# Beta-blockers and ARBs: friends or competitors?

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# Why competitors ?

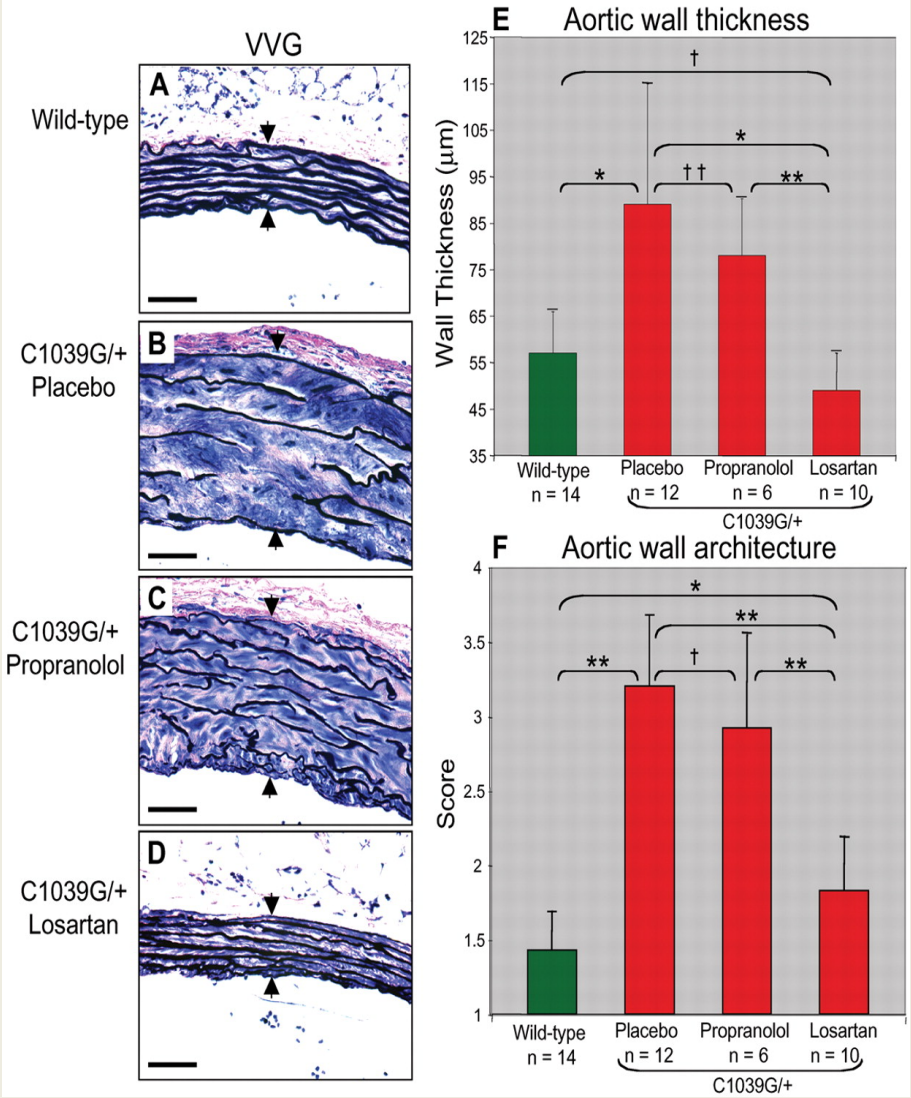
Positive hemodynamic effect

- Bradycardia (less cardiac ejection): BB
- Aortic compliance : decreased rebound wave: ARB
- Decreased blood pressure : BB and ARB

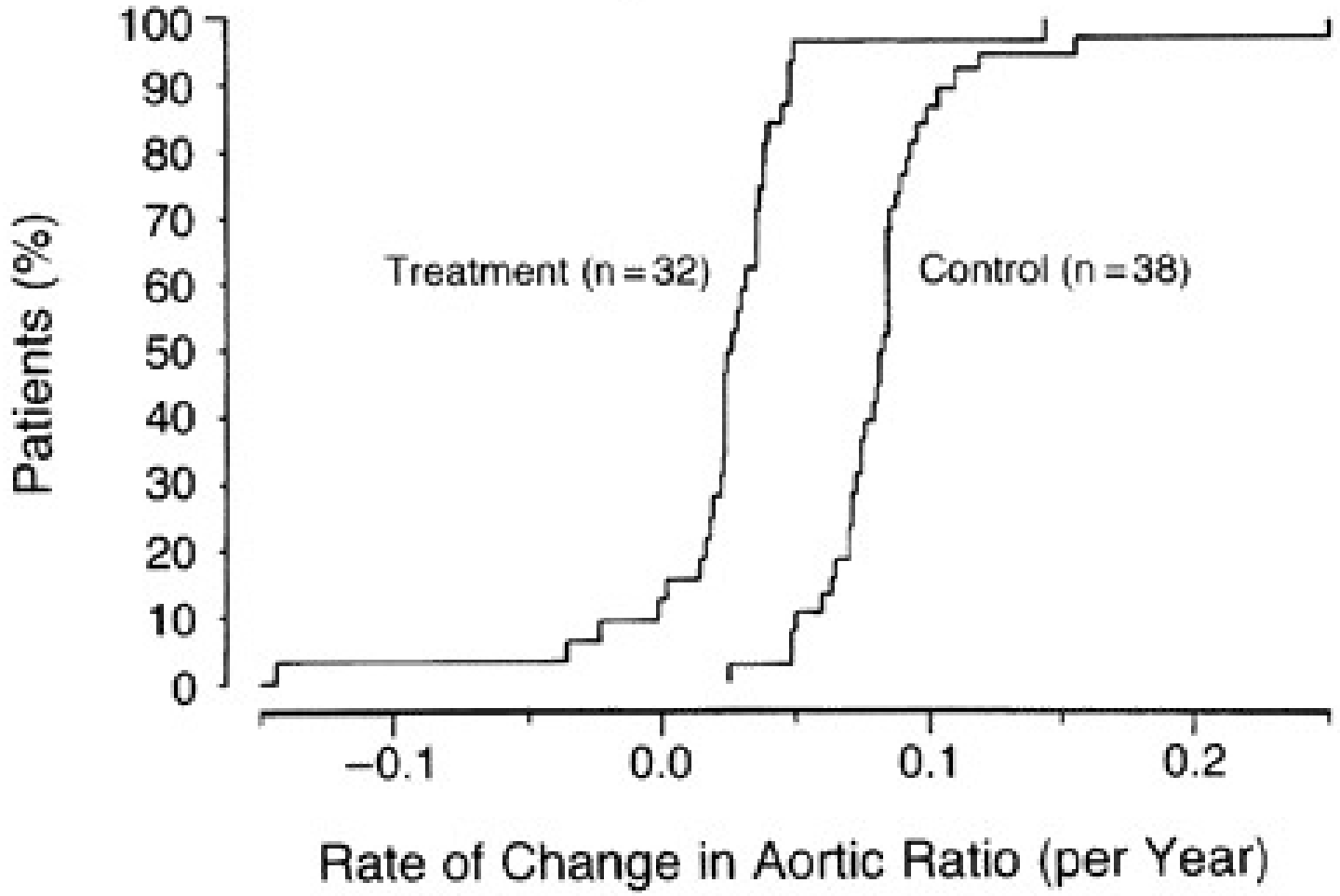
Side effect

- Renal action : ARB
- Asthma, fatigue, libido, bradycardia: BB
- Blood pressure

# Habashi JP Science 2006;312:117



# NEJM


100
90
80
70
60
50
40
30
20
10
0
Patients (%)
Treatment (n = 32)
Control (n = 38)
−0.1
0.0
0.1
0.2
Rate of Change in Aortic Ratio (per Year)

# Decrease in BP Shores

| Characteristic | Control (N = 38) | | Treatment (N = 32) | |
|---|---|---|---|---|
| | Male (N = 19) | Female (N = 19) | Male (N = 20) | Female (N = 12) |
| Initial aortic diameter | | | | |
| Measured (mm) | 31.1±6.9 | 29.4±6.8 | 36.7±9.3† | 31.2±5.3 |
| Expected (mm) | 24.6±3.9 | 23.3±3.2 | 25.5±4.1 | 23.3±4.2 |
| Ratio | 1.27±0.19 | 1.27±0.26 | 1.43±0.26 | 1.37±0.20 |
| No. with mitral-valve prolapse | 12 | 14 | 12 | 10 |
| No. with mitral regurgitation | 5 | 5 | 5 | 7 |
| Blood pressure (mm Hg) | | | | |
| At entry | 118/72±14/11 | 110/70±13/10 | 115/73±13/10 | 115/69±14/13 |
| During optimal dose | — | — | 108/66±15/11‡ | 108/63±8/7§ |
| Heart rate (beats/min) | | | | |
| At entry | 78±18 | 79±17 | 74±9 | 84±14 |
| During optimal dose | — | — | 59±9.1¶ | 59±8¶ |
| Systolic time interval | | | | |
| At entry | 0.38±0.22 | 0.36±0.18 | 0.39±0.17 | 0.35±0.15 |
| During optimal dose | — | — | 0.56±0.22¶ | 0.47±0.26¶ |

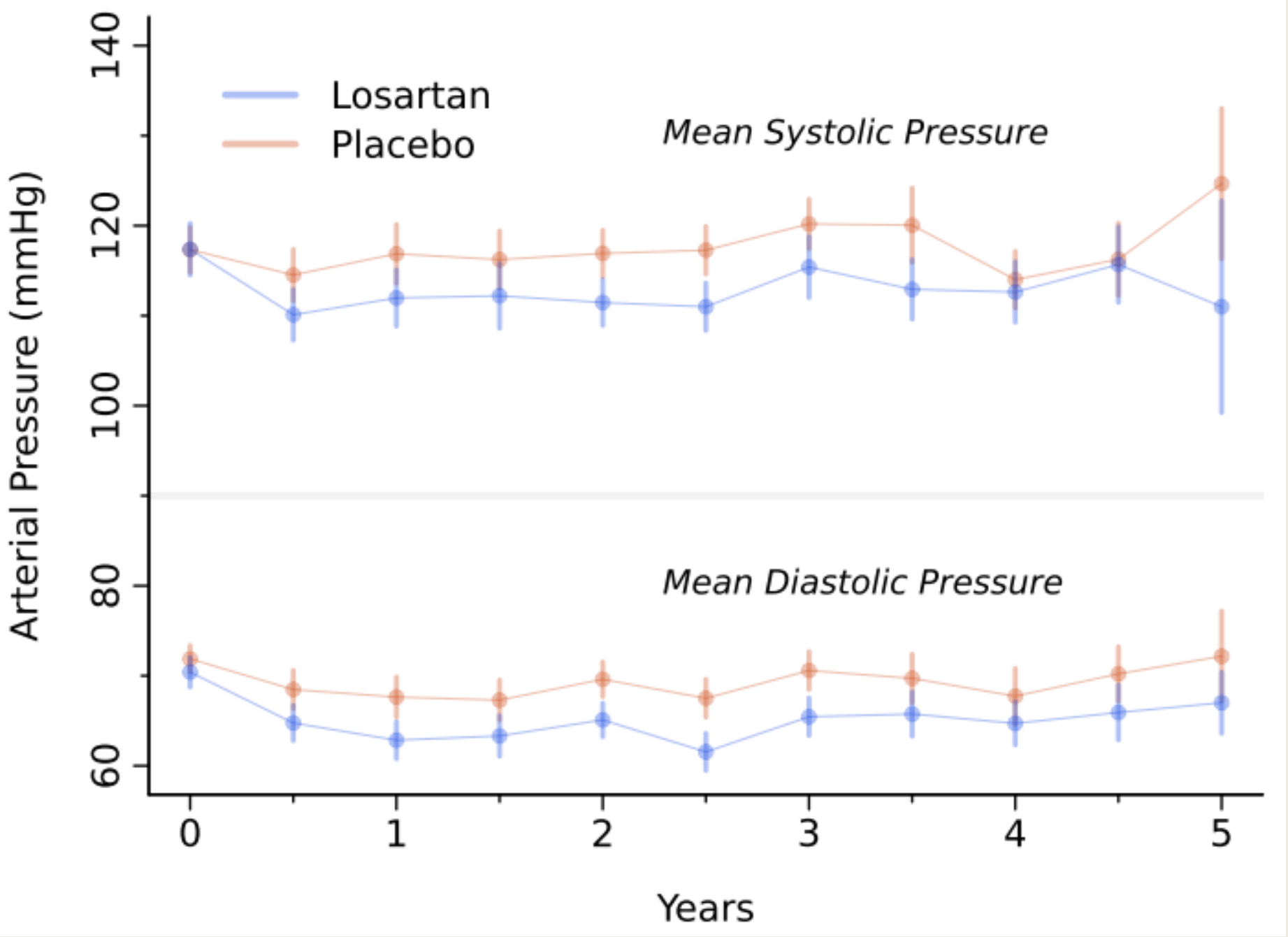
*Plus–minus values are means ±SD.

†$P<0.05$ for the comparison with the male controls.

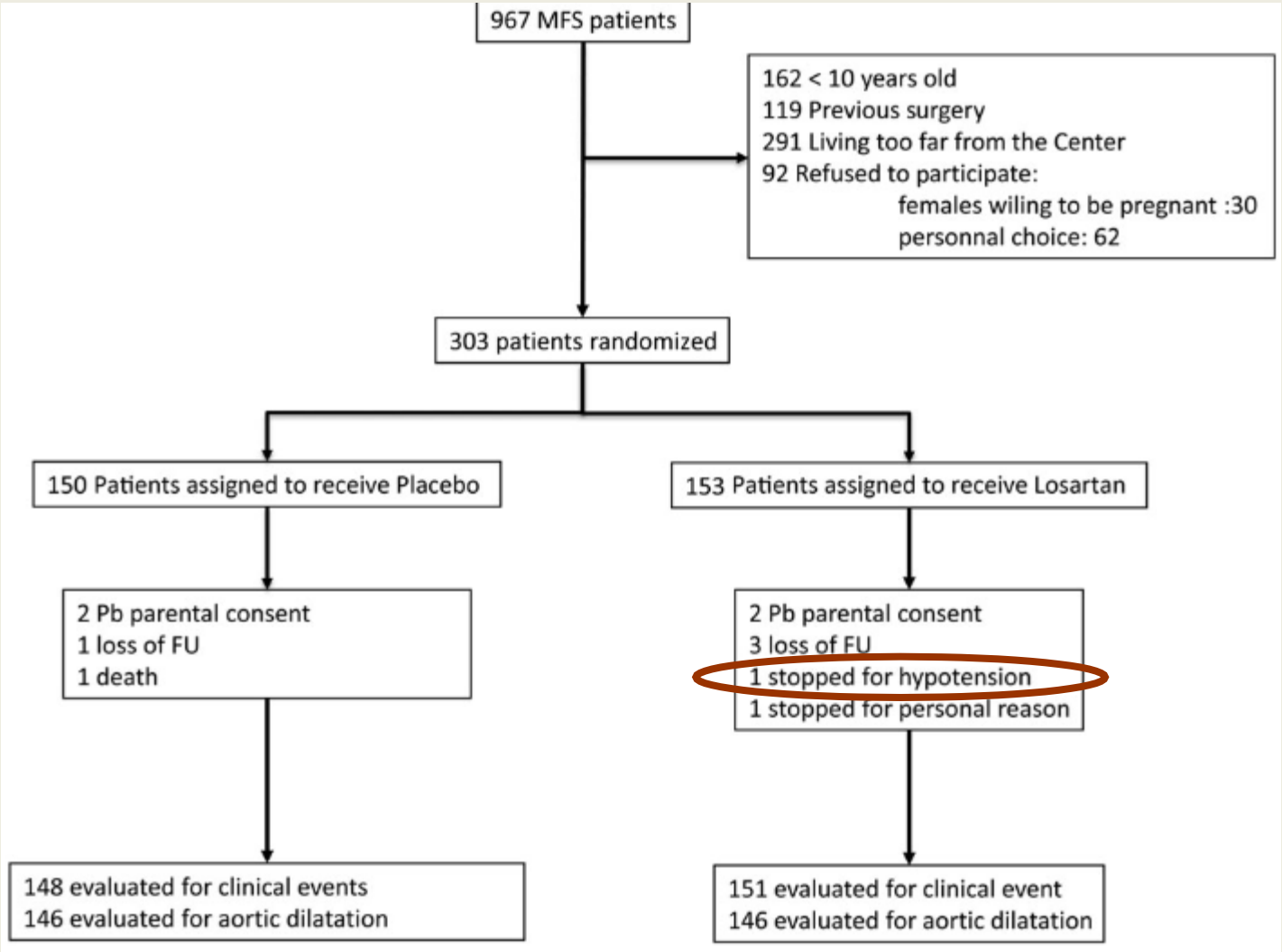
‡$P = 0.006$ for the comparison with the mean systolic pressure at entry and $P = 0.045$ for the comparison with the mean diastolic pressure at entry.

§$P = 0.06$ for the comparison with the mean systolic pressure at entry and $P = 0.051$ for the comparison with the mean diastolic pressure at entry.

