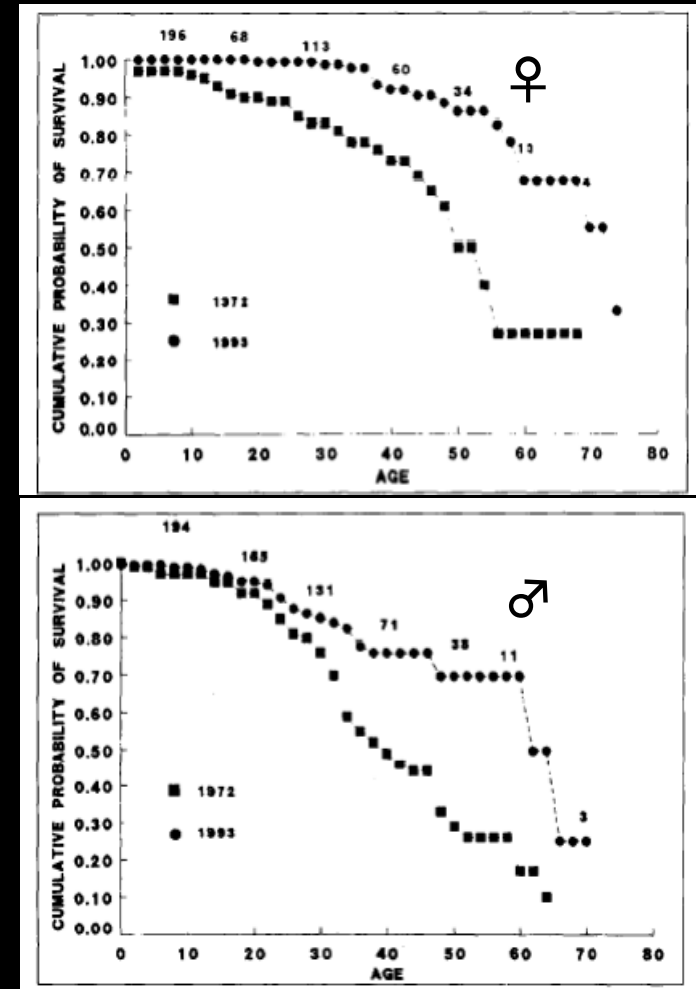
↑ Survival:

Earlier diagnosis

Surgical treatment

Medical treatment

YES



Silverman et al, Am J Cardiol 1995

Current Medical Treatment in MFS

β -blockers

Hemodynamic effect (lower dp/dt)

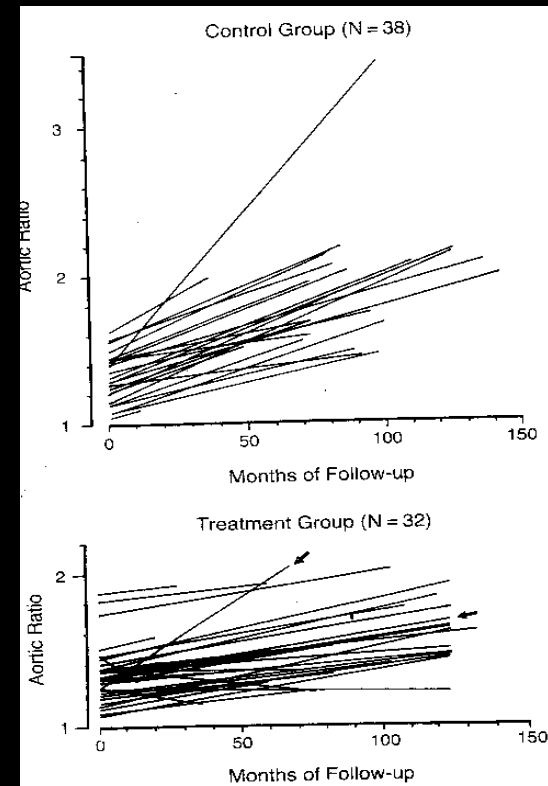
→ Slow rate of aortic dilatation

Optimal result when

- Started early in life
- Aortic diameter $\leq 40\text{mm}$

Non-responders

No hard end-points!



Shores et al, NEJM 1994

Current Medical Treatment in MFS

β -blockers - Pro's and Con's

“Beta-blockade appears to limit aortic dilatation during childhood in patients affected by Marfan syndrome. Therefore this treatment should be recommended as soon as the diagnosis is made”

M Ladouceur Am J Cardiol 2007;99:406-409



“This study suggests that beta-blocker therapy does not significantly alter the rate of aortic root dilatation in children with Marfan syndrome. Based on these data, the recommendation of lifetime beta-blocker therapy instituted during childhood should be reassessed”

S Tierney J Pediatr 2007; 150:77-82

Alternatives?

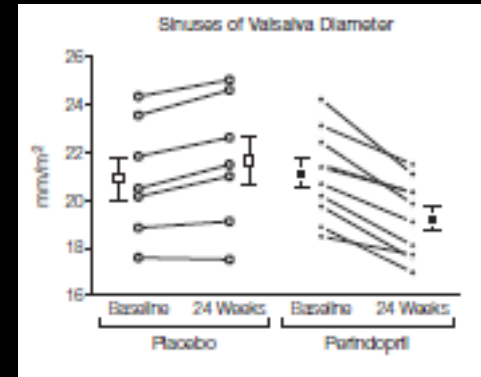
Calcium channel blockers?

