3rd International Meeting on Aortic Diseases

New insights into an old problem
CHU Liège, FAD, APF

Biomarkers of TAAD and an Effective Medical Therapy for Thoracic Aneurysms: Statins

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"Biomarker": A biologic indicator of a disease process--often, but not always a blood-based test.

THORACIC AORTIC ANEURYSM

- Asymptomatic Disease
- Lethal First Presentation

----------→ Cries out for Biomarkers