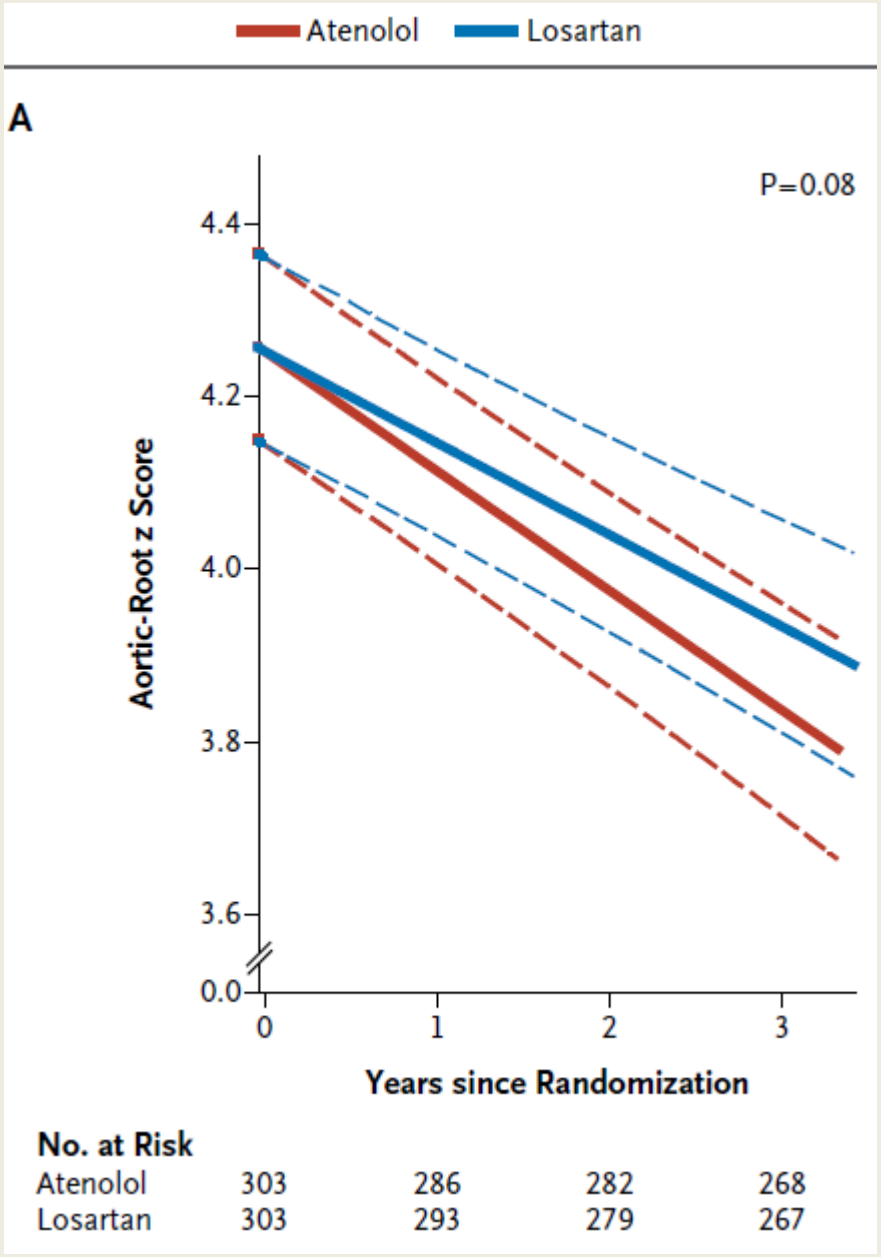
¶$P<0.001$ for the comparison with the value at entry.

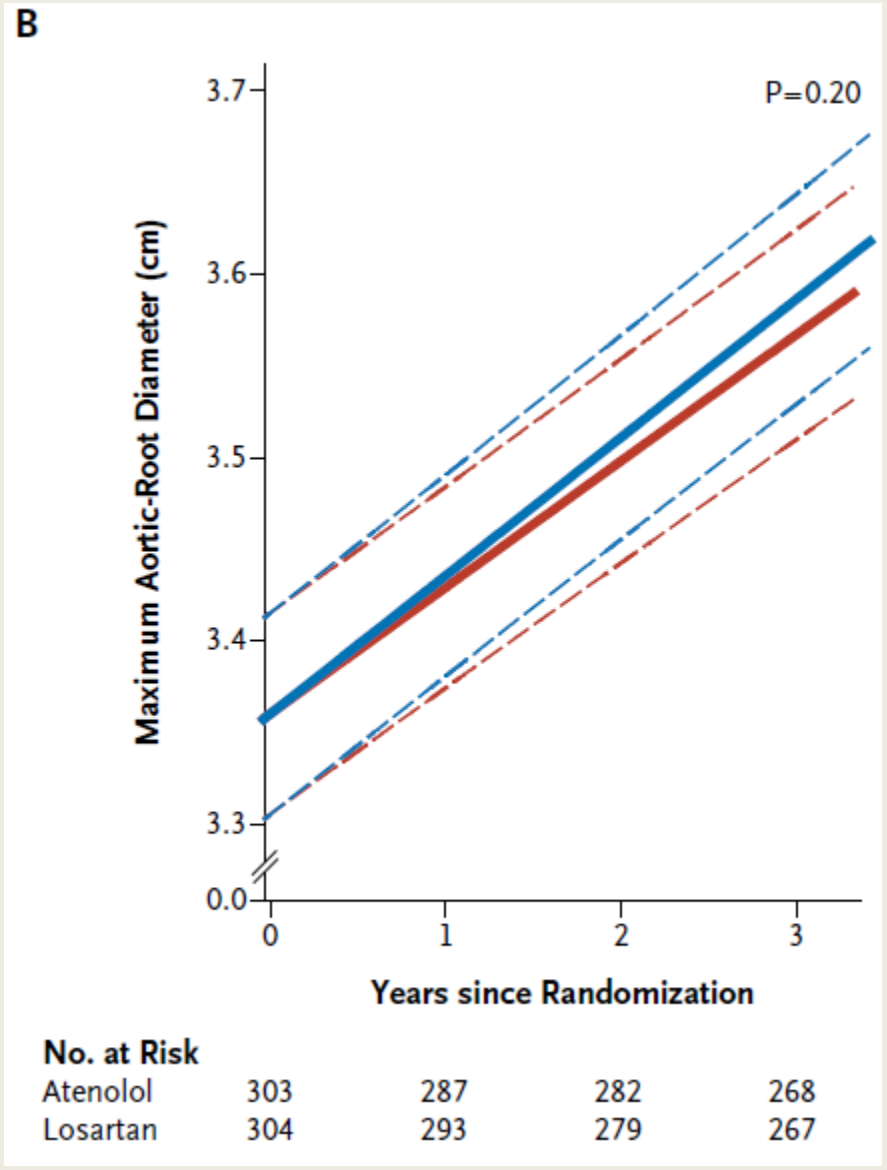

Losartan
Placebo
Mean Systolic Pressure
Mean Diastolic Pressure
Arterial Pressure (mmHg)
140
120
100
80
60
0
1
2
3
4
5
Years

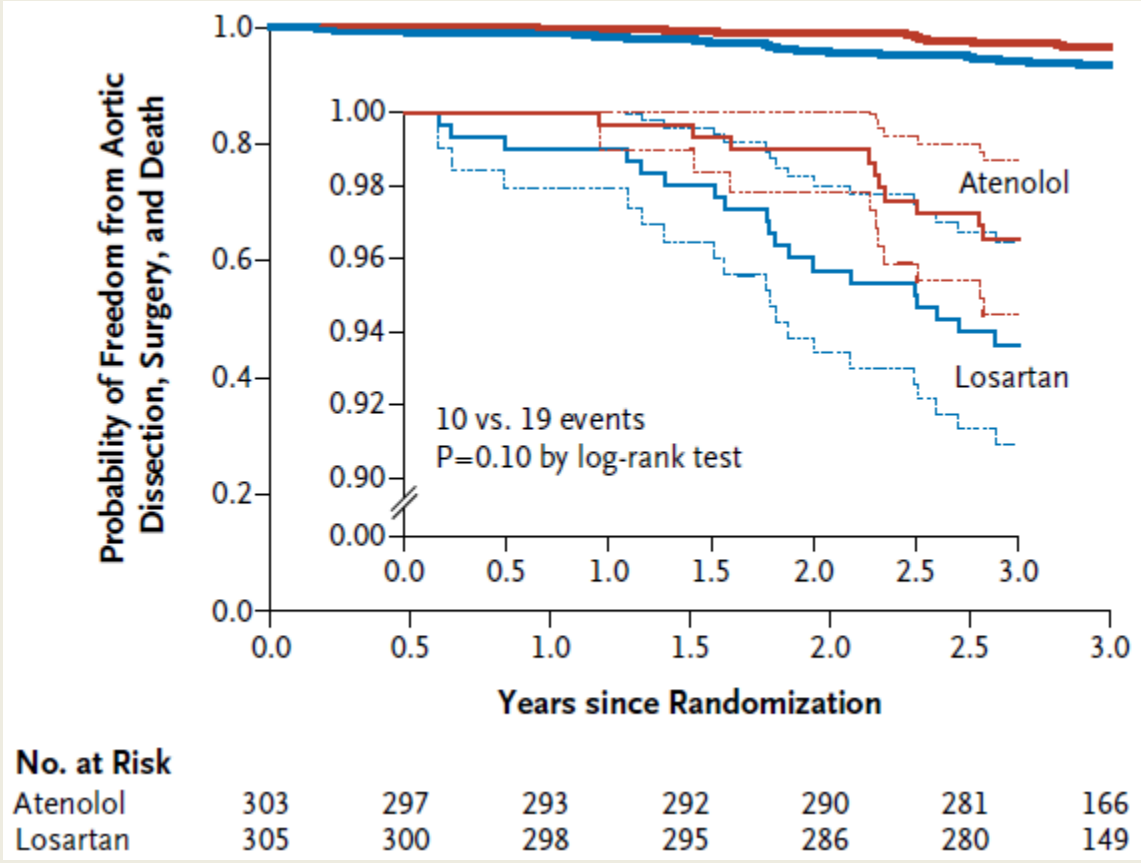
# Fr (Marfan Sartan)



# Competition


Atenolol
Losartan
A
P=0.08
Aortic-Root z Score
4.4
4.2
4.0
3.8
3.6
0.0
0
1
2
3
Years since Randomization
No. at Risk
Atenolol 303 286 282 268
Losartan 303 293 279 267

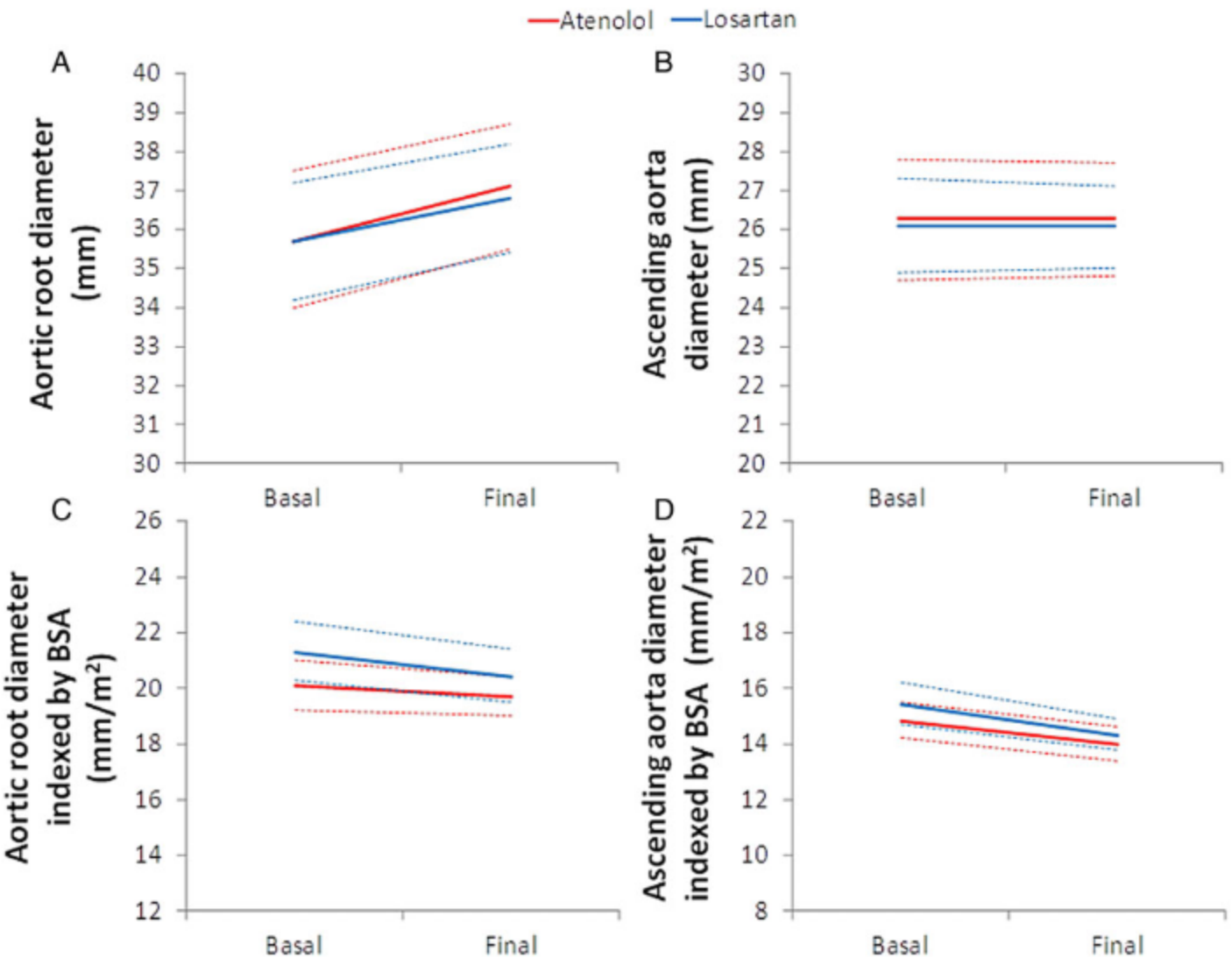

B
P=0.20
Maximum Aortic-Root Diameter (cm)
3.7
3.6
3.5
3.4
3.3
0.0
0
1
2
3
Years since Randomization
No. at Risk
Atenolol 303 287 282 268
Losartan 304 293 279 267




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Atenolol | 303 | 297 | 293 | 292 | 290 | 281 | 166 |
| Losartan | 305 | 300 | 298 | 295 | 286 | 280 | 149 |

# LOAT (Sp)


Atenolol
Losartan
A
Aortic root diameter (mm)
40
39
38
37
36
35
34
33
32
31
30
Basal
Final
B
Ascending aorta diameter (mm)
30
29
28
27
26
25
24
23
22
21
20
Basal
Final
C
Aortic root diameter indexed by BSA (mm/m²)
26
24
22
20
18
16
14
12
Basal
Final
D
Ascending aorta diameter indexed by BSA (mm/m²)
22
20
18
16
14
12
10
8
Basal
Final

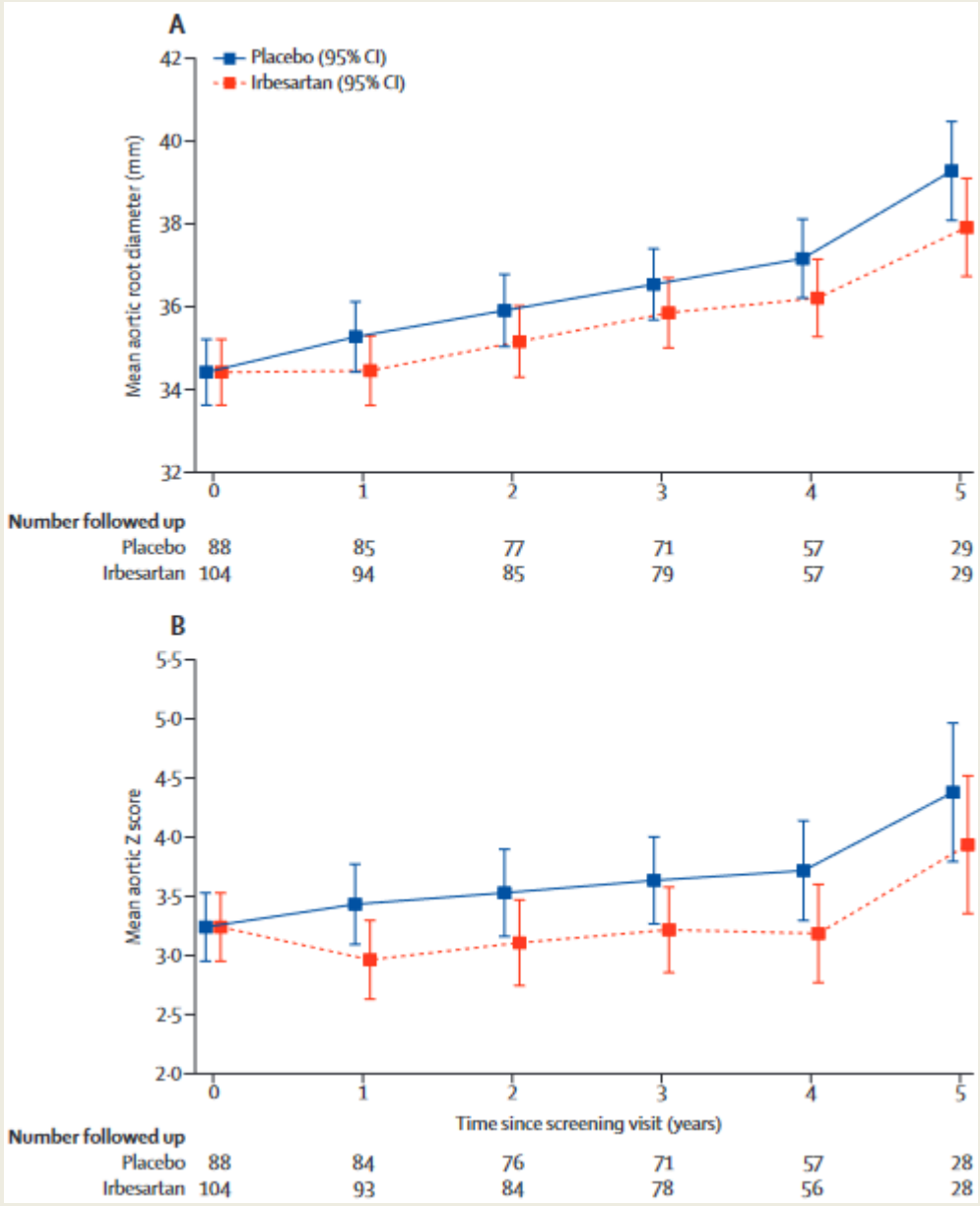
# Addition ?