Rossi-Foulkes, R., et al., Am J Cardiol, 1999

ACE inhibitors?

Yetman, A. Tet al., Am J Cardiol, 2005

Ahimastos, A.A., et al., Jama, 2007



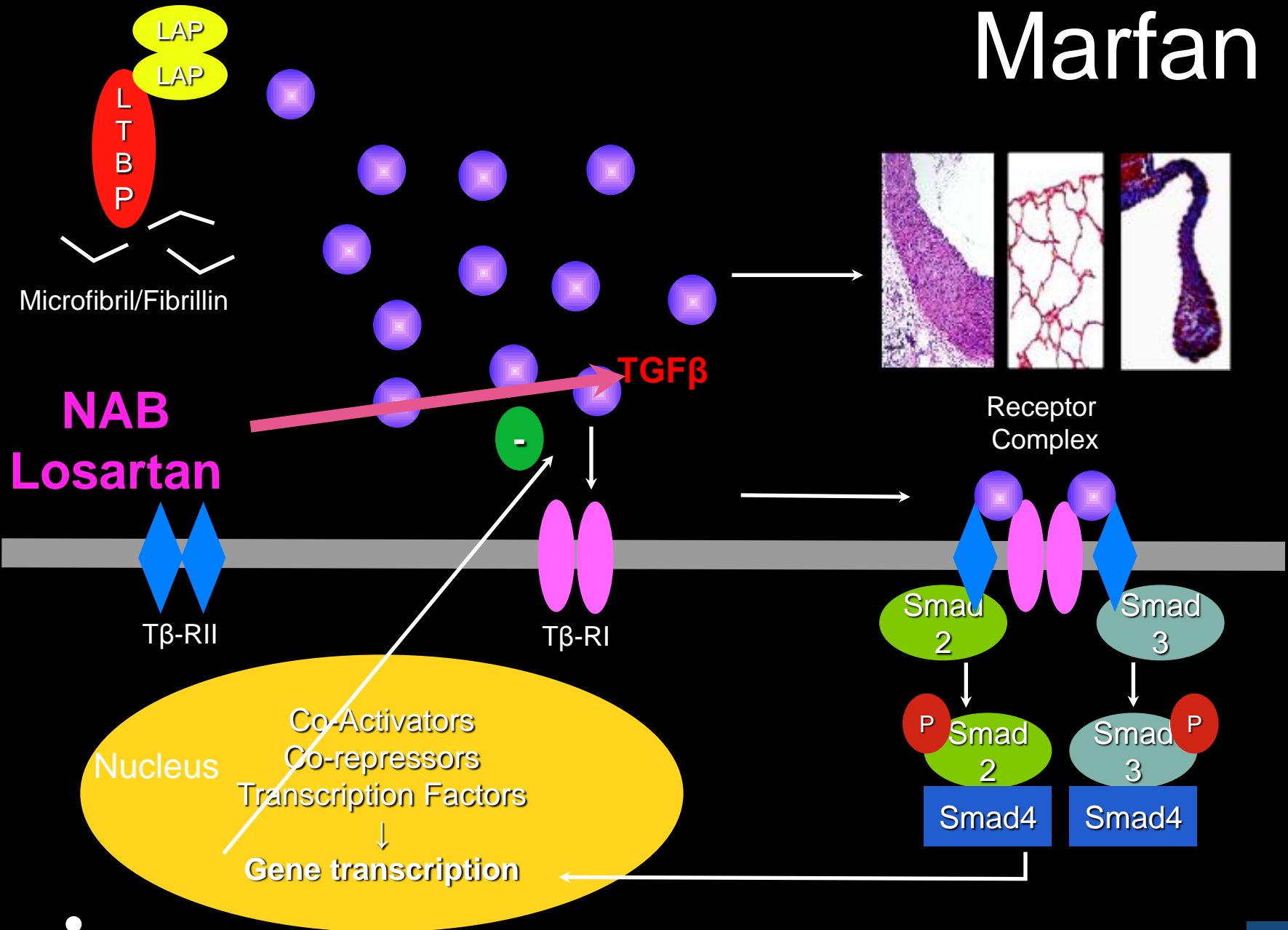
➔ Based on the assumption of similar hemodynamic effects as beta-blockers

Mainly used in patients intolerant for beta-blockers

Alternatives?

