Losartan in Marfan syndrome

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September 15, 2017

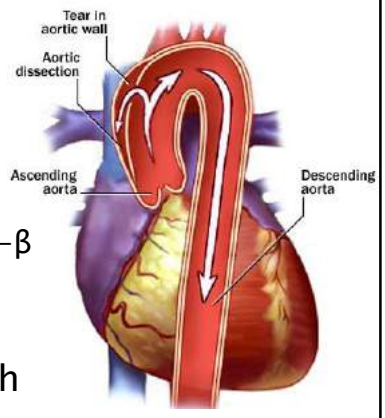
Content of this presentation

1. Why losartan in Marfan syndrome?
2. Overview of losartan studies
3. Variable phenotype and variable treatment response
4. What means dominant negative and haploinsufficiency?
5. To give or not to give losartan?

Why losartan in Marfan syndrome?

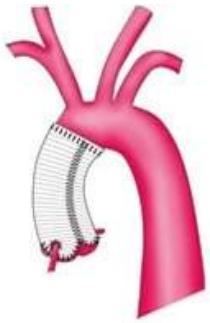
Aortic complications in Marfan

- Connective tissue disorder
- Fibrillin-1 defect
  - Structural disfunction of the aortic media
  - Regulatory dysfunction of TGF-β
- Aortic dilation → aortic dissection and sudden death



Clinical management – surgery

Indications	Class[a]	Level[b]
Patients should undergo surgery when aortic root maximal diameter is:		
• >50 mm	I	C[c]
• 46–50 mm with		
- family history of dissection or	I	C
- progressive dilation >2 mm/year as confirmed by repeated measurement or	I	C
- severe AR or MR or	I	C
- desire of pregnancy	I	C
• Patients should be considered for surgery when other parts of the aorta >50 mm or dilation is progressive	IIa	C



ESC guidelines for the managment of grown-up congenital heart disease 2010

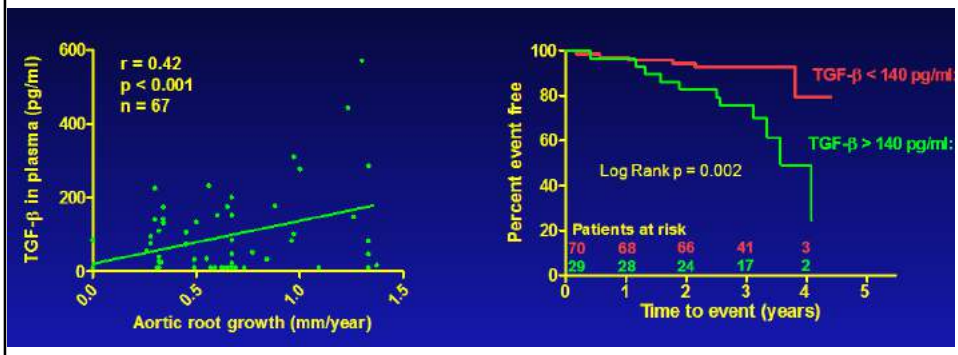
Clinical management – Drugs

Medical therapy

Both medical and surgical therapies have improved life expectancy substantially up to 60–70 years. β-Blockers might reduce the rate of aortic dilation and might improve survival, at least in adults.[63,64] Rigorous antihypertensive medical treatment, aiming at a systolic blood pressure <120 mmHg, and 110 mmHg in patients with aortic dissection, is important. The angiotensin II receptor 1 blocker losartan is potentially useful because it leads to TGF-β antagonism. Clinical trials are presently ongoing to evaluate its beneficial effect. Presently, the standard of care for prevention of aortic complications remains, in most centres, β-blockade. Medical treatment should be continued after surgery.