# Study of sartan vs control: BB vs BB+S

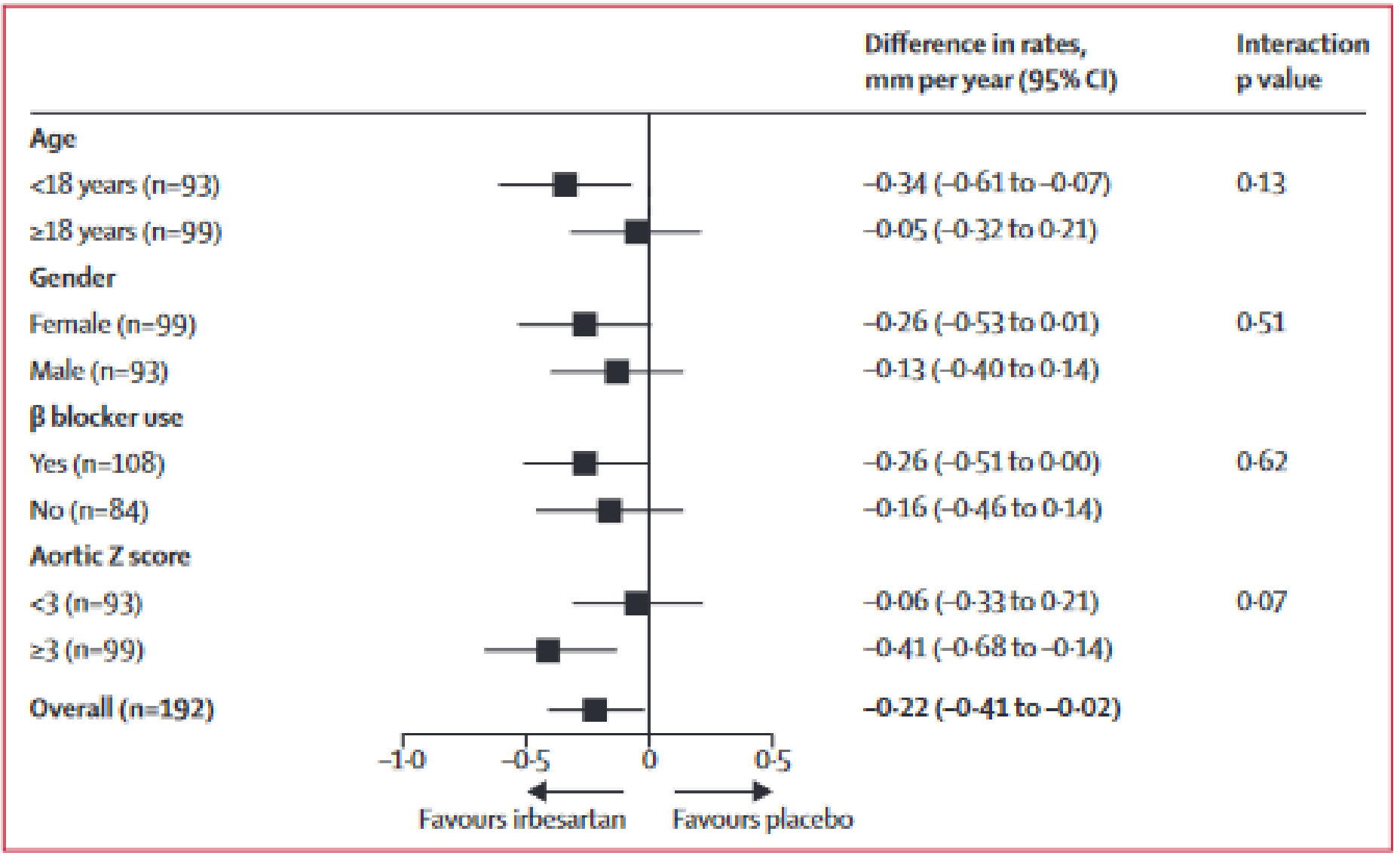
Sartan vs control: % pop receiving beta-blocker

- COMPARE: 79%
- AIMS: 56%
- Marfan Sartan: 86% (no interaction)

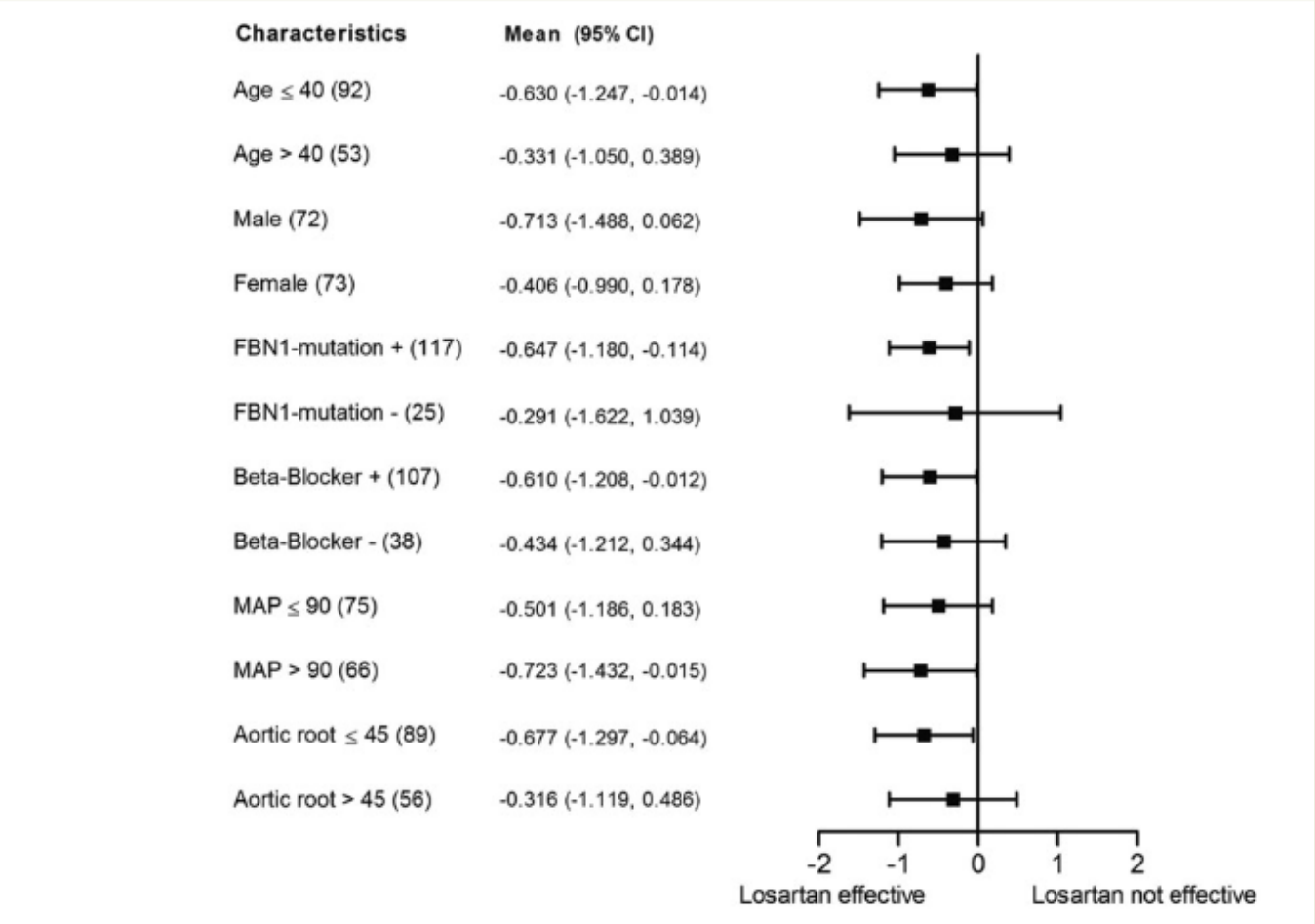
# AIMS (UK)


A
Placebo (95% CI)
Irbesartan (95% CI)
Mean aortic root diameter (mm)
42
40
38
36
34
32
0
1
2
3
4
5
Number followed up
Placebo 88 85 77 71 57 29
Irbesartan 104 94 85 79 57 29
B
Mean aortic Z score
5·5
5·0
4·5
4·0
3·5
3·0
2·5
2·0
0
1
2
3
4
5
Time since screening visit (years)
Number followed up
Placebo 88 84 76 71 57 28
Irbesartan 104 93 84 78 56 28

# (AIMS) UK


Difference in rates, mm per year (95% CI)
Interaction p value
Age
<18 years (n=93)
–0·34 (–0·61 to –0·07)
0·13
≥18 years (n=99)
–0·05 (–0·32 to 0·21)
Gender
Female (n=99)
–0·26 (–0·53 to 0·01)
0·51
Male (n=93)
–0·13 (–0·40 to 0·14)
β blocker use
Yes (n=108)
–0·26 (–0·51 to 0·00)
0·62
No (n=84)
–0·16 (–0·46 to 0·14)
Aortic Z score
<3 (n=93)
–0·06 (–0·33 to 0·21)
0·07
≥3 (n=99)
–0·41 (–0·68 to –0·14)
Overall (n=192)
–0·22 (–0·41 to –0·02)
–1·0
–0·5
0
0·5
Favours irbesartan
Favours placebo

# COMPARE (NI)


Characteristics
Mean (95% CI)
Age ≤ 40 (92)
-0.630 (-1.247, -0.014)
Age > 40 (53)
-0.331 (-1.050, 0.389)
Male (72)
-0.713 (-1.488, 0.062)
Female (73)
-0.406 (-0.990, 0.178)
FBN1-mutation + (117)
-0.647 (-1.180, -0.114)
FBN1-mutation - (25)
-0.291 (-1.622, 1.039)
Beta-Blocker + (107)
-0.610 (-1.208, -0.012)
Beta-Blocker - (38)
-0.434 (-1.212, 0.344)
MAP ≤ 90 (75)
-0.501 (-1.186, 0.183)
MAP > 90 (66)
-0.723 (-1.432, -0.015)
Aortic root ≤ 45 (89)
-0.677 (-1.297, -0.064)
Aortic root > 45 (56)
-0.316 (-1.119, 0.486)
-2
-1
0
1
2
Losartan effective
Losartan not effective

# Beta-blockers and ARBs: friends or competitors?

Friends

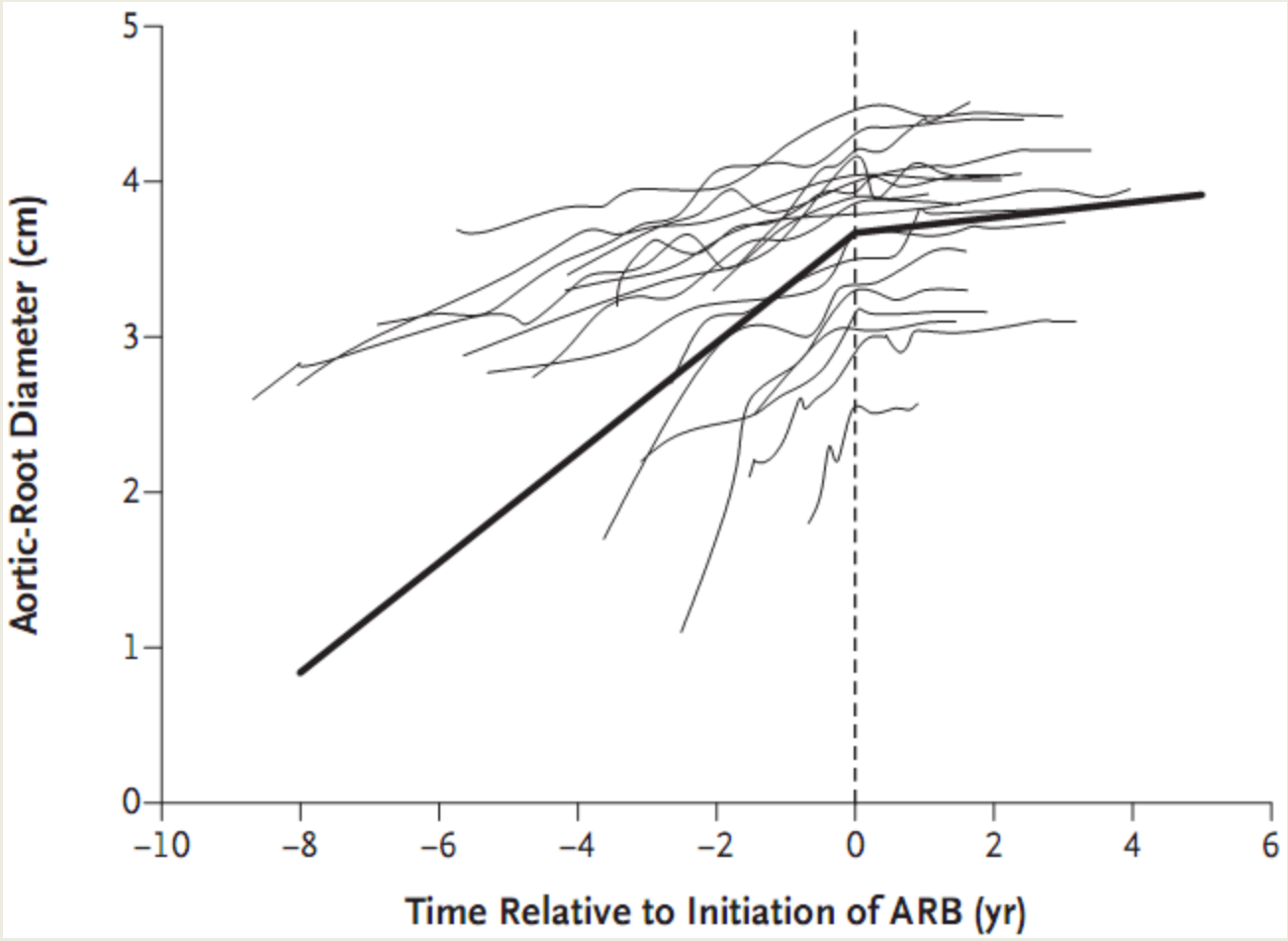
- competition for blood pressure
- good tolerance

Useful friends ?

- friends always useful…

Thanks

*Brooke BS N Engl J Med 2008;358:2787-95*



# Beta-blockers

Described by veterinary surgeons as preventing dissecting aortic aneurysms in turkeys.