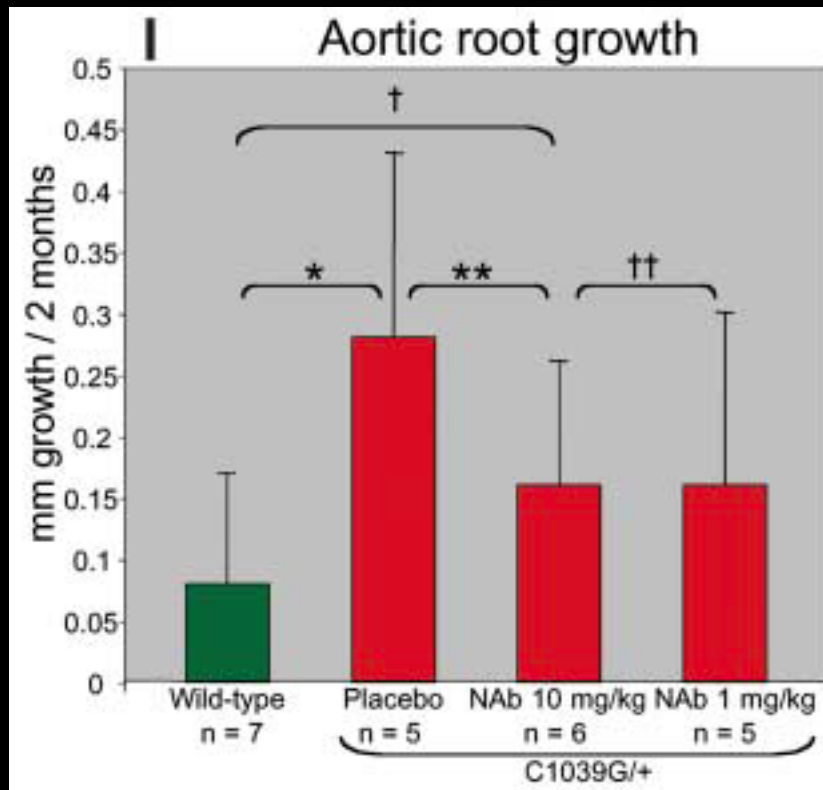


Marfan

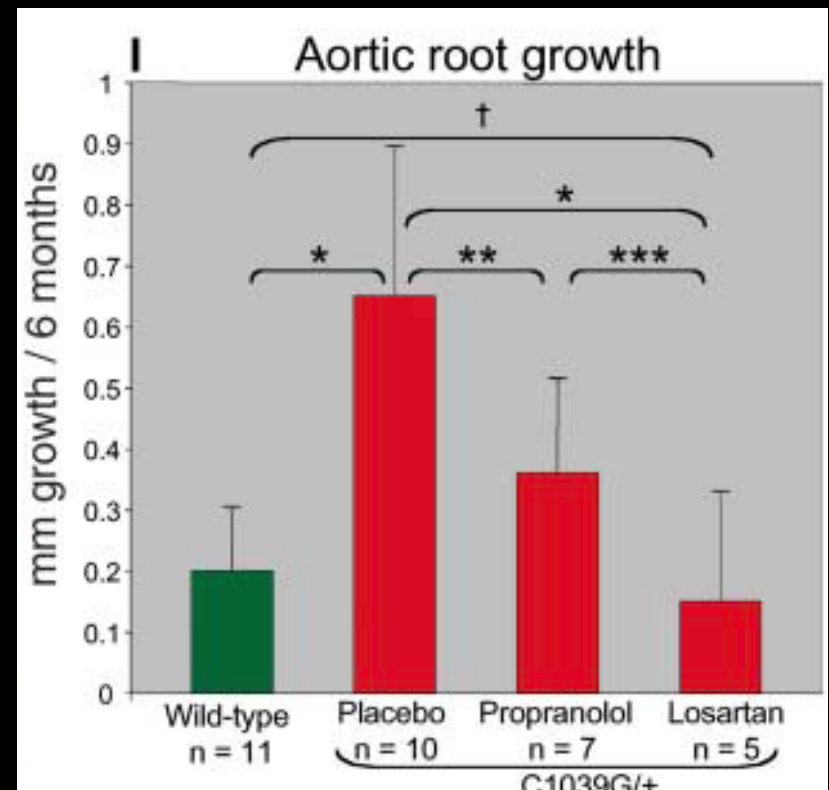


TGF β -inhibition

TGF β -NAB

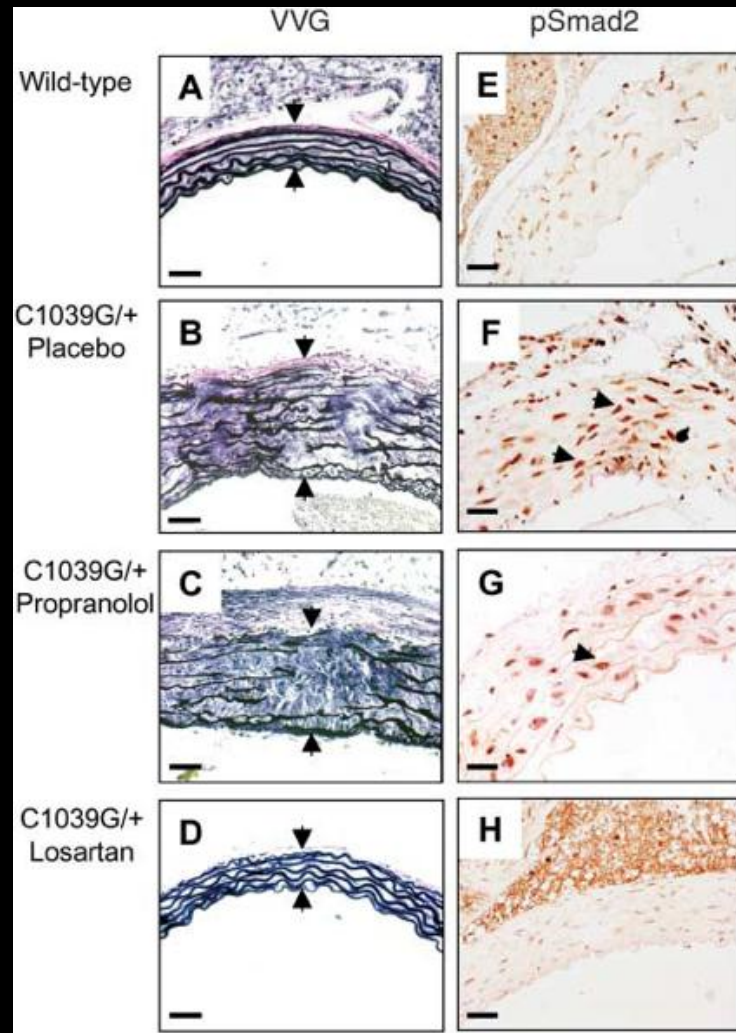


Losartan



Habashi et al, Science 312, 117 (2006)