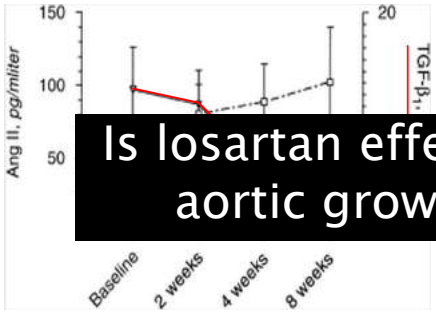
ESC guidelines for the managment of grown-up congenital heart disease 2010

Increased plasma TGF-β in severely affected Marfan patients

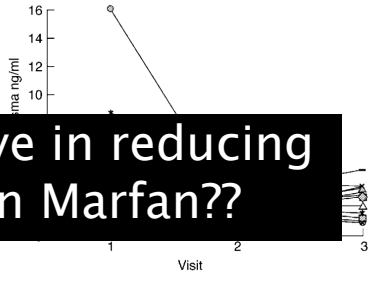


Franken R. et al, Int J Cardiol. 2013

Losartan reduces TGF-β levels



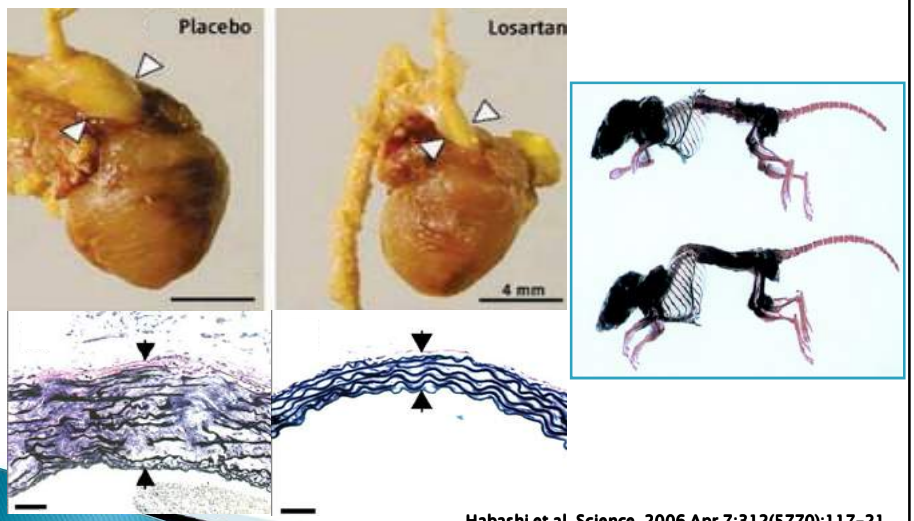
Campistol JP, et al. Nature 1999



Esmatjes E, et al. Nefrol Dial Transplant 2001

Is losartan effective in reducing aortic growth in Marfan??

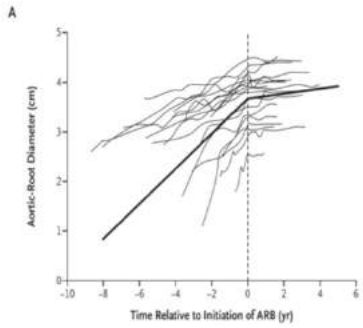
Beneficial effects of losartan in a Marfan mouse model



Habashi et al. Science. 2006 Apr 7;312(5770):117-21.

Beneficial effects of losartan on aortic growth in children

in 18 children (retrospective)



Brooke BS et al, NEJM 2008

Multiple randomized controlled trials

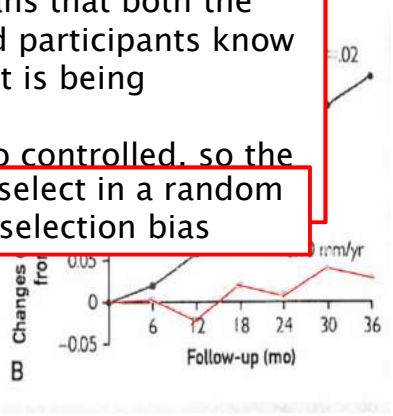
Overview of losartan studies

1. Mayo trial in Taiwan

- Open label, pilot
- Randomisation:
  - Children with Ma
  - Losartan + BB (n
  - 35 r
- 33% (3 pt) L + BB
  - reduction of aortic diameter!
- No difference in aortic stiffness
- Safe

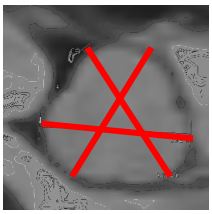
Open label means that both the researchers and participants know which treatment is being administered.
It is not placebo controlled, so the