*Report on field cases of aortic rupture in turkeys treated with Reserpine. Morrison WD, 1960*

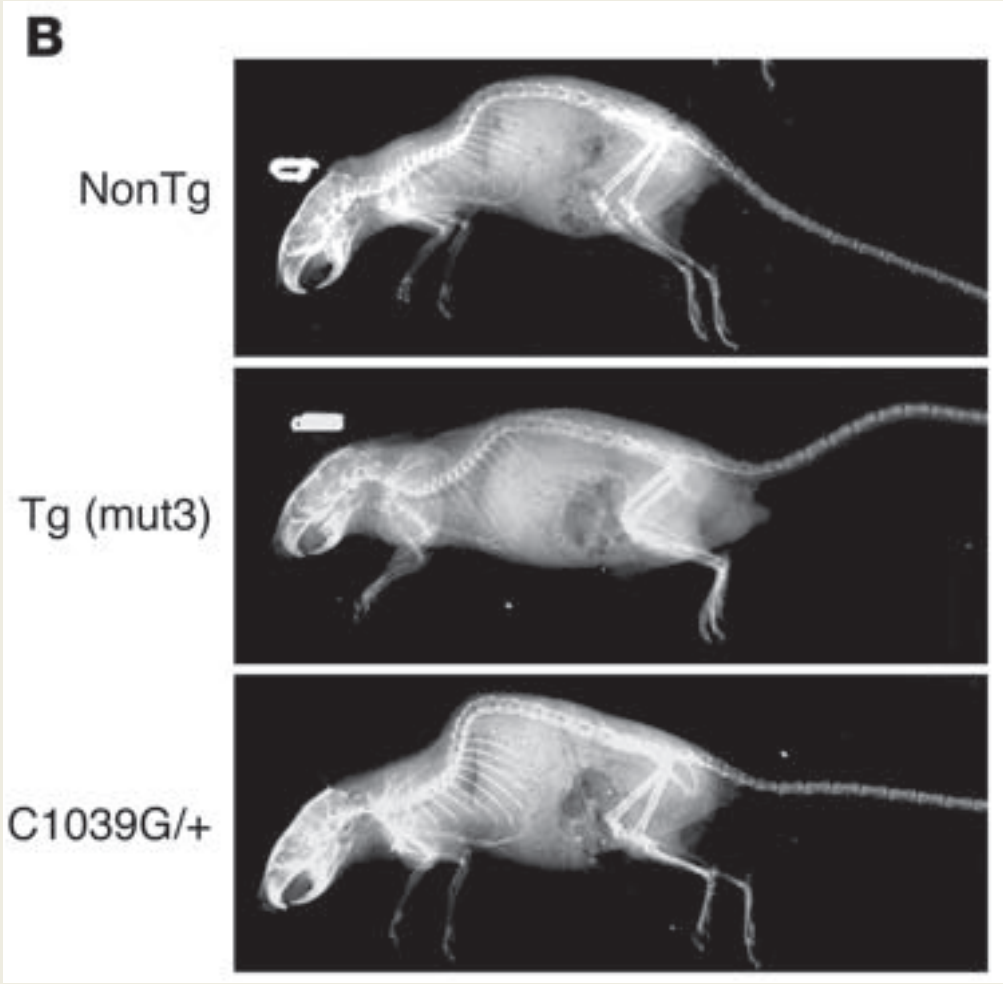
Was then found to be useful by some in treating dissected aortic aneurysms in humans.

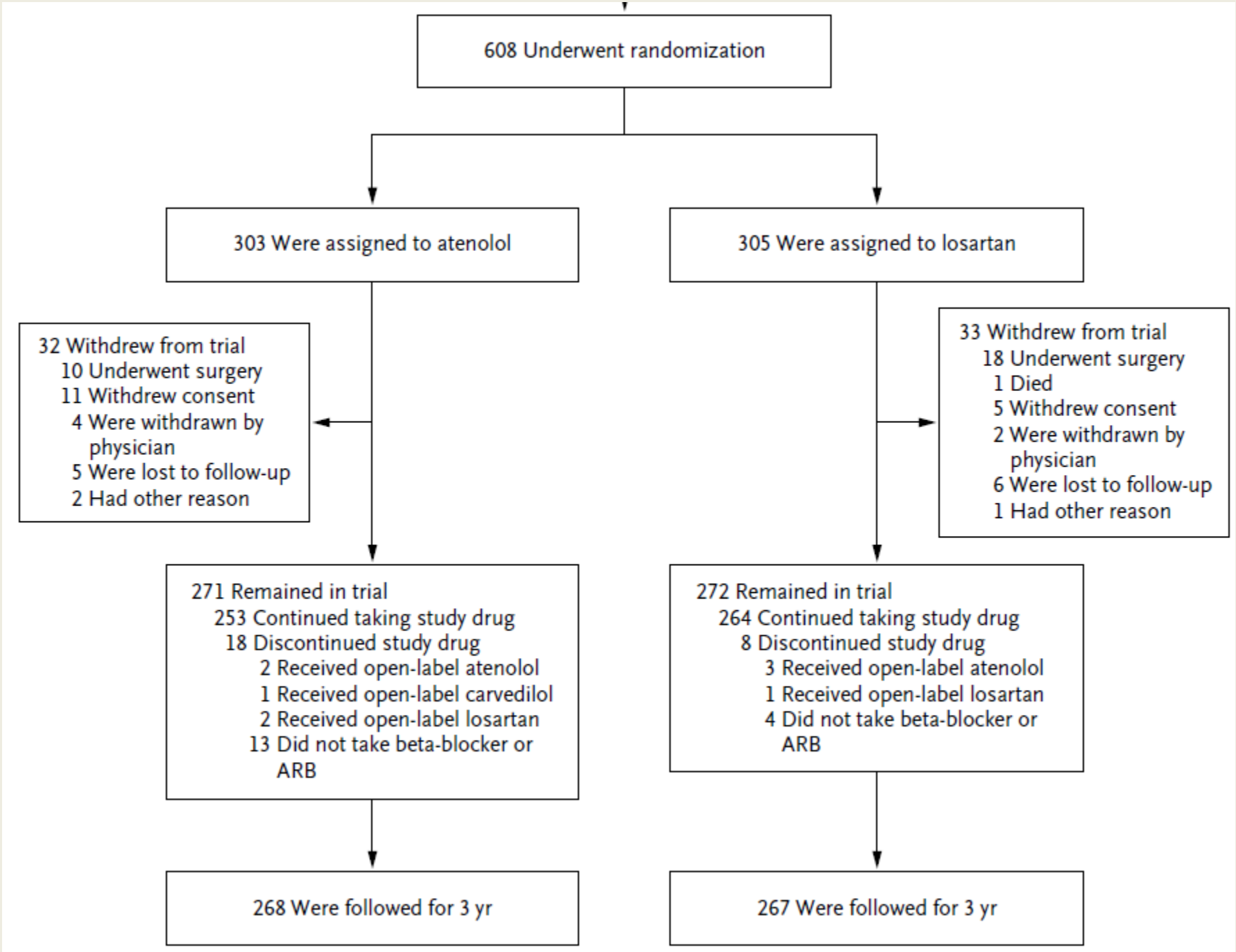
*Acute dissecting aneurysms of the aorta, Treatment and results in 64 patients.*

*Wheat MW et al. J Thor Cardiovasc Surg. 1969;58:344*

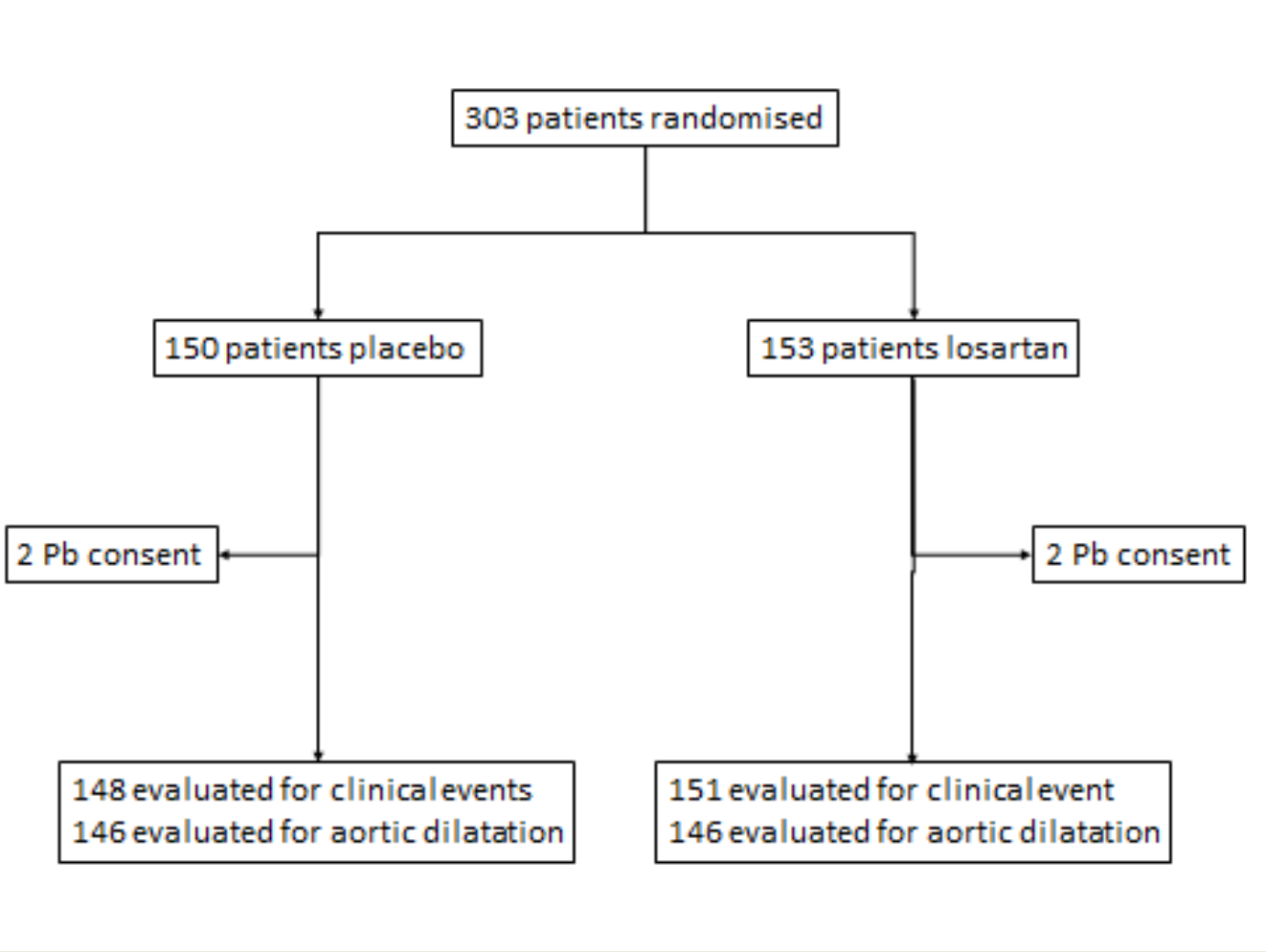
# Judge J. Clin. Invest. 114:172–181 (2004)

- Mouse C1663R cystein within cbEGF-like domain
  - No clinical or histologic features of MFS
  - Immunohistochemistry: presence of human epitope : bioavailability and competence of cysteine-substituted fibrillin-1 to participate in microfibrillar assembly
- Mouse C1039G cystein within cbEGF-like domain
  - Clinical and histologic features of MFS



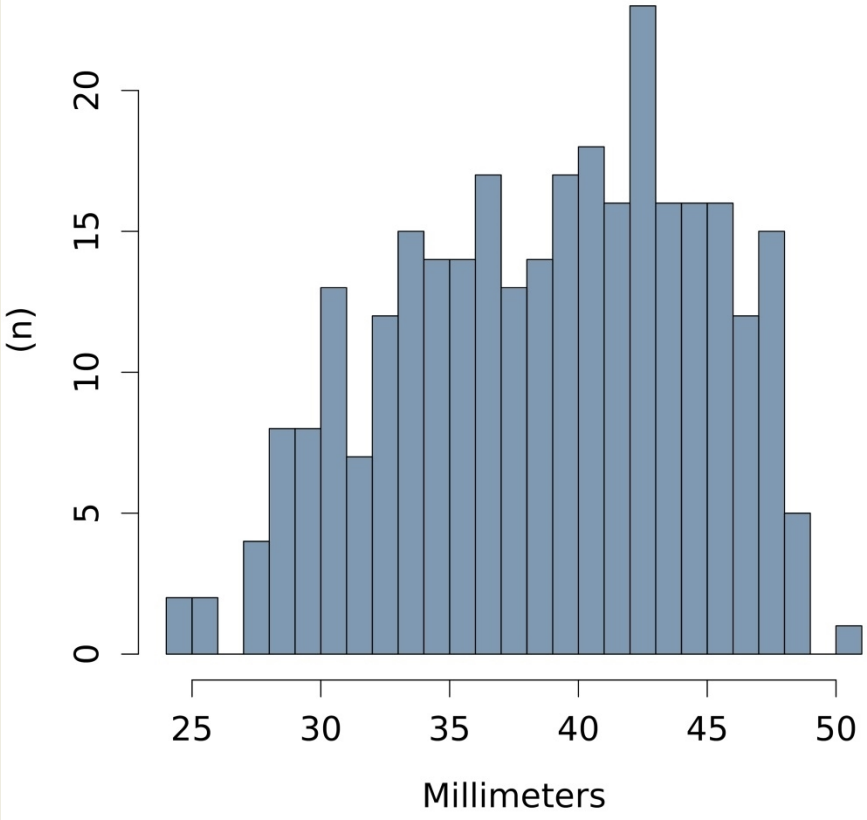

608 Underwent randomization
303 Were assigned to atenolol
305 Were assigned to losartan
32 Withdrew from trial
10 Underwent surgery
11 Withdrew consent
4 Were withdrawn by physician
5 Were lost to follow-up
2 Had other reason
33 Withdrew from trial
18 Underwent surgery
1 Died
5 Withdrew consent
2 Were withdrawn by physician
6 Were lost to follow-up
1 Had other reason
271 Remained in trial
253 Continued taking study drug
18 Discontinued study drug
2 Received open-label atenolol
1 Received open-label carvedilol
2 Received open-label losartan
13 Did not take beta-blocker or ARB
272 Remained in trial
264 Continued taking study drug
8 Discontinued study drug
3 Received open-label atenolol
1 Received open-label losartan
4 Did not take beta-blocker or ARB
268 Were followed for 3 yr
267 Were followed for 3 yr

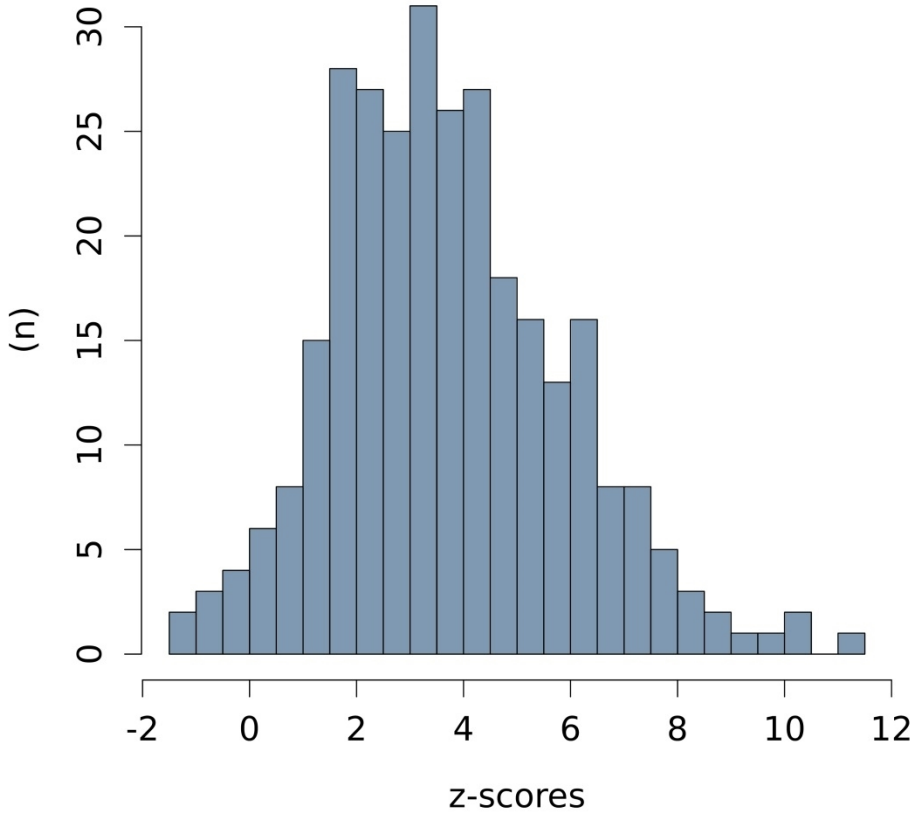
| Characteristic | Atenolol (N=303) | Losartan (N=305) |
|---|---|---|
| Age — yr | 11.5±6.5 | 11.0±6.2 |
| Young adult — no. (%)† | 76 (25) | 75 (25) |
| Male sex — no. (%) | 180 (59) | 186 (61) |
| Race — no. (%)‡ | | |
| White | 266 (88) | 260 (85) |
| Black | 21 (7) | 25 (8) |
| Asian | 6 (2) | 10 (3) |
| Other | 10 (3) | 10 (3) |
| Hispanic — no./total no. (%)‡ | 36/302 (12) | 46/305 (15) |
| Presence of causal *FBN1* mutation — no. (%) | | |
| Yes | 93 (31) | 88 (29) |
| No | 9 (3) | 15 (5) |
| Unknown | 201 (66) | 202 (66) |
| Family history of Marfan's syndrome — no./total no. (%) | 180/295 (61) | 181/290 (62) |
| Echocardiographic findings§ | | |
| Maximum aortic-root diameter — cm | 3.4±0.7 | 3.4±0.7 |
| Maximum aortic-root-diameter z score | | |
| Median | 4.0 | 4.0 |
| Interquartile range | 3.5–4.8 | 3.3–5.0 |
| ≥4.5 — no./total no. (%) | 106/303 (35) | 114/304 (38) |
| Medical history — no. (%) | | |