TGF β -inhibition



New treatment opportunities

Losartan in Humans:

“a small molecule for a large disease”

The NEW ENGLAND JOURNAL of MEDICINE

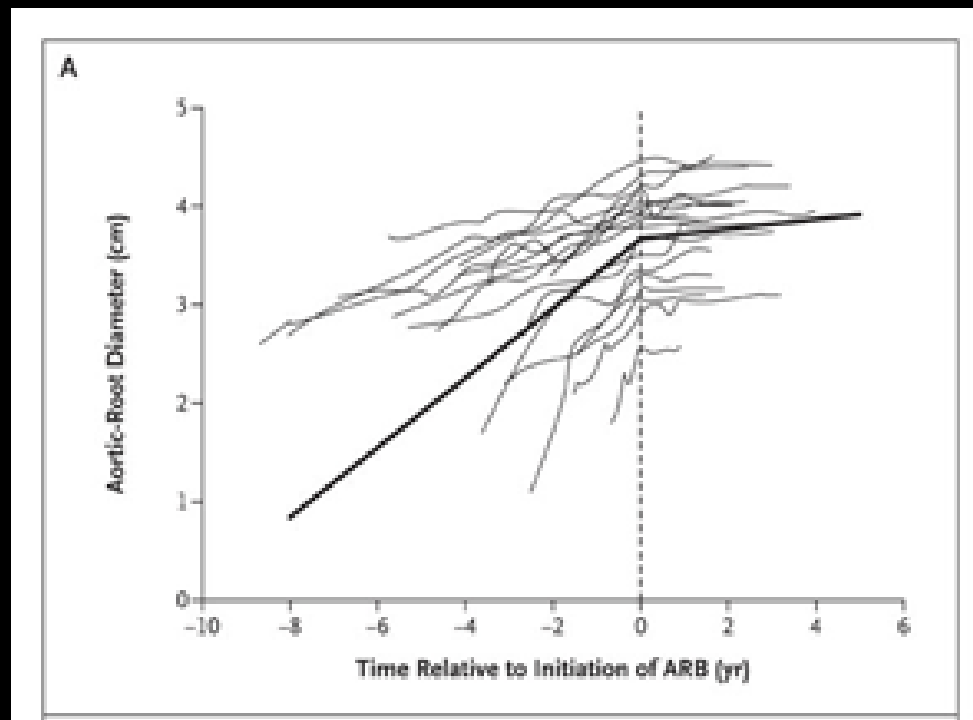
ORIGINAL ARTICLE

Angiotensin II Blockade and Aortic-Root Dilation in Marfan's Syndrome

Benjamin S. Brooke, M.D., Jennifer P. Habashi, M.D., Daniel P. Judge, M.D.,
Nishant Patel, B.A., Bart Loeys, M.D., Ph.D., and Harry C. Dietz III, M.D.

New treatment opportunities

Results: aortic root growth



Losartan Trials

	Study Drug	Design	Target Number	Inclusion
PHN	Atenolol vs Losartan	Single Blind	604	6m-25y Z>3
Boston	Atenolol vs losartan	Double Blind	50	>25
Canada	Atenolol vs losartan	Double Blind	17	12-25
Ghent (B)	Losartan vs Placebo – on BBI	Double Blind	174	>10y Z>2
Amsterdam (NI)	Losartan vs nothing – on BBI	Open Label	300	>18y Z>2
Paris (Fr)	Losartan vs Placebo – on BBI	Double Blind	300	>10y
Barcelona & Madrid	Losartan vs Atenolol	Double Blind	150	6-60y
Pavia (It)	Losartan vs Nobiten vs combined	Open Label	291	>18y Z≥2.5
Taiwan	Losartan vs nothing – on BBI	Open Label		Z>2
United Kingdom	Irbesartan vs placebo	Double Blind	490	6-40y

The Marfan Trialists' Collaboration

A prospective, collaborative meta-analysis of individual patient data from all randomised trials of angiotensin receptor antagonists in Marfan syndrome