Randomisation means to select in a random manner in order to avoid selection bias

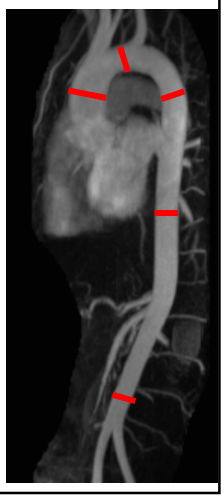


Chiu HH et al, Mayo Clin Proc 2013

2. Compare trial – methods



In 4 Dutch Marfan centres in the Netherlands
Open label, blinded endpoints



1) Aortic dilation rate at any level
2) mortality; aortic surgery; aortic dissection

- Randomisation:
  - Adult Marfan patients, max 1 operation
  - Losartan 100 mg (n=116) vs. no losartan (n=117)
  - Previously prescribed medication was continued

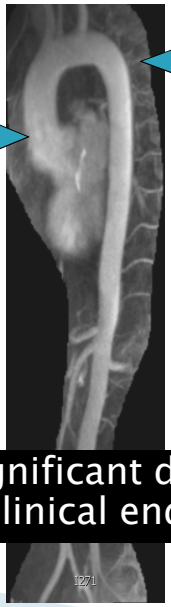
MRI scan at inclusion and after 3 years

Trials. 2010 Jan 12;11:3. doi: 10.1186/1745-6215-11-3.

Compare trial – results

Unoperated patients

Operated patients



a significantly lower aortic root dilatation rate

a significantly lower dilatation rate of aortic arch

no significant differences beyond the root in the to population

no significant differences in clinical endpoints

Groenink M, Franken R, et al, EHJ 2013

3. Pediatric Heart Network

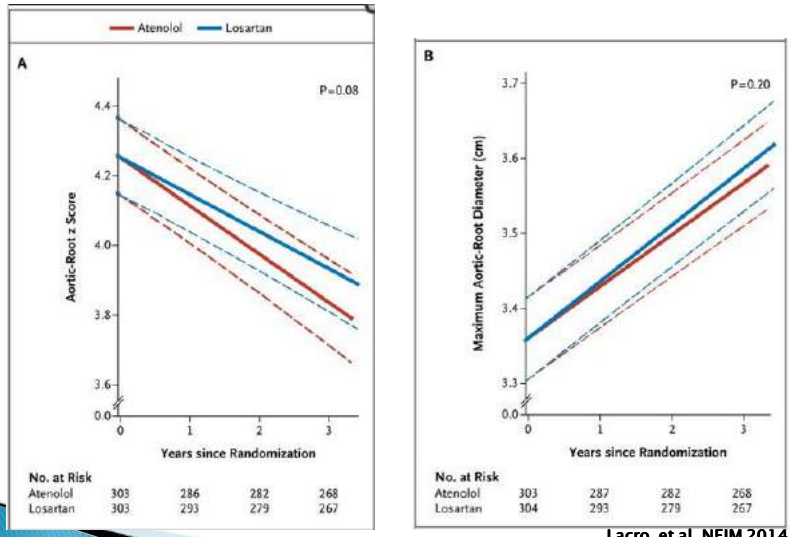
In USA, Double blinded, using echocardiography, 3 yrs FU

1) Aortic dilation rate at the root (diameter and Z-score)

- Randomisation:
  - Marfan children (0,5 – 25 years)
  - Losartan max 100 mg (=85 mg, n=305) vs. atenolol max 250 mg (=150 mg, n=303)

Lacro, et al, NEJM 2014

USA – Results



Lacro, et al, NEJM 2014

4. Sartan trial

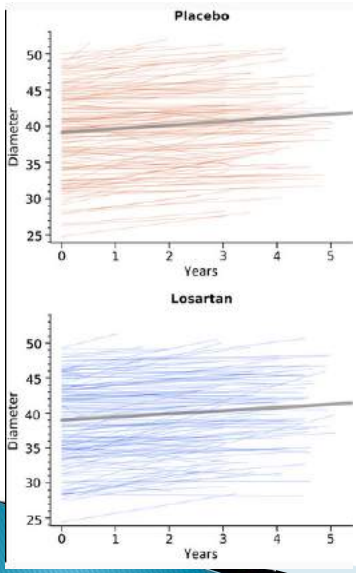
In France, Double blinded, using echo a 6 mo, 3,5 yrs FU