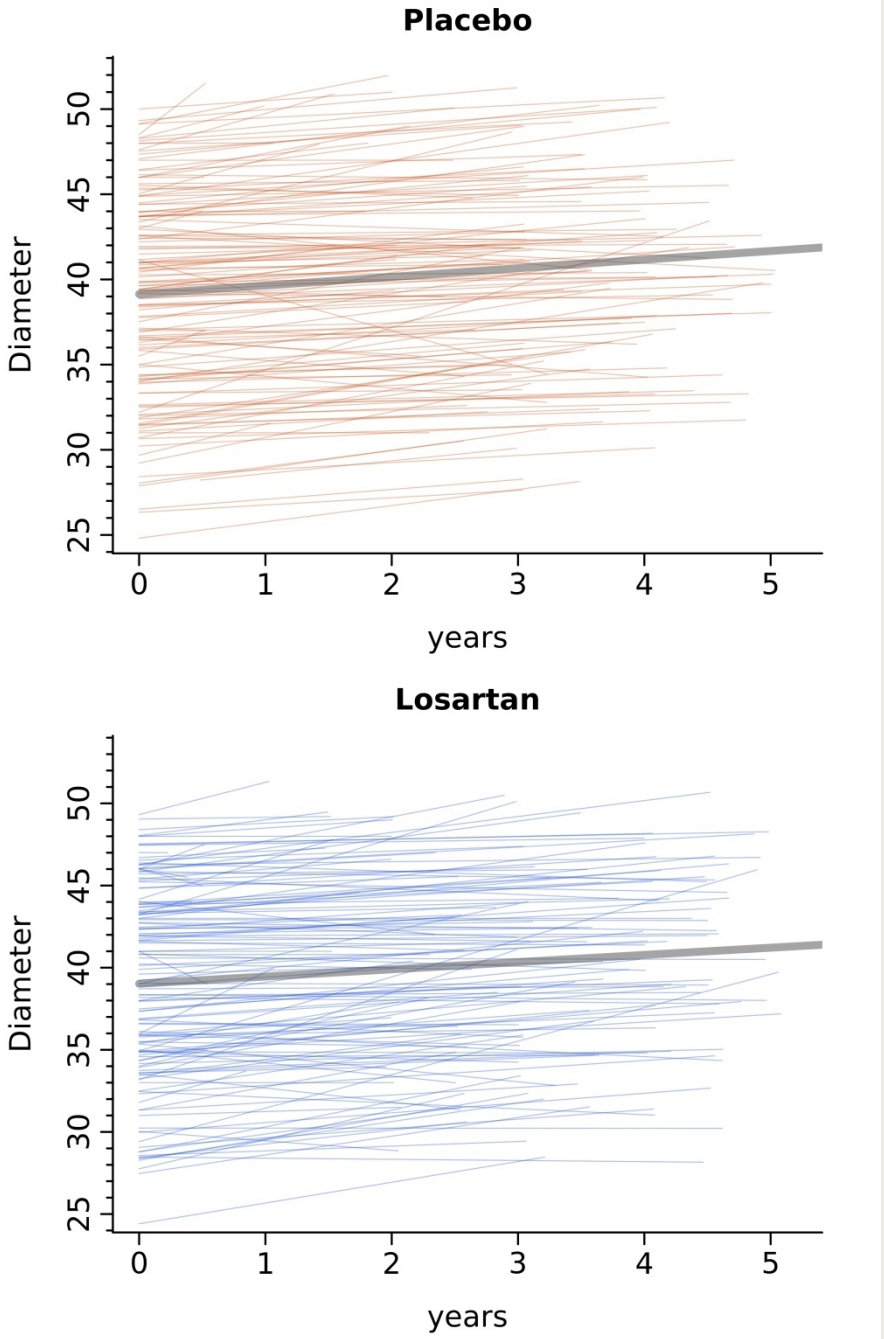



Mean FU 3,5 years

| | Losartan (n=151) | Placebo (n=148) |
|---|---|---|
| Age: years (SD) | 30·9 (15.9) | 28·9 (13.6) |
| <18 years | 44 (29%) | 40 (27%) |
| >18 years | 107 (71%) | 108 (73%) |
| Height (cm) | 177·7 (11.9) | 178·8 (11.6) |
| Female | 85 (56%) | 87 (59%) |
| Valsalva diameter (mm (SD)) | 39.1 (5.8) | 39.2 (5.9) |
| z-score | 3.74 (2.3) | 3.69 (2.0) |
| Baseline therapy | 138 (91%) | 135 (91%) |
| Beta-blocker | 130 (86%) | 127 (86%) |


(n)
0
5
10
15
20
25
30
35
40
45
50
Millimeters


(n)
0
5
10
15
20
25
30
-2
0
2
4
6
8
10
12
z-scores

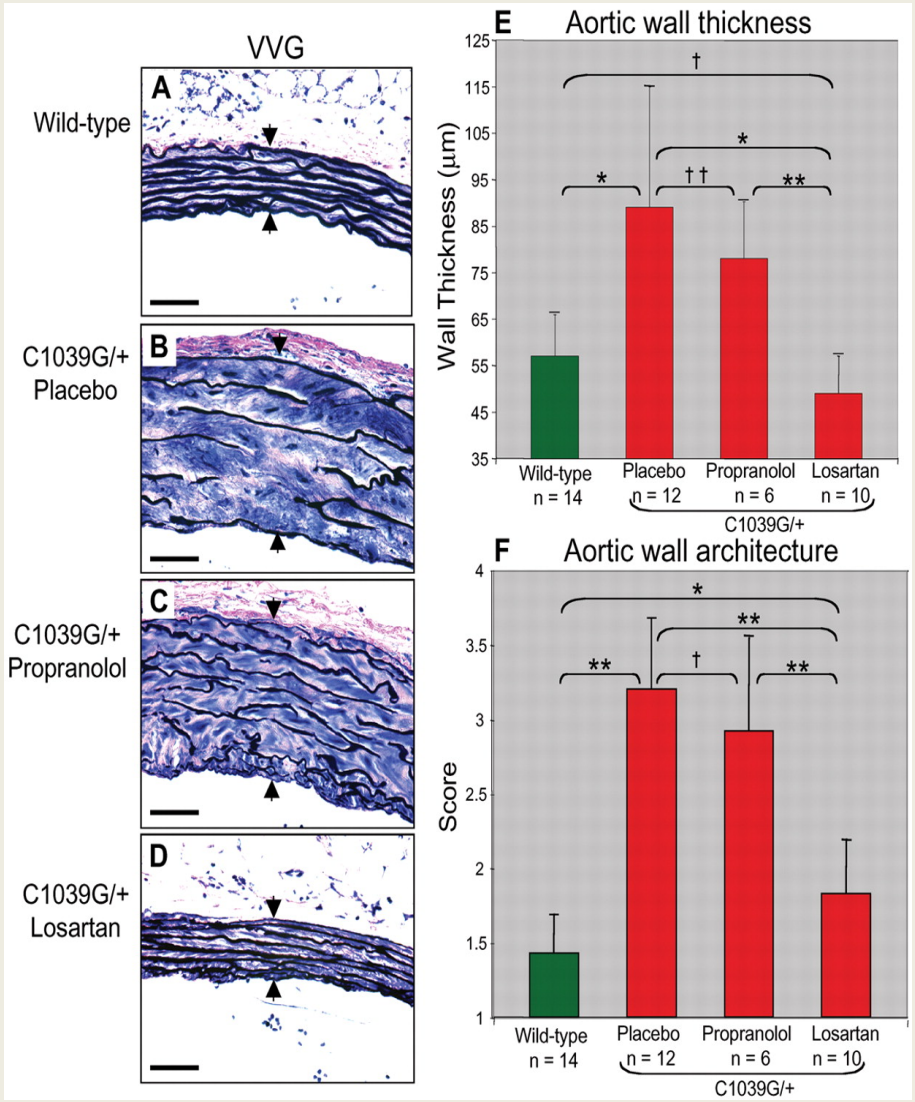

Placebo
Diameter
25
30
35
40
45
50
0
1
2
3
4
5
years
Losartan
Diameter
25
30
35
40
45
50
0
1
2
3
4
5
years

# Evolution of aortic diameter at different aorta localisations in the 2 groups

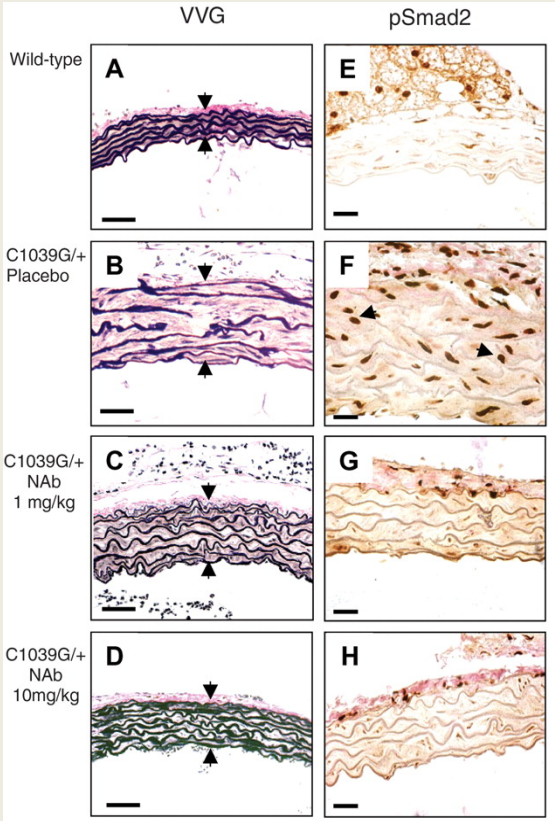
| | Losartan mean (se) | Placebo mean (se) | p-value |
|---|---|---|---|
| Sinuses of Valsalva (z-score/year) | -0.03 (0.03) | -0.01 (0.03) | 0.69 |
| Sinuses of Valsalva (mm/year) | 0.44 (0.07) | 0.51 (0.06) | 0.36 |
| Aortic annulus (mm/year) | 0.16 (0.09) | 0.23 (0.09) | 0.46 |
| Sino-tubular junction (mm/year) | 0.40 (0.17) | 0.28 (0.18) | 0.65 |
| Ascending aorta (mm/year) | 0.32 (0.22) | 0.45 (0.11) | 0.62 |
| Aortic arch (mm/year) | 0.34 (0.13) | 0.42 (0.12) | 0.82 |
| Descending thoracic aorta (mm/year) | 0.26 (0.31) | 0.27 (0.19) | 0.98 |
| Abdominal aorta (mm/year) | 0.16 (0.14) | 0.25 (0.10) | 0.59 |

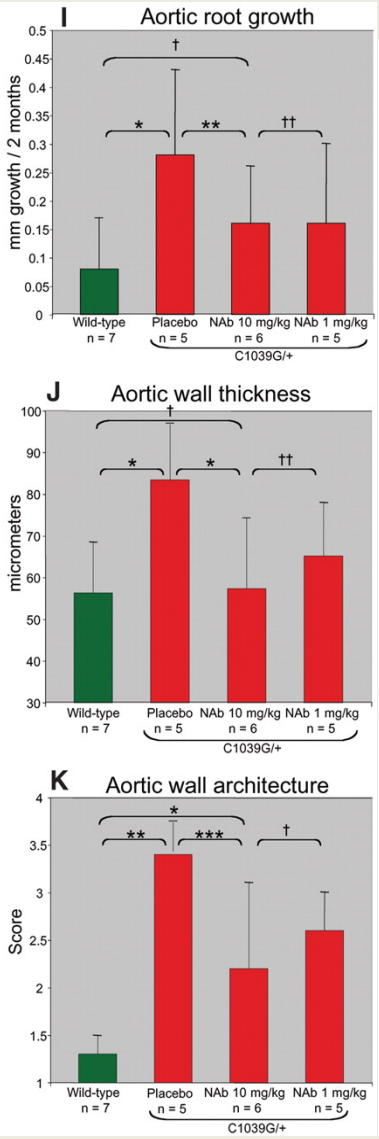
| | Losartan (n=151) | Placebo (n=148) |
|---|---|---|
| Any serious adverse event | 51 (33.7%) | 48 (32.4%) |
| -possibly related to drug | 6 (3.9%) | 0 |
| Death | 0 (0.0%) | 3 (2.0%) |
| Aortic surgery | 15 (9.9%) | 11 (7.4%) |
| Number of patients with: | | |
| -K+>5.5mmol/l | 0 (0.0%) | 0 (0.0%) |
| -creatinine> ULN (120µmol/l) | 1 (0.6%) | 0 (0.0%) |
| -creatinine increase> 26.4 µmol/l (0.3 mg/dl) | 13 (8.6%) | 11 (7.4%) |