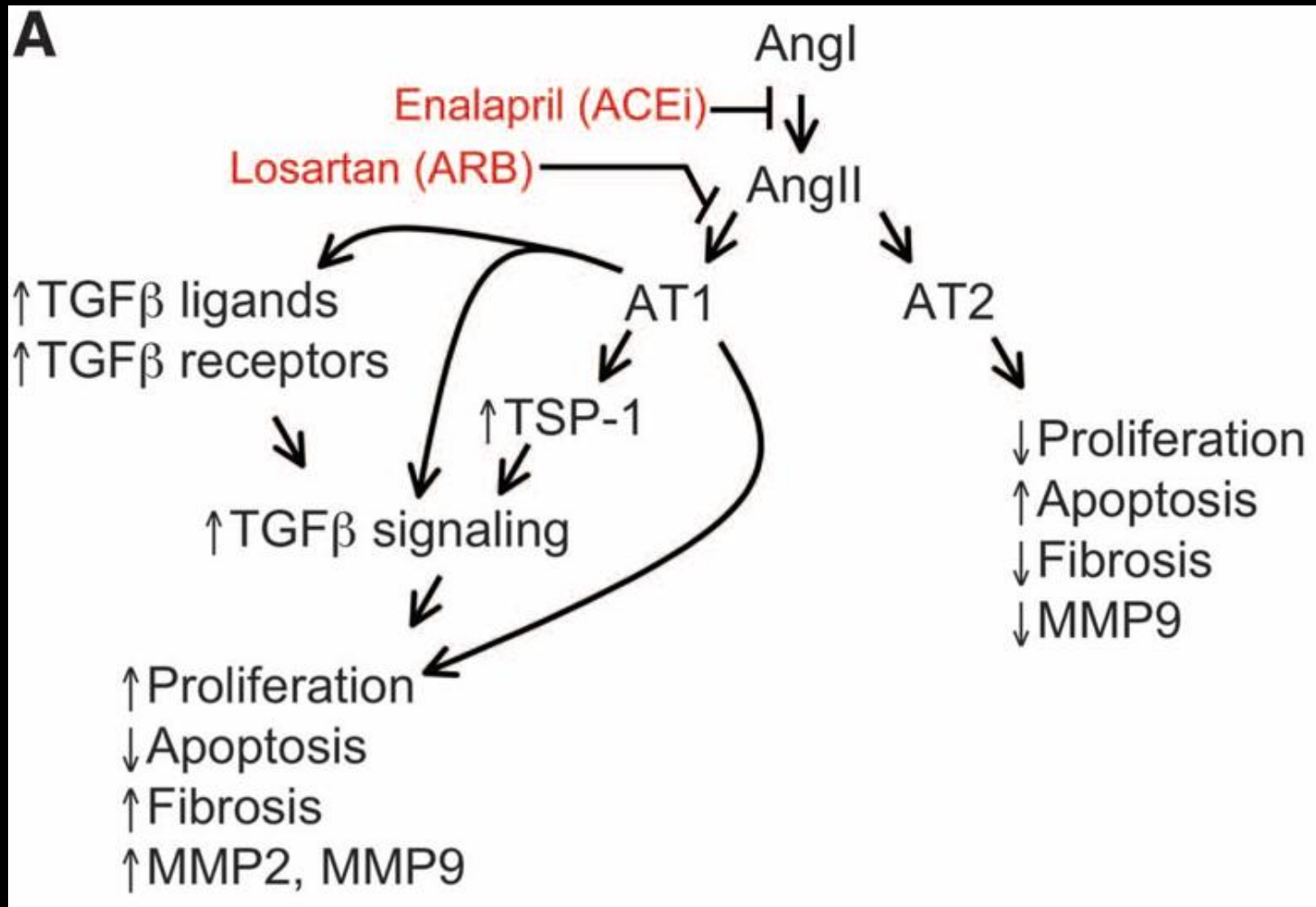
- >2,400 patients: reliable estimate of effect size
- Large enough to explore variation in effect size
- Maximise power to detect clinical endpoint differences
- Estimates of effect sizes for ARBs.....and Beta-blockers

A. Pitcher – Oxford UK

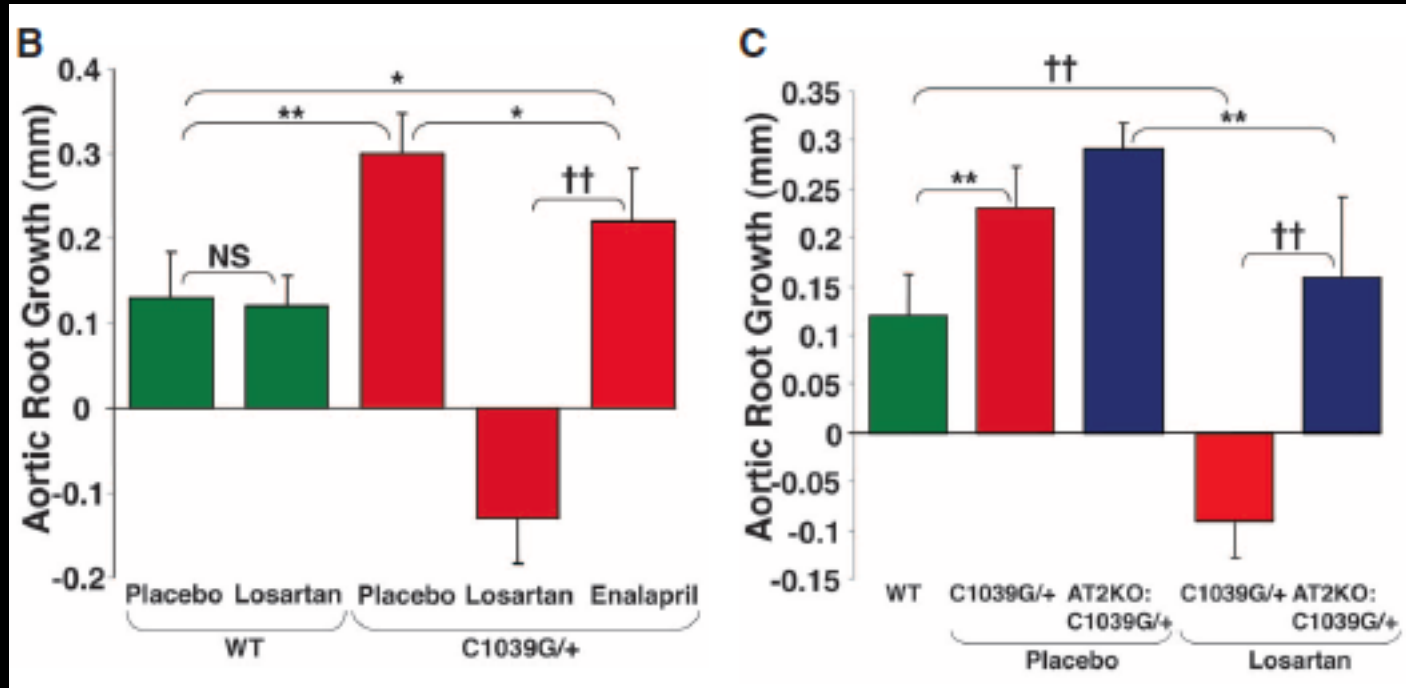
Alternatives?