1) Change in Z-score per year at the aortic root

- Randomisation:
  - Marfan patients (0,5 – 25 years)
  - Losartan vs no losartan on top of standard care (BB)
  - Losartan 50-100 mg (n=146) vs. no losartan (n=146)

Milleron, et al, EHJ 2015

Sartan – results



Placebo 0.51 mm/year
vs
Losartan 0.44 mm/year
(p = 0.37)

NB: in patients with *FBN1* mutation

Placebo 0.51 mm/year
vs
Losartan 0,40 mm/year
(p = not significant)

Milleron, et al, EHJ 2015

5. Spain

- randomised, double-blind study
- MRI, 36 months

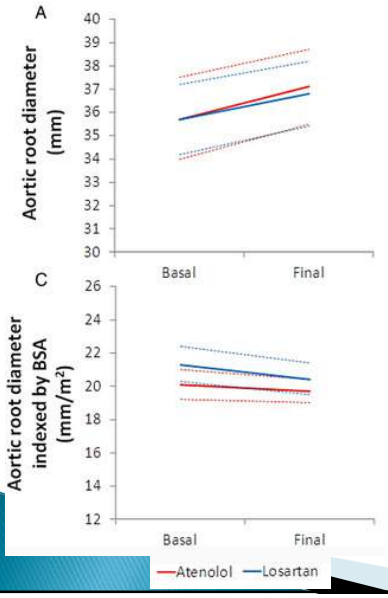
- 140 MFS patients (5-60 years)
- maximum aortic diameter <45 mm

- losartan (n = 70) vs atenolol (n = 70)
- maximum of 1.4 mg/kg/day or 100 mg/day

- change in aortic root maximum diameter and indexed by BSA

Forteza, et al. EHJ 2016

Results Spain



Losartan 1.1 mm/3year
vs
Atenolol 1.4 mm/3year
(p=0.382)

Losartan -0.9 mm/m^2
vs
Atenolol -0.4 mm/m^2
(p=0.092)

Forteza, et al. EHJ 2016

6. Belgium + results

- double-blind, randomized placebo-controlled
- 22 patients, 3 years, echo
- both groups (median 1 mm, IQR [−1–1.5] and 1 mm, IQR [−0.25–1] in the losartan and placebo group, respectively, p = 1).

Acta Cardiol. 2017 Jun 28:1-9. doi: 10.1080/00015385.2017

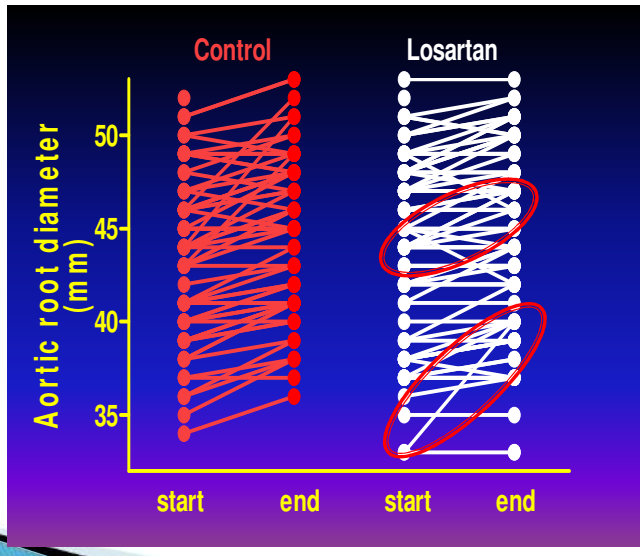
Country	Design	Treatment	FU	Age (years)	Number	Imaging	AoD (mm/yr)	Death and dissection
Taiwan	OL, BE	L + BB vs BB	35	13 ± 6	29 (28)	US	0.10 vs 0.89 (p=0.02)	1 vs 0
Holland	OL, BE	L vs no L	37	38 (>18)	233 (145)	MRI/US	0.26 vs 0.45 (p=0.014)	0 vs 2
USA	DB	L vs BB	36	11(0-25)	608 (535)	US	0.75 vs 0.69 (p=0.20)	3 vs 0
France	DB	L vs placebo	42	30 (>10)	297 (292)	US	0.44 vs 0.51 (p=0.37)	1 vs 5
Spain	DB	L vs BB	36	5-60	150	MRI/US	0.37 vs 0.47 (p=0.326)	1 vs 4
Belgium	DB	L vs placebo	36	>10	22	US	0.33 vs 0.33 (p=1.0)	0 vs 1
UK	DB	I vs placebo	48	6-40	490	US		
Italy	OL, BE	L vs BB vs L+BB	48	1-55	291	US		