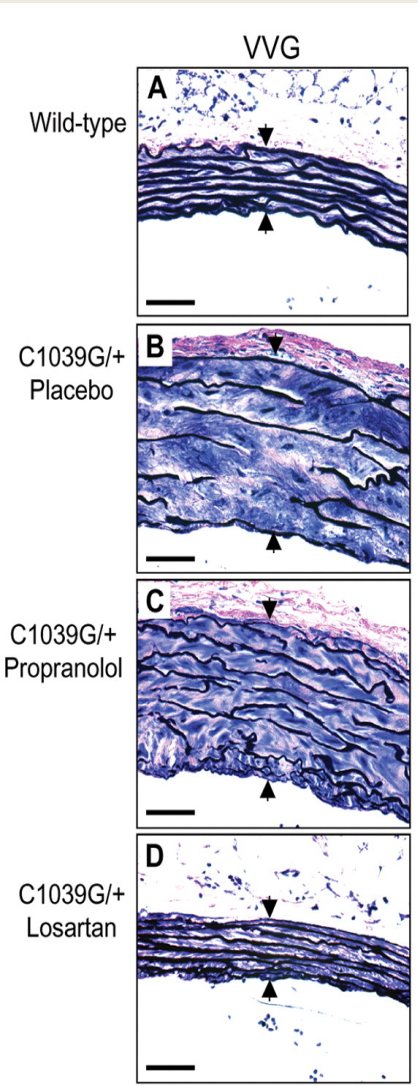
*Habashi JP Science 2006;312:117*

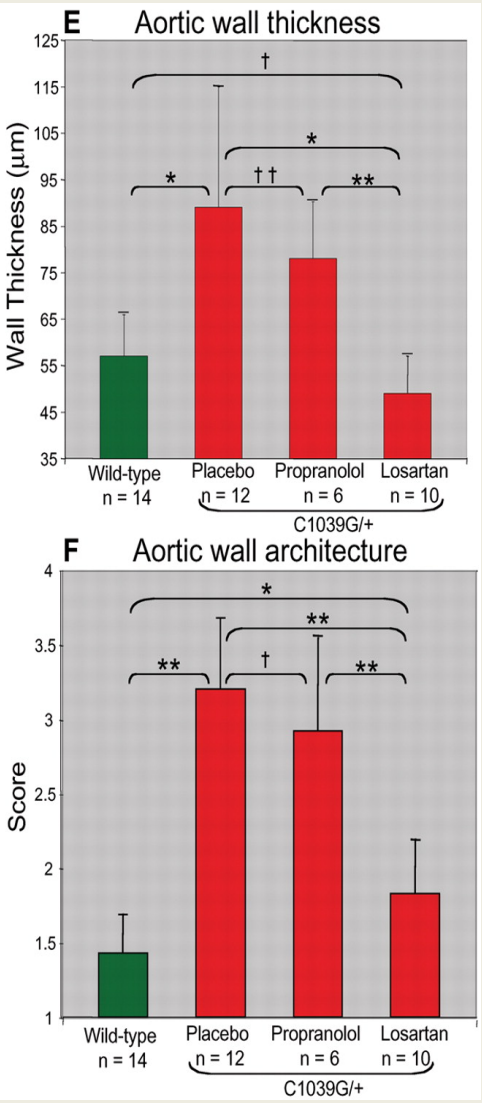


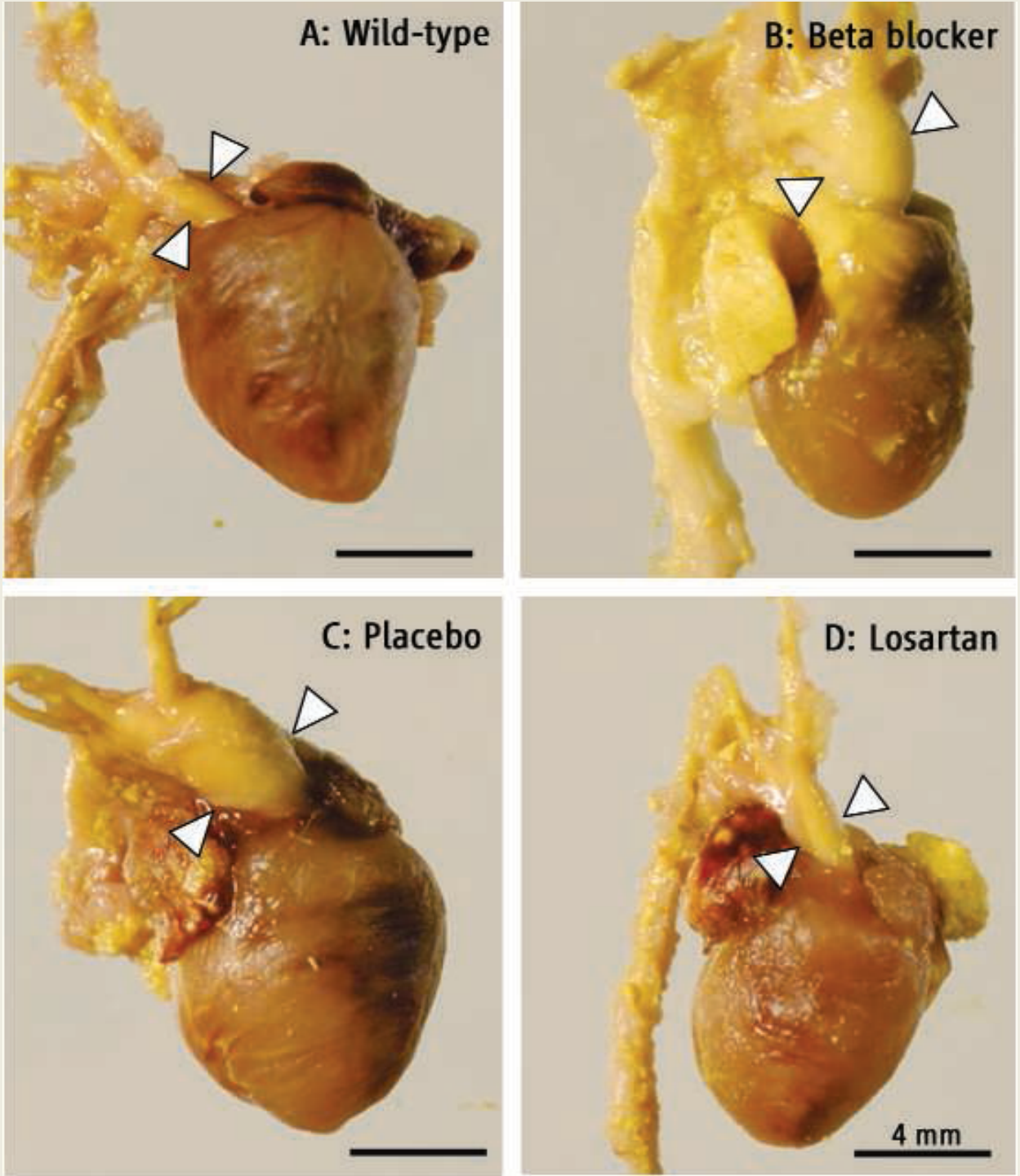
# Habashi JP Science 2006;312:117

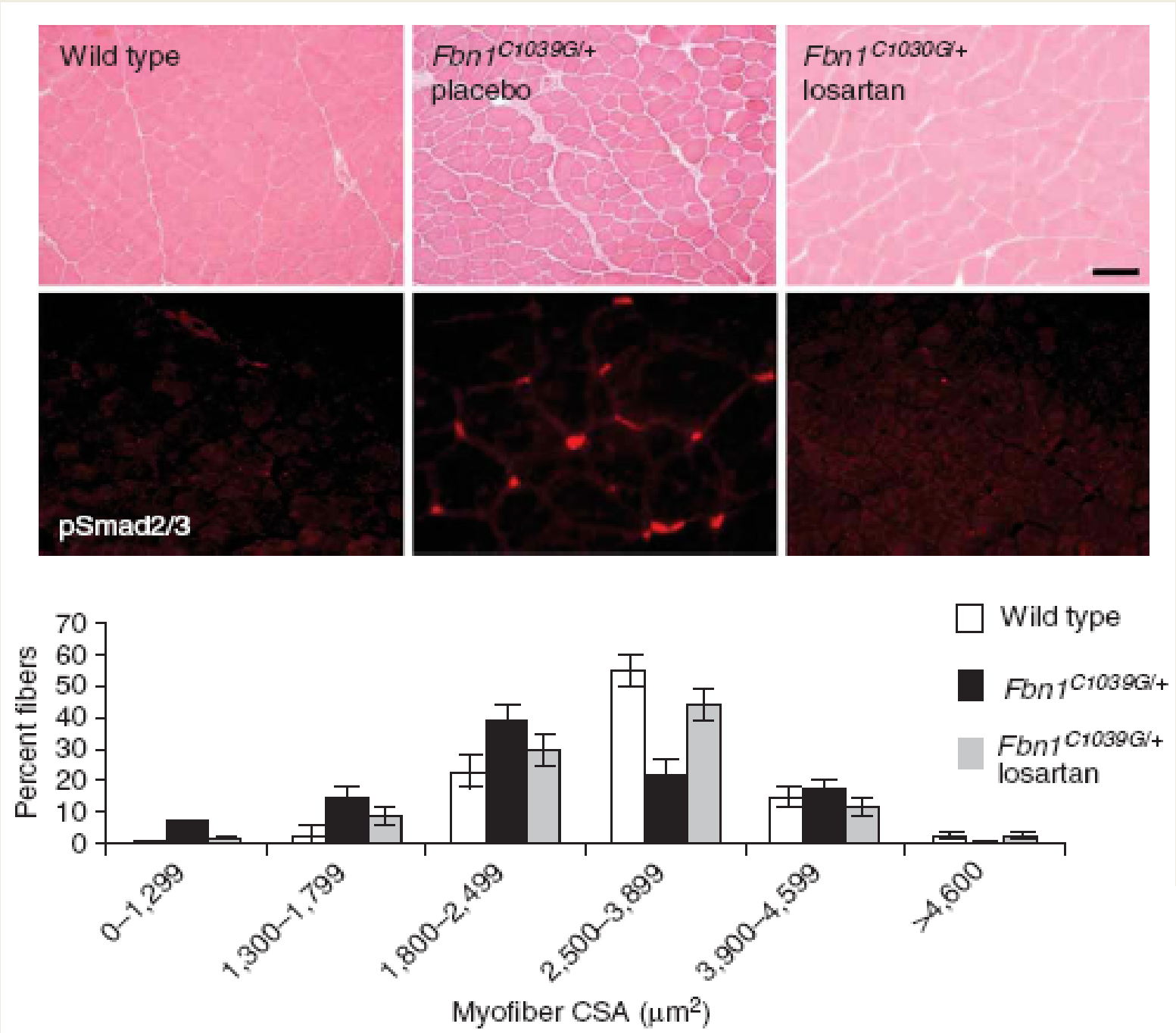


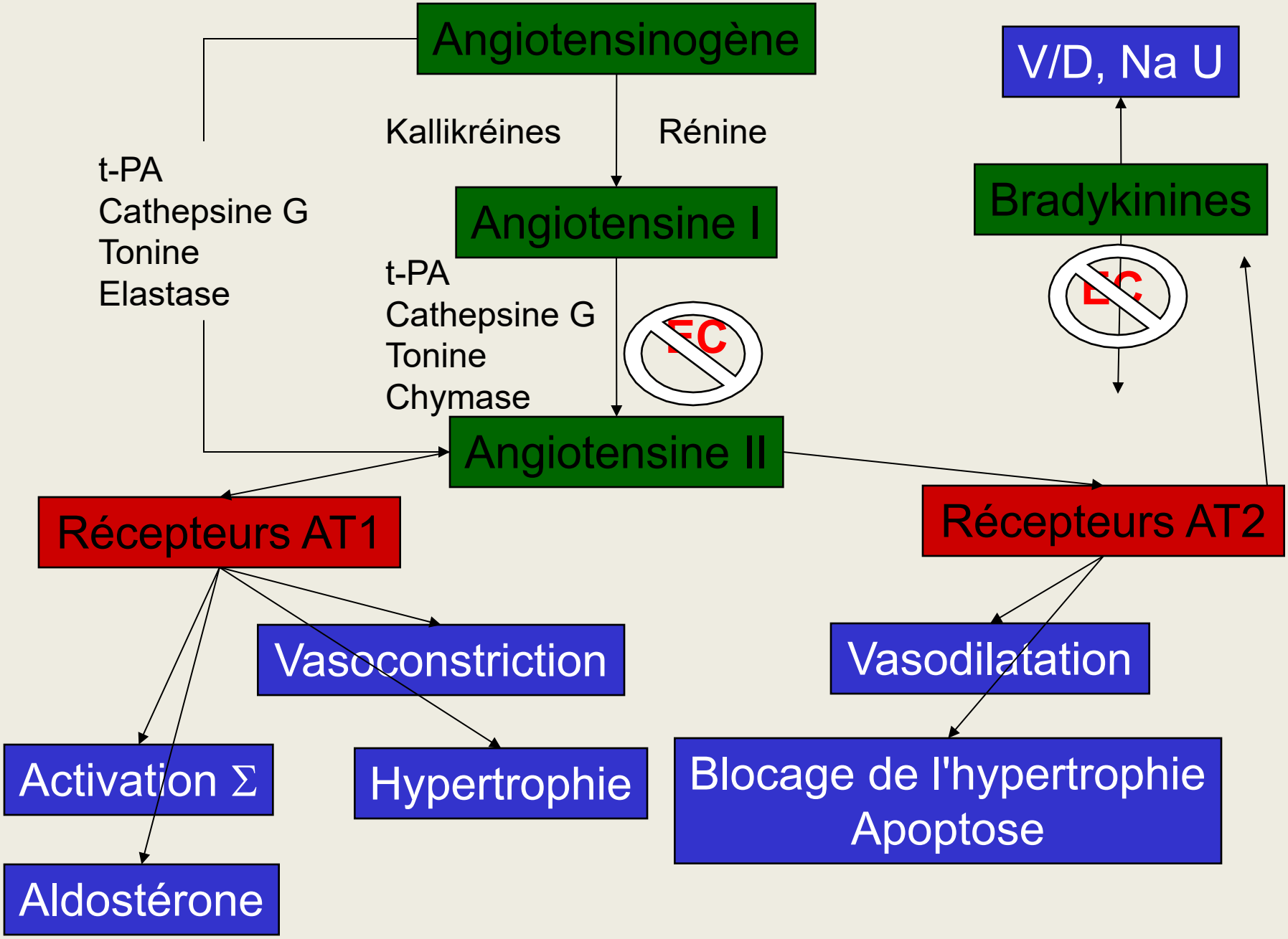



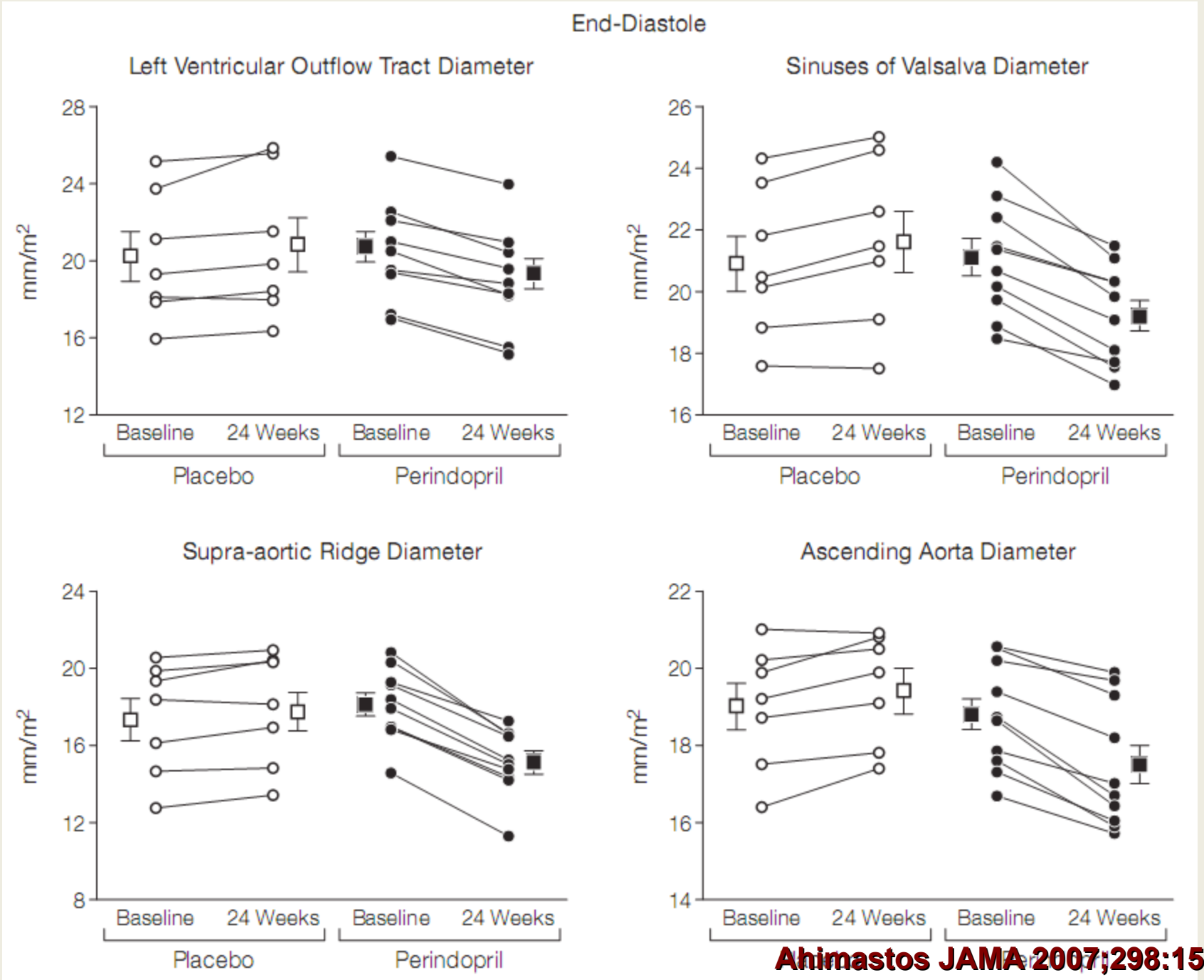



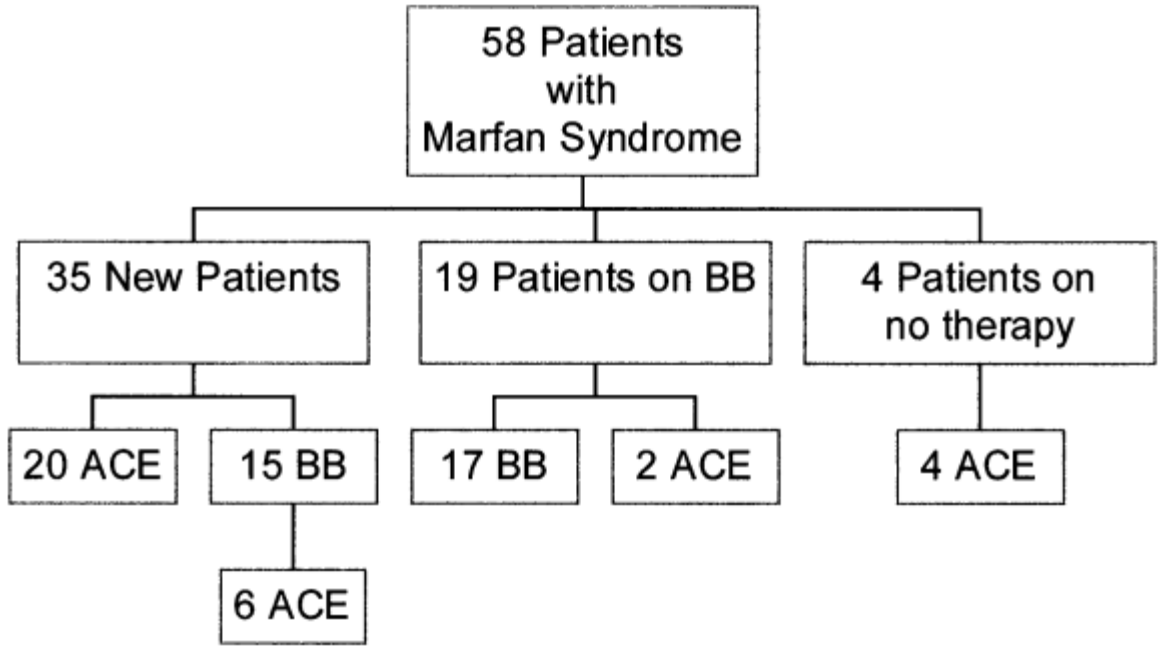

A: Wild-type
B: Beta blocker
C: Placebo
D: Losartan
4 mm


Wild type
Fbn1C1039G/+ placebo
Fbn1C1030G/+ losartan
pSmad2/3
Wild type
Fbn1C1039G/+
Fbn1C1039G/+ losartan
Percent fibers
0
10
20
30
40
50
60
70
0–1,299
1,300–1,799
1,800–2,499
2,500–3,899
3,900–4,599
>4,600
Myofiber CSA (μm2)


Angiotensinogène
Kallikréines
Rénine
t-PA
Cathepsine G
Tonine
Elastase
Angiotensine I
t-PA
Cathepsine G
Tonine
Chymase
EC
Angiotensine II
V/D, Na U
Bradykinines
EC
Récepteurs AT1
Récepteurs AT2
Vasoconstriction
Vasodilatation
Activation Σ
Hypertrophie
Blocage de l'hypertrophie
Apoptose
Aldostérone



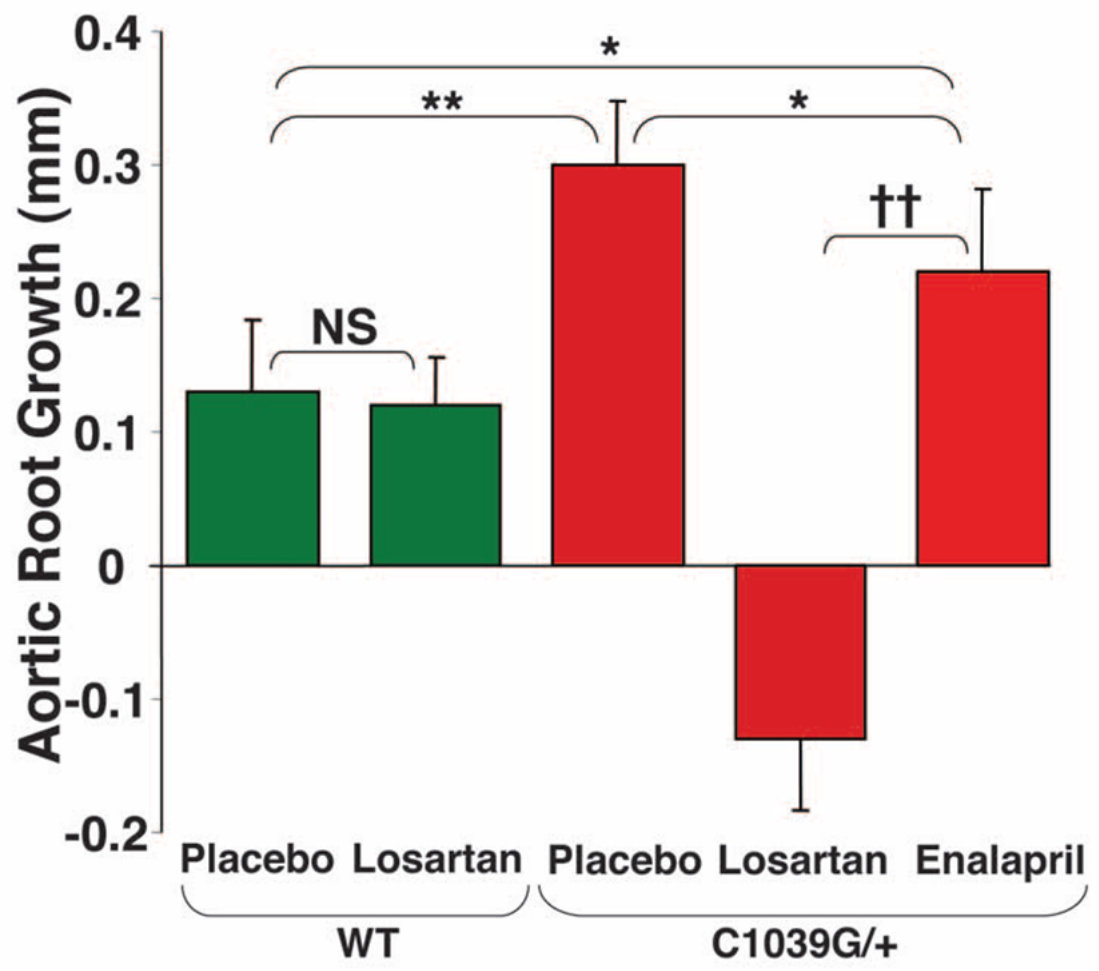

Ahimastos JAMA 2007;298:1539




| | Enalapril (n = 32) | Propranolol/Atenolol (n = 25) | |
|---|---|---|---|
| Rate of change in % predicted aortic size over time (%/yr) | −2.5 ± 1.0 | 3.7 ± 1.4 | 0.005 |

*Yetman Am J Cardiol 2005;95:1125*

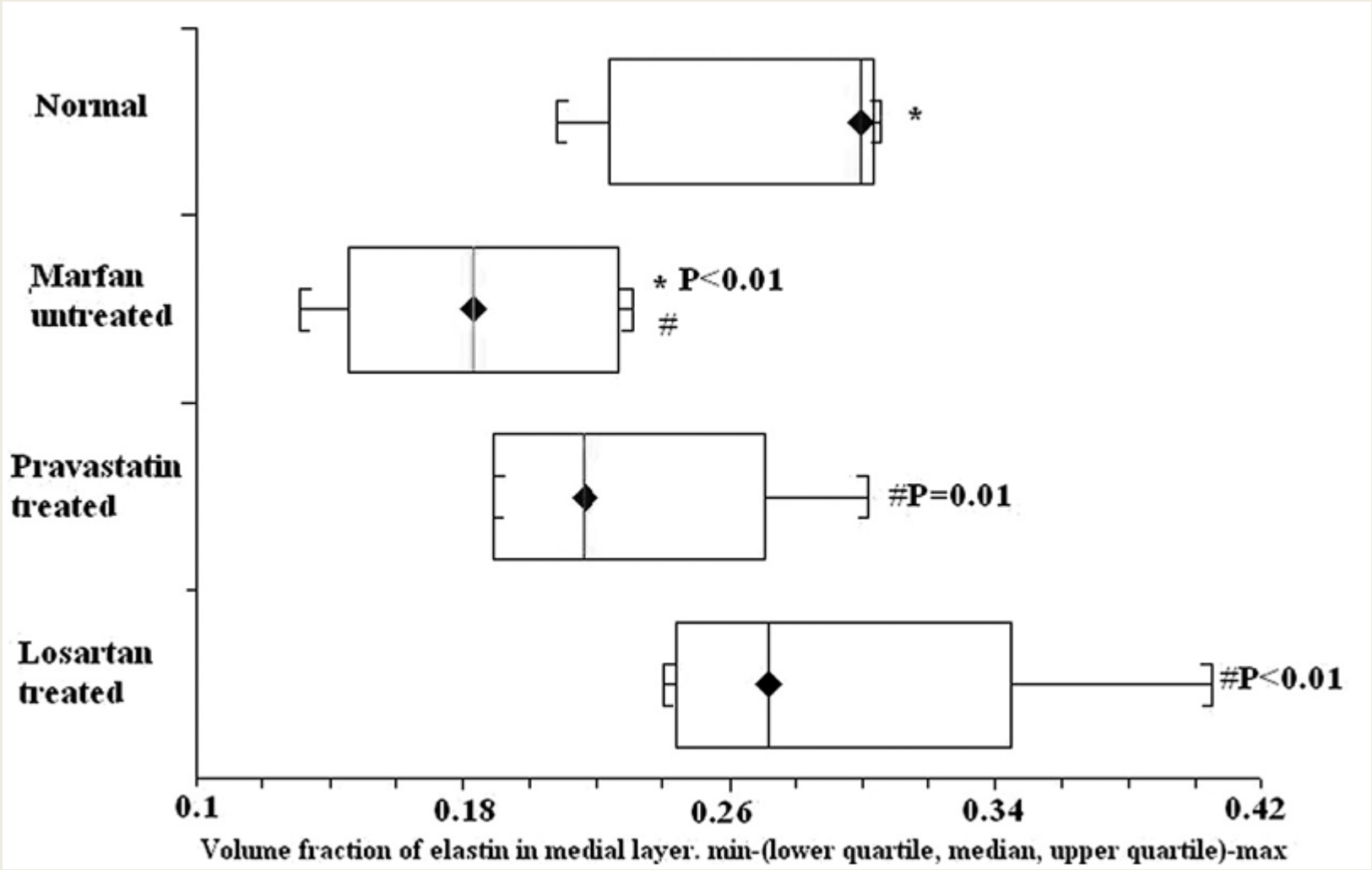
# ACEI/ARB in mouse

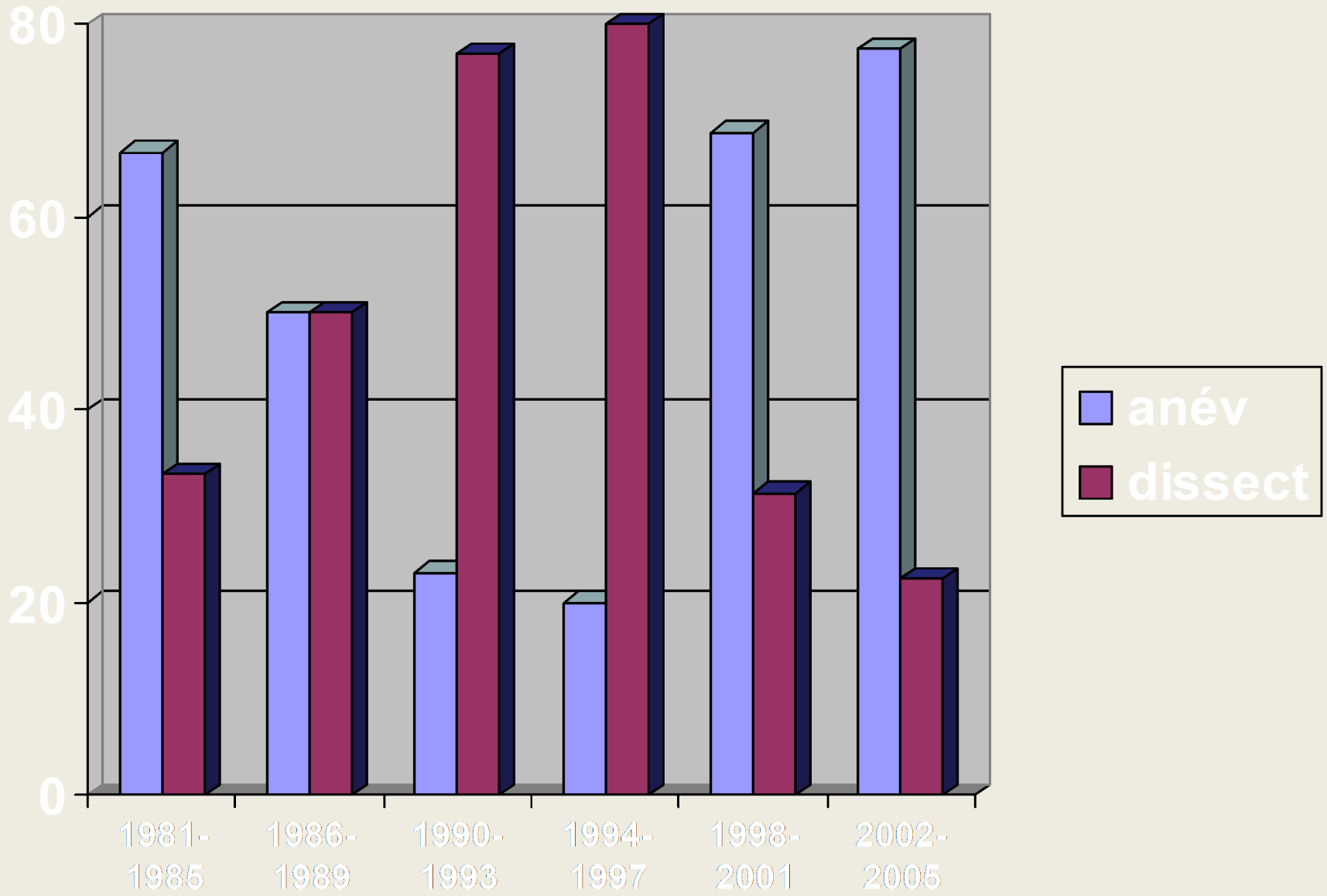



*Habashi Sciences 2011;332:361*

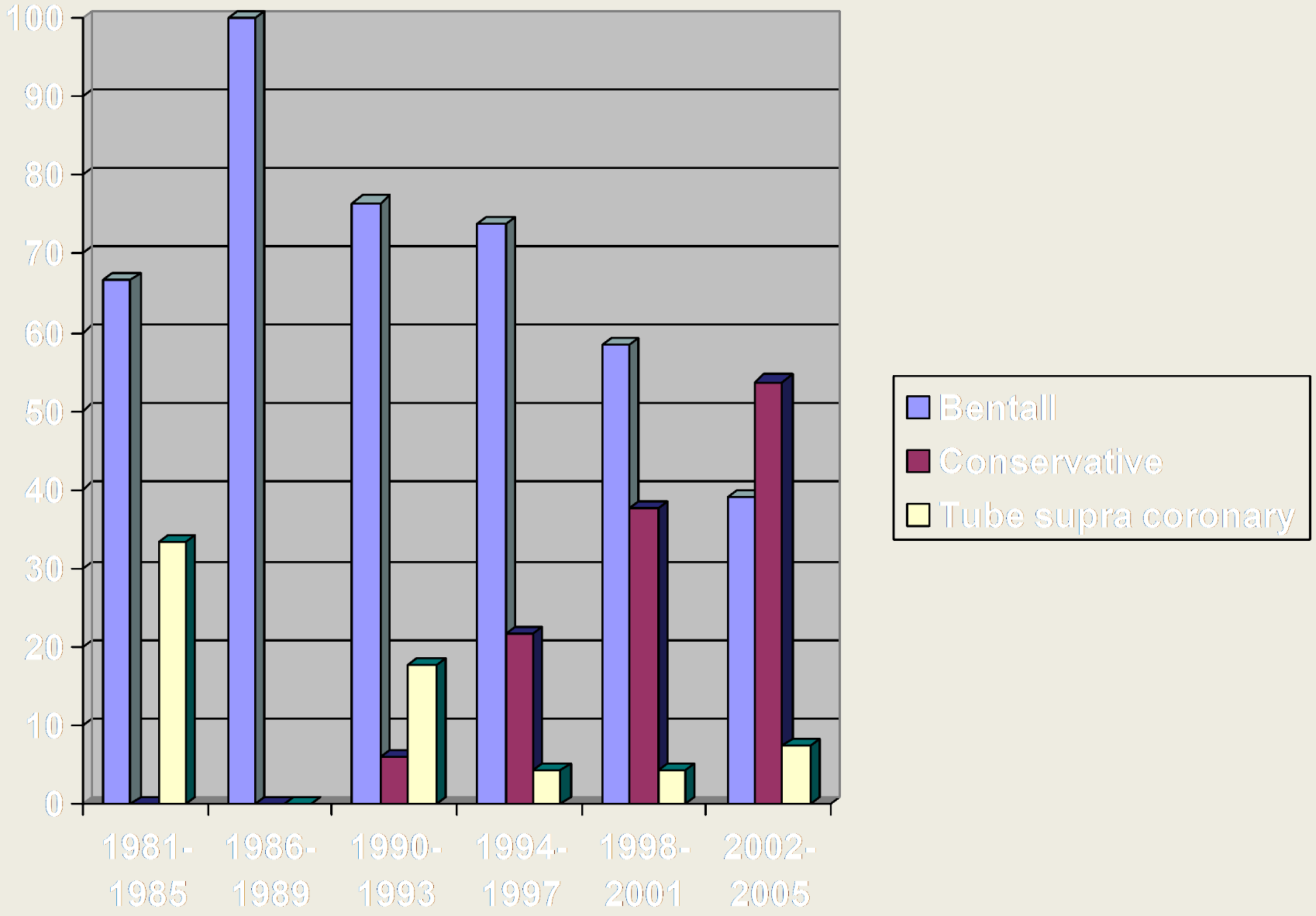
# Statines ?

## McLoughlin Circulation 2011;124;S168




80
60
40
20
0
1981-1985
1986-1989
1990-1993
1994-1997
1998-2001
2002-2005
anév
dissect

## - Type de chirurgie de l'aorte ascendante



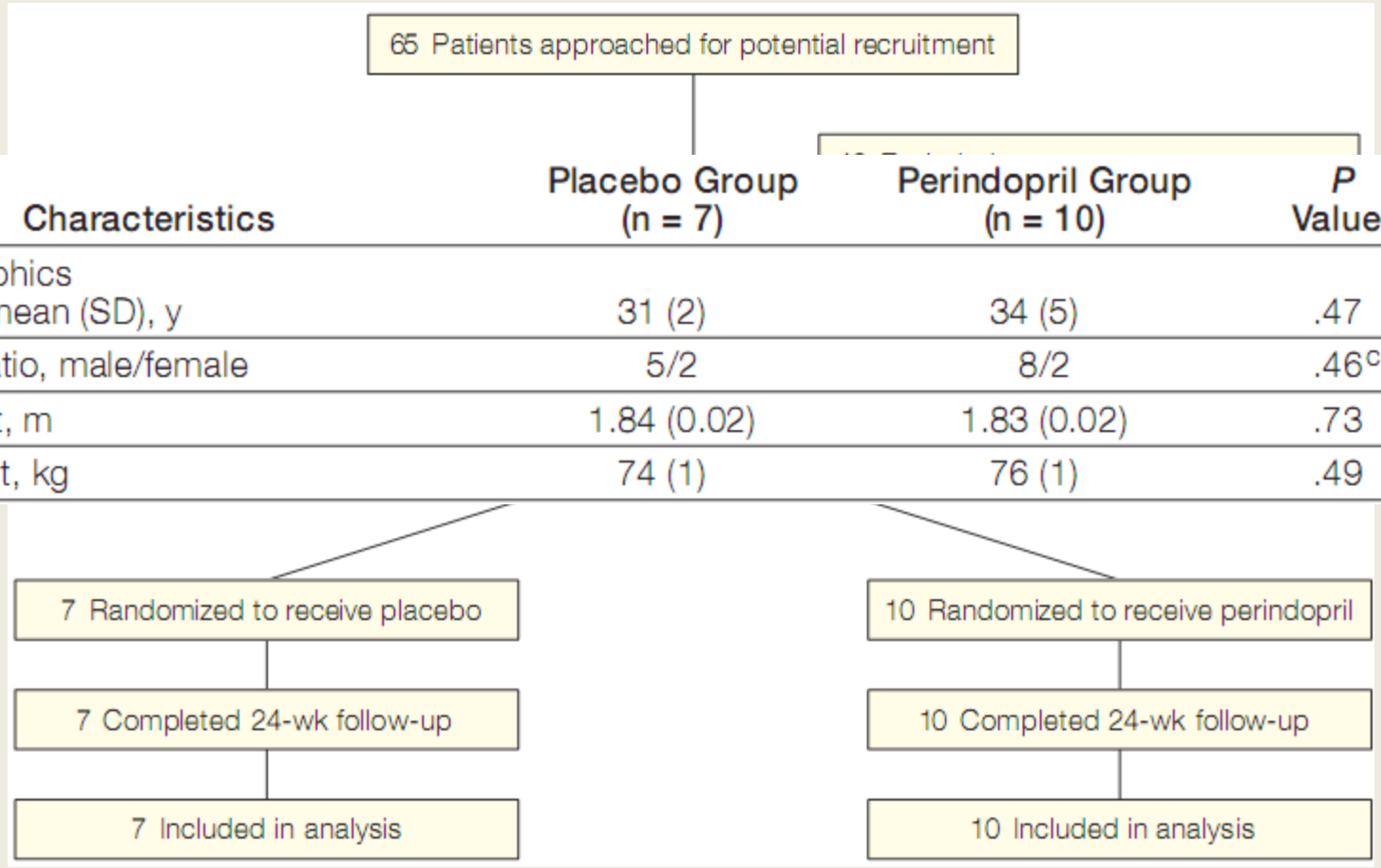
# Conclusions

Medical therapy when aortic fragility

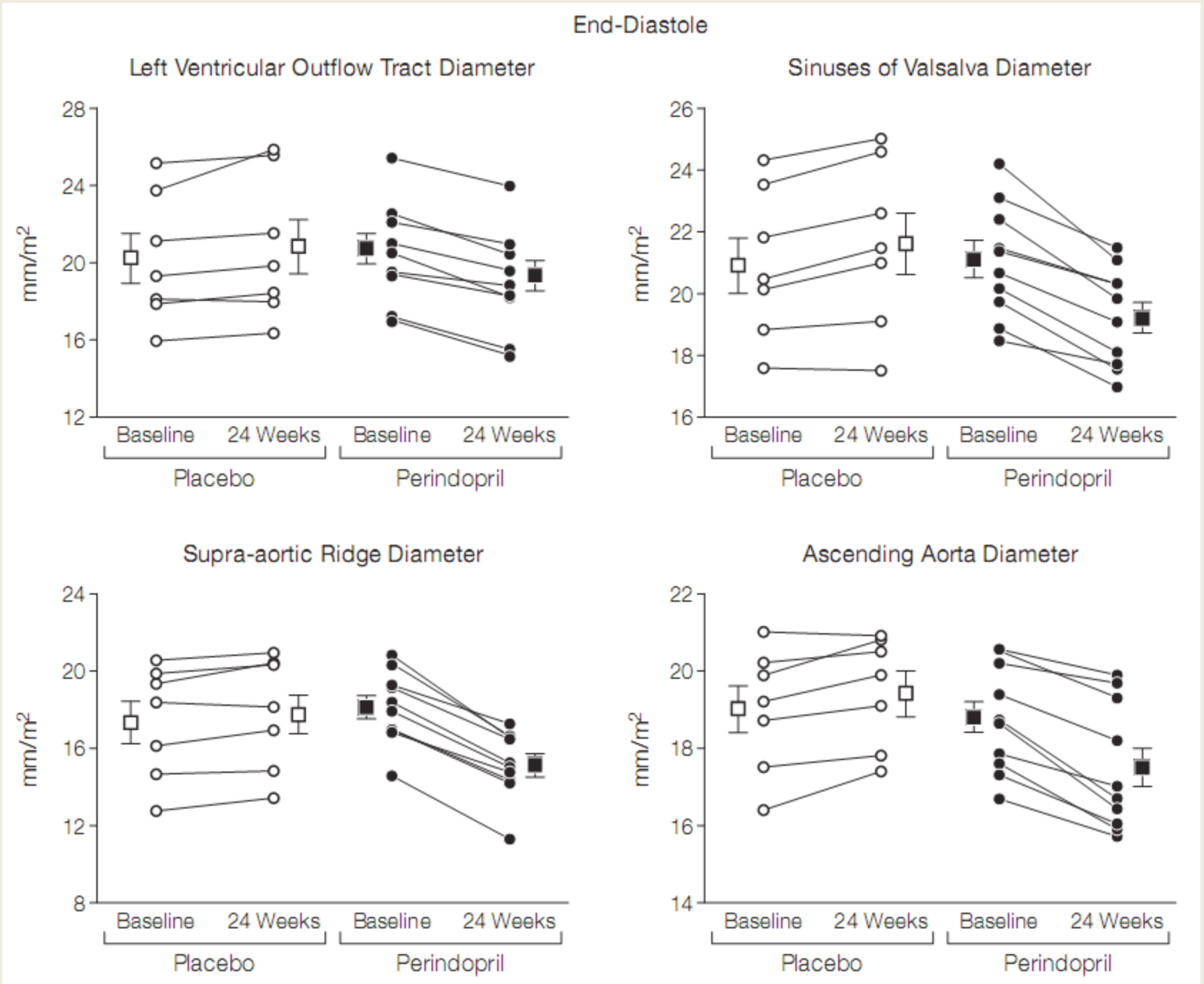
Based on

- beta-blockers (calcium antagonists ?)
- ARB : no
- ACEI : ?

# Ahimastos JAMA 2007;298:1539

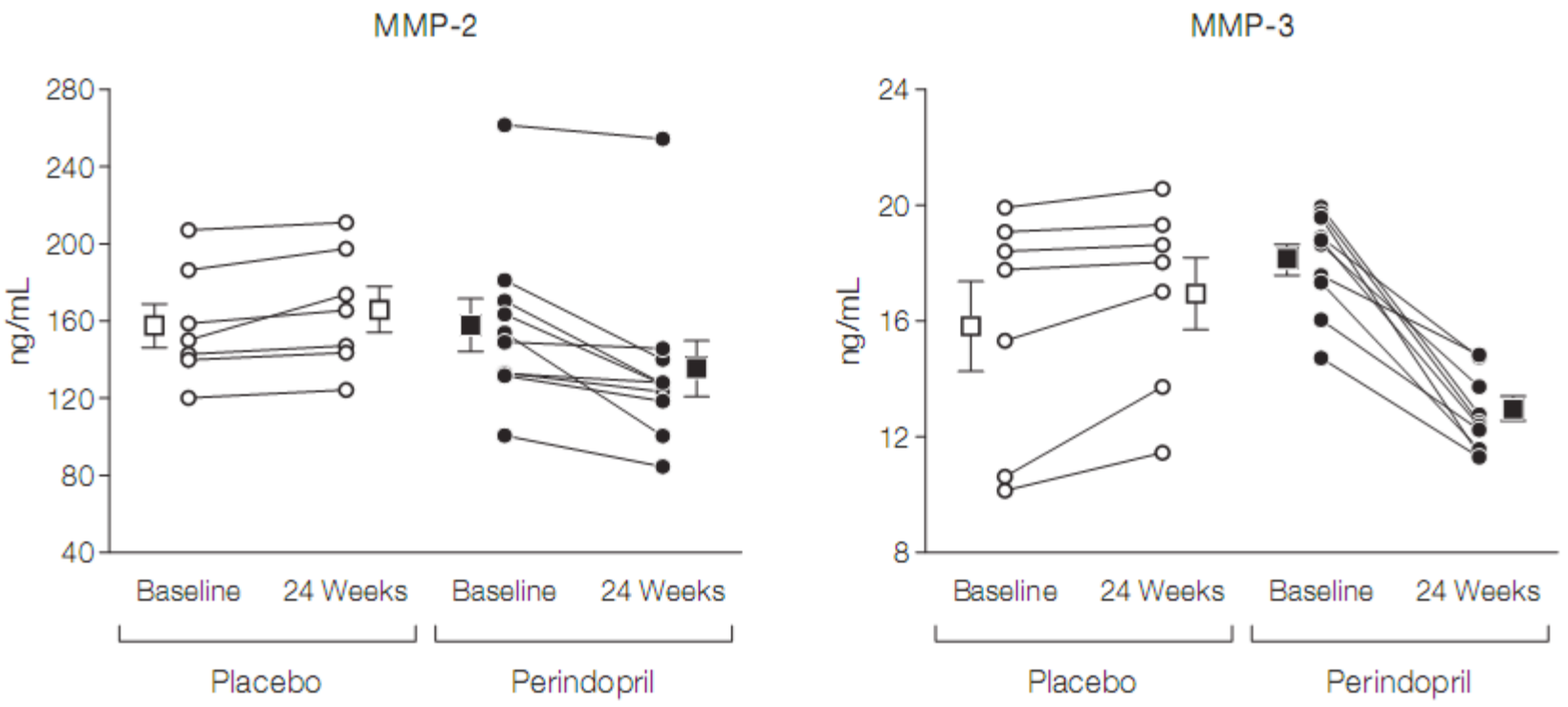



| Characteristics | Placebo Group (n = 7) | Perindopril Group (n = 10) | *P* Value[b] |
|---|---|---|---|
| Demographics | | | |
| Age, mean (SD), y | 31 (2) | 34 (5) | .47 |
| Sex ratio, male/female | 5/2 | 8/2 | .46[c] |
| Height, m | 1.84 (0.02) | 1.83 (0.02) | .73 |
| Weight, kg | 74 (1) | 76 (1) | .49 |


End-Diastole
Left Ventricular Outflow Tract Diameter
mm/m²
28
24
20
16
12
Baseline
24 Weeks
Baseline
24 Weeks
Placebo
Perindopril
Sinuses of Valsalva Diameter
mm/m²
26
24
22
20
18
16
Baseline
24 Weeks
Baseline
24 Weeks
Placebo
Perindopril
Supra-aortic Ridge Diameter
mm/m²
24
20
16
12
8
Baseline
24 Weeks
Baseline
24 Weeks
Placebo
Perindopril
Ascending Aorta Diameter
mm/m²
22
20
18
16
14
Baseline
24 Weeks
Baseline
24 Weeks
Placebo
Perindopril

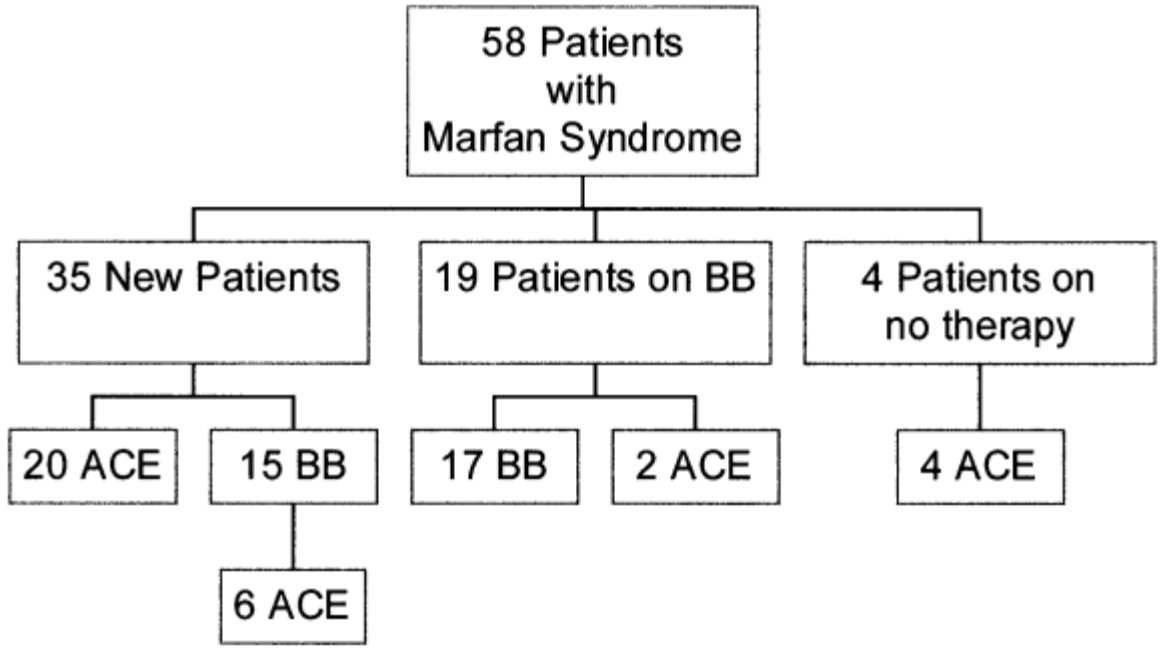
# Ahimastos JAMA 2007;298:1539

**Figure 4.** Individual Matrix Metalloproteinase (MMP)-2 and MMP-3 Protein Levels




Squares indicate mean (SEM) values. $P < .001$ for both plots.

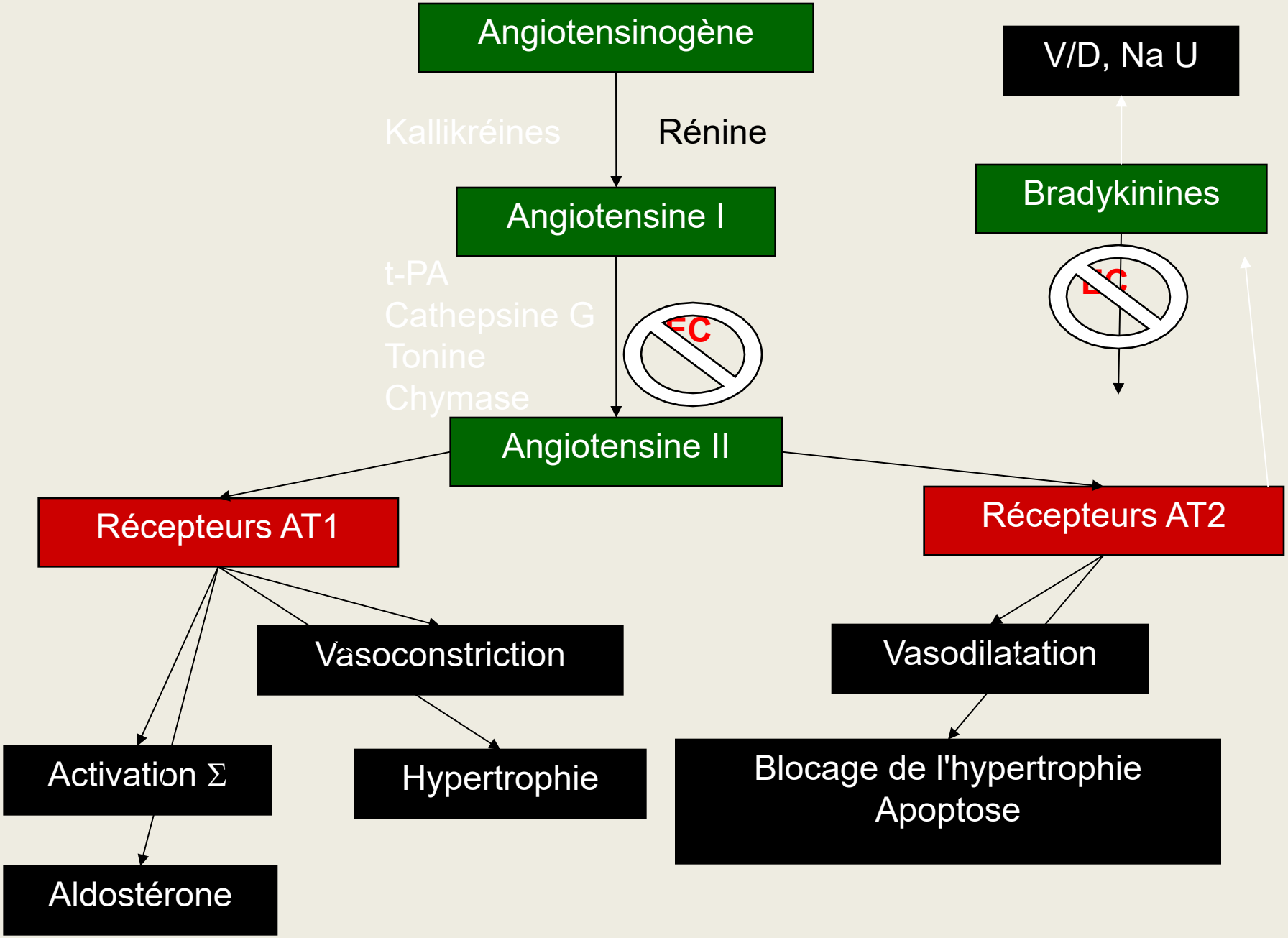
# Yetman Am J Cardiol 2005;95:1125




| | Enalapril (n = 32) | Propranolol/Atenolol (n = 25) | |
|---|---|---|---|
| Rate of change in % predicted aortic size over time (%/yr) | −2.5 ± 1.0 | 3.7 ± 1.4 | 0.005 |

# IEC et modèle murin FBN1

- Les IEC ne marcheraient pas
  - Le blocage des récepteurs AT2 à à l'angiotensine bloquerait le bénéfice des sartans


Angiotensinogène
Kallikréines
Rénine
Angiotensine I
t-PA
Cathepsine G
Tonine
Chymase
EC
Angiotensine II
V/D, Na U
Bradykinines
EC
Récepteurs AT1
Récepteurs AT2
Vasoconstriction
Vasodilatation
Activation Σ
Hypertrophie
Blocage de l'hypertrophie
Apoptose
Aldostérone

# Friends or competitors ?

Additional effect on

BP:

direct evaluation

indirect evaluation: tolerance of the 2

No competition on

Bradycardia

Direct effect

Animal model