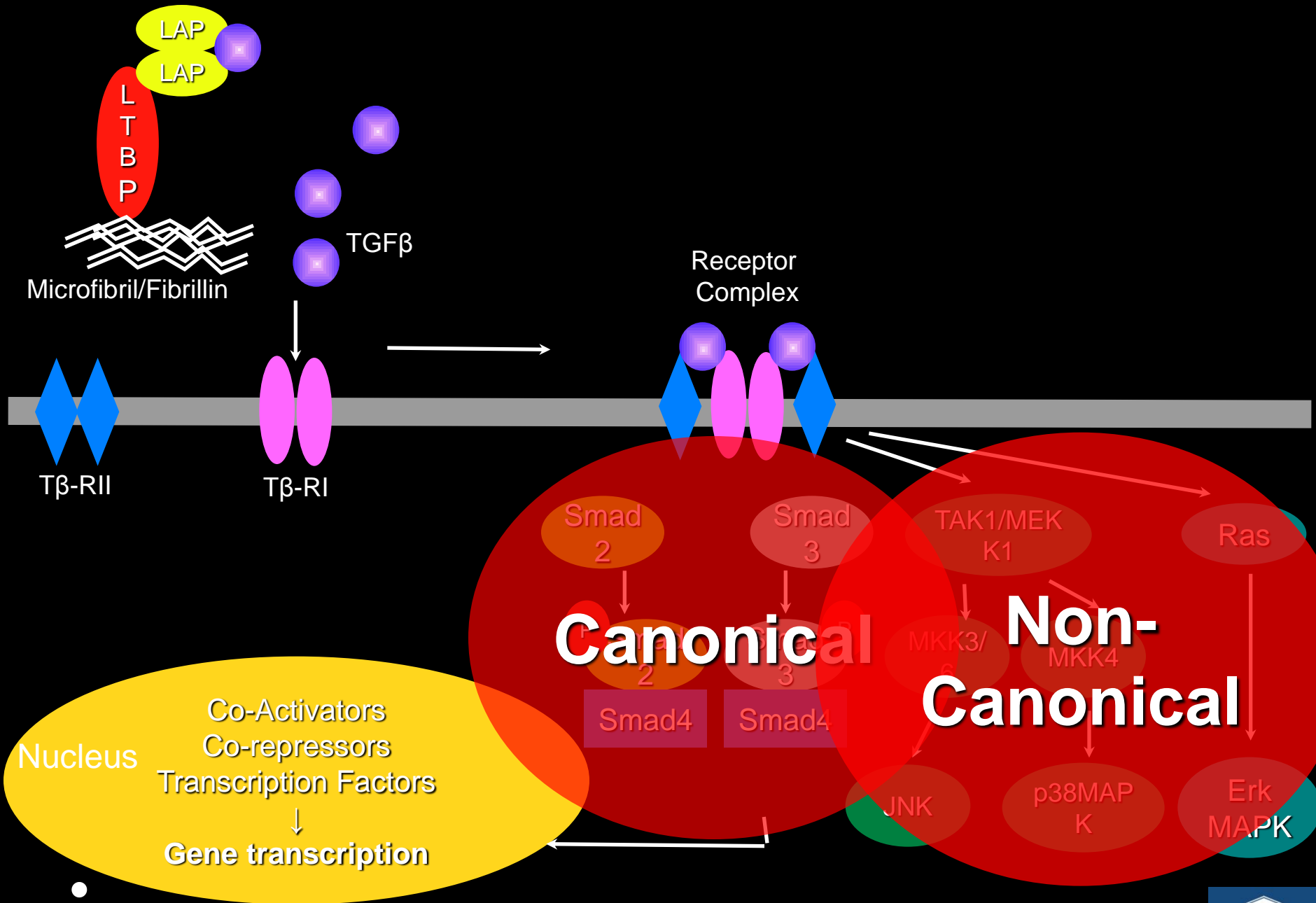
Angiotensin pathway



Angiotensin pathway



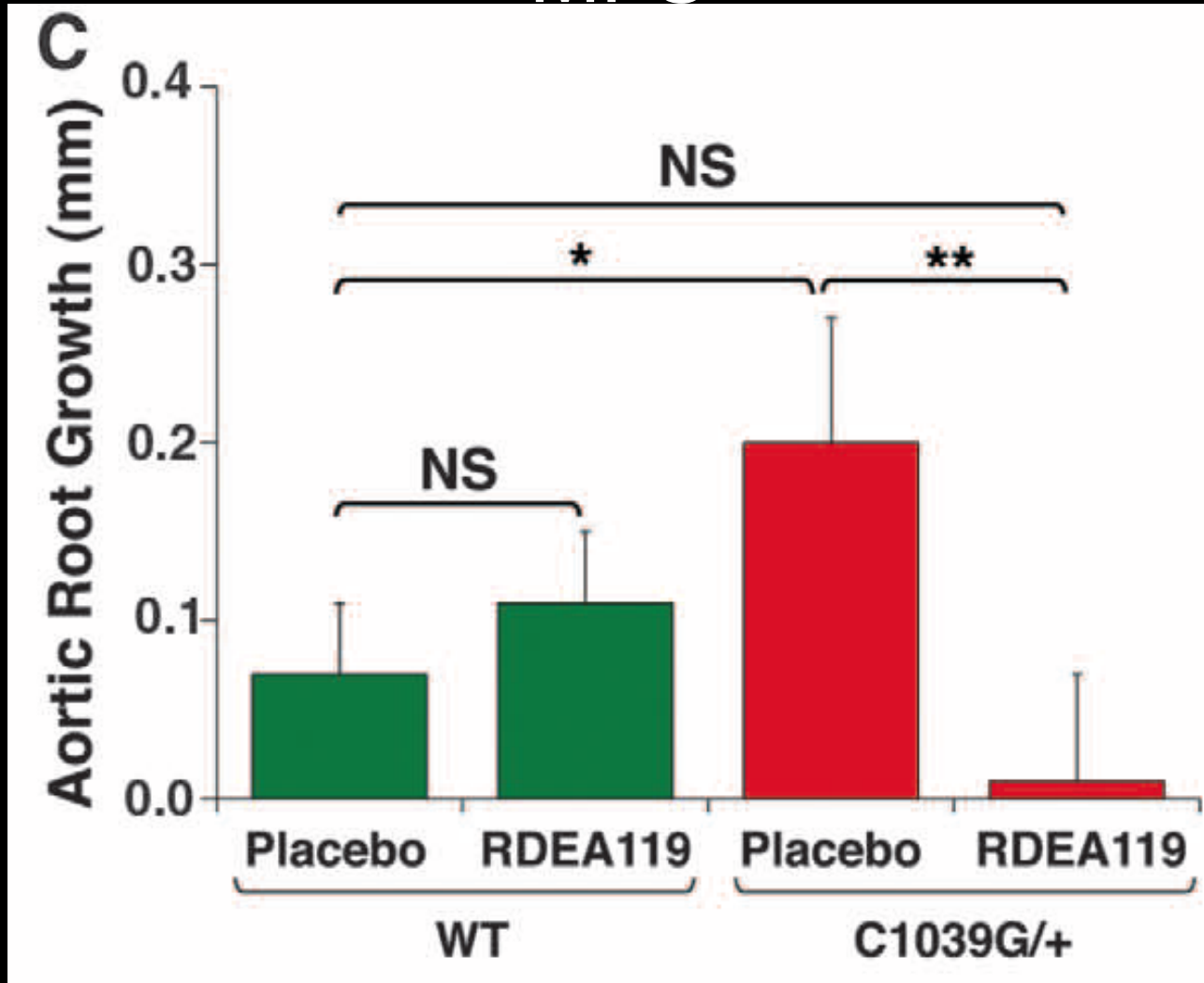
- Losartan uniquely inhibits TGF β mediated activation of ERK, by allowing continued signaling through AT2
- Enalapril limits signaling through both receptors and is less effective