AoD: aortic root dilation rate, BB: beta-blocker, BE: blinded endpoints, FU: follow-up (in months), I: irbesartan, L: losartan, OL: open label

Franken R, Mulder BJM, Nature Reviews 2016

Variable phenotype and variable treatment response

Heterogeneous effect of losartan



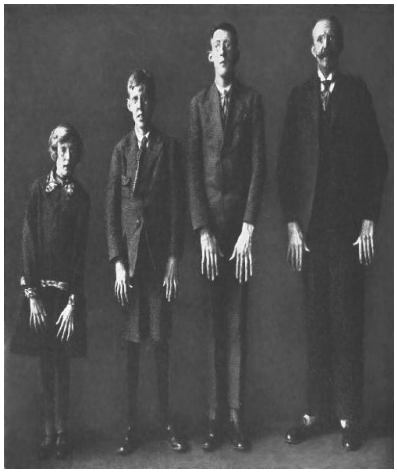
Groenink M, Franken R, et al, EHJ 2013

Possible explanations

- Study design: placebo vs open label
  - In favour of losartan
- Losartan on top of or instead of BB
- Differences in dosis of BB (250 mg!!!)
- MRI vs echo
  - More inter/intraobserver variability in echo
- Differences in age and sample sizes

Highly variable phenotypic expression

- Age of onset
- Various manifestations
- Responsiveness to treatment
- Different countries
- Families sharing the same mutation



In 90% of Marfan patients an *FBN1* mutation is found

Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

In the absence of family history:
(1) Ao (Z ≥2) AND EL=MFS*
(2) Ao (Z ≥2) AND *FBN1*=MFS
(3) Ao (Z ≥2) AND Syst (≥7pts)=MFS*
(4) EL AND *FBN1* with known Ao=MFS

In the presence of family history:
(5) EL AND FH of MFS (as defined above)=MFS
(6) Syst (≥7 pts) AND FH of MFS (as defined above)=MFS*
(7) Ao (Z≥2 above 20 years old, ≥3 below 20 years) +FH of MFS (as defined above)=MFS*

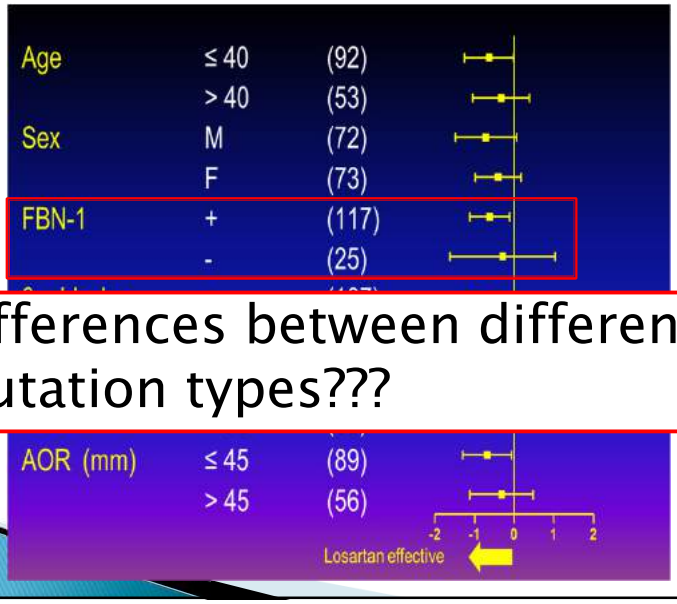
Box 2 Scoring of systemic features

- Wrist AND thumb sign — 3 (wrist OR thumb sign — 1)
- Pectus carinatum deformity — 2 (pectus excavatum or chest asymmetry — 1)
- Hindfoot deformity — 2 (plain pes planus — 1)
- Pneumothorax — 2
- Dural ectasia — 2
- Protrusio acetabuli — 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis — 1
- Scoliosis or thoracolumbar kyphosis — 1
- Reduced elbow extension — 1
- Facial features (3/5) — 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae — 1
- Myopia > 3 diopters - 1
- Mitral valve prolapse (all types) — 1

Maximum total: 20 points; score ≥7 indicates systemic involvement; US/LS, upper segment/lower segment ratio.

Loeys BJ, et al. J Med Genet. 2010

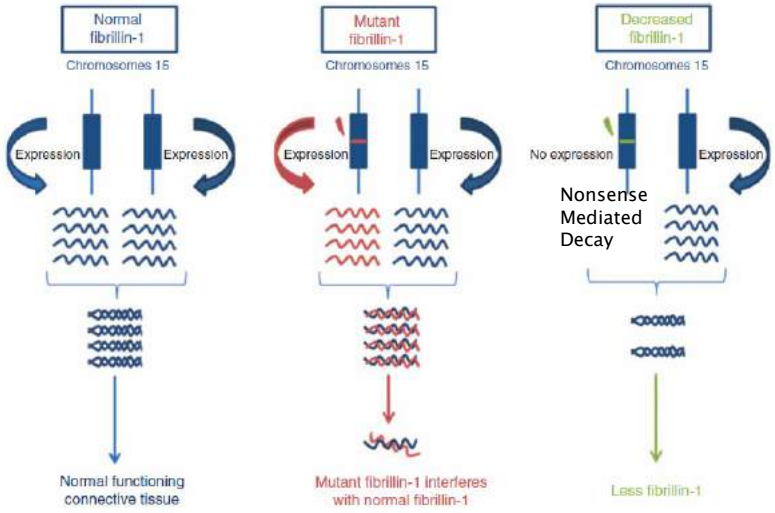
Beneficial effect of losartan



Differences between different mutation types???

What means dominant negative and haploinsufficiency?

dominant negative vs haploinsufficiency

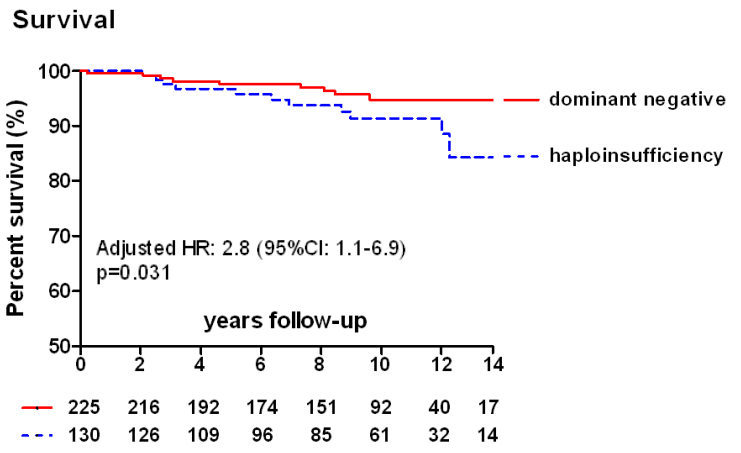


Franken R, Expert Opin Orphan Drugs 2014 Aug;2(10):1–14.

Nonsense mediated decay

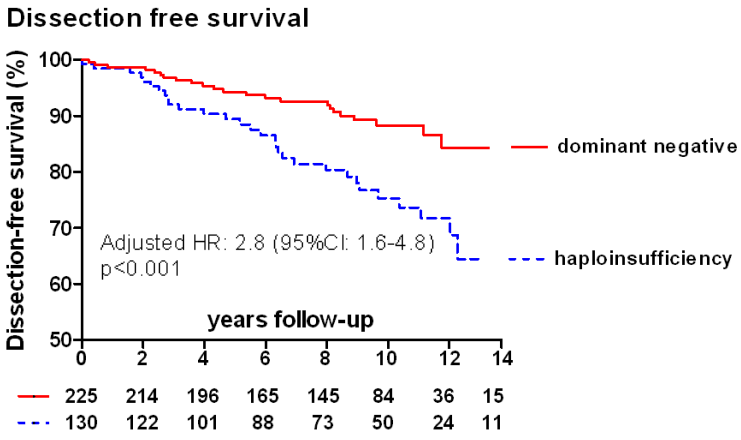
- A surveillance pathway that exists in all eukaryotes.
- Function: **reduce errors in gene expression** by eliminating mRNA transcripts that contain premature stop codons
- If a **premature stop codon** is detected then the mRNA transcript is signaled for degradation.