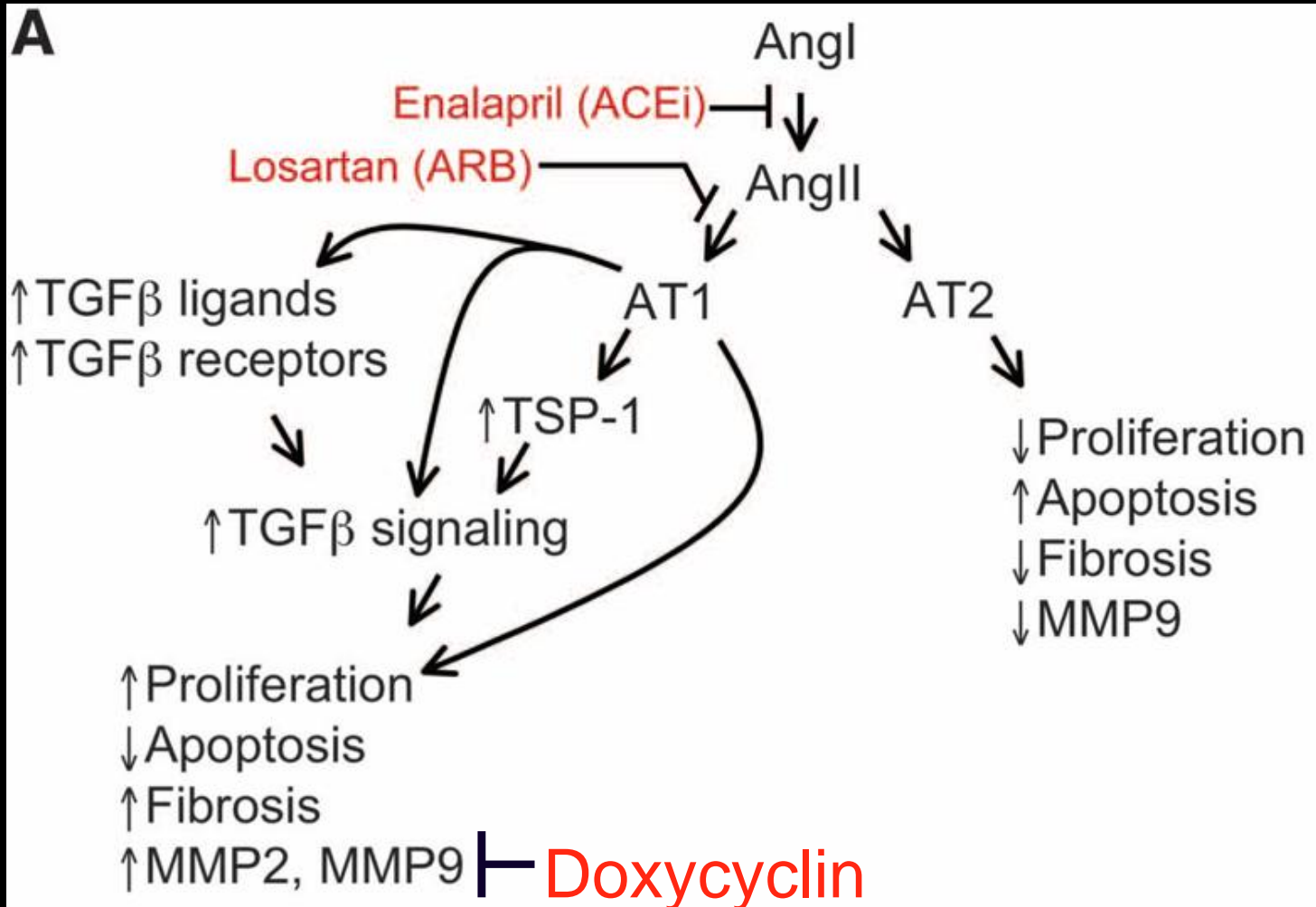
New Treatment Opportunities

- Both pathways (canonical and non-canonical) are activated in a MFS mouse model
- Both are inhibited by R/ directed against TGF β (NAB, losartan)
- Selective ERK inhibition ameliorates aortic growth
- Smad 4 deficiency exacerbates aortic disease
- Non-canonical (Smad-independent) TGF β signaling is a prominent driver of aortic disease
- ERK1/2 or JNK inhibition is a potential therapeutic target

ERK1/2 Antagonist RDEA-119 Arrests Aortic Root Growth in a Mouse Model of MFS



Doxycyclin

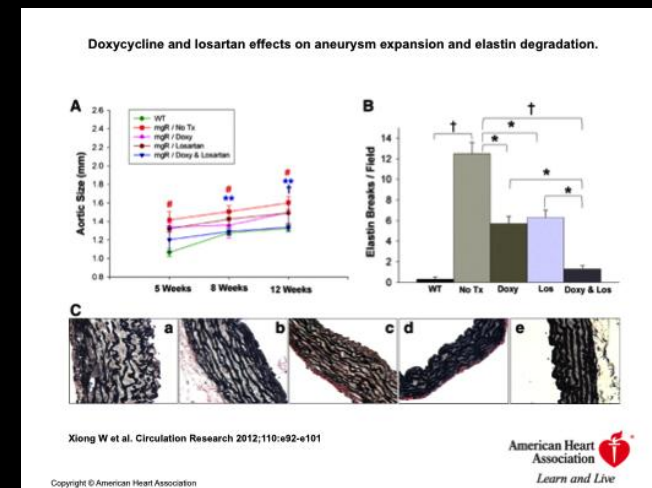
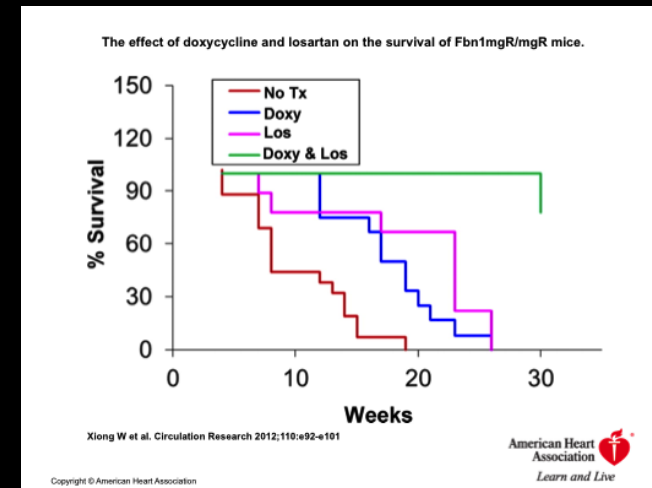


Doxycyclin

- Inhibition of MMP-2 by doxycycline delays the manifestations of MFS, in part, through its ability to decrease active TGF- β and the noncanonical signaling cascade downstream of TGF- β

- Combination therapy with doxycycline and losartan was more effective than either drug alone

➤ targeting TGF- β signaling at different points might be a more effective strategy for inhibiting disease progression.



Conclusions

Treatment of cardiovascular manifestations in patients with Marfan syndrome has a significant effect on life-expectancy

Medical treatment with β -blockers is effective in most patients

Recent insights into the pathophysiology of Marfan syndrome offer promising opportunities for medical treatment via interaction with the TGF β pathway

Large scale trials with losartan are underway and results need to be awaited before treating larger groups of patients