Haploinsufficiency leads to increased mortality rate



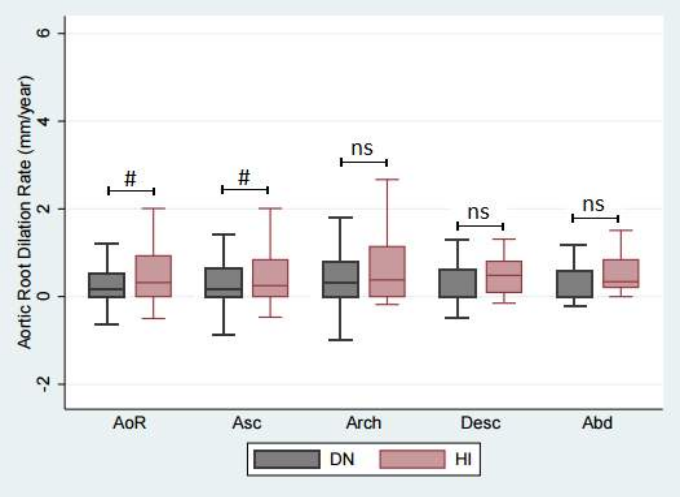
Franken R. Eur Heart J. 2016, Nov 14;37(43):3285-3290

Haploinsufficiency leads to a more severe phenotype



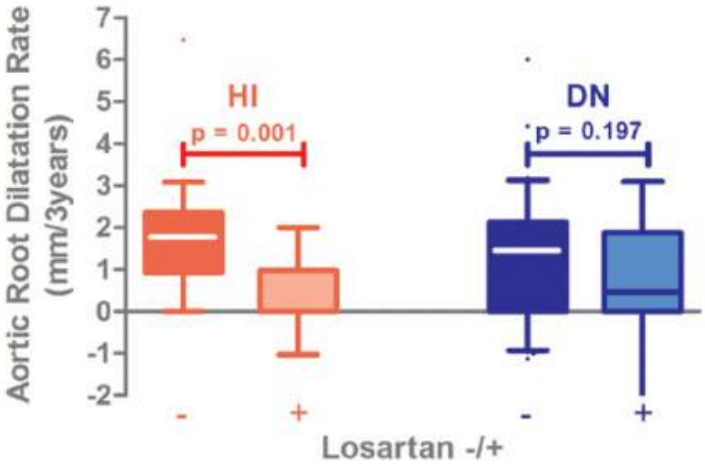
Franken R. Eur Heart J. 2016, Nov 14;37(43):3285-3290

Validation cohort in Spain
HI aorta dilates faster than DN



Franken R. Heart. 2017

Losartan effect HI vs DN



Franken R. Circ Cardiovasc Genet 2015 Apr;8(2):383-8.

To give or not to give losartan?

Meta-analysis

- Six randomized trials with 1398 subjects
- Losartan versus no losartan

- losartan therapy decreased the rate of aortic dilation (−0.13 with 95% CI −0.25 to 0.00, p = 0.04).
- No effect on clinical events (OR= 1.04 with 95% CI of 0.57–1.87).

Gao, et al, IJC 2016

Conclusion

- Losartan is not more effective in reducing aortic dilation rate than a high dosage BB
- Losartan on top of (a low dosage) BB seems to be more effective than a low dosage of BB
- Even when added to BB, losartan is well-tolerated and safe
- Losartan can be administered as an alternative of BB when BB is not tolerated
- Not the solution we all hoped for, possibly due to genetic differences

Thank you

Questions: r.franken@amc.uva.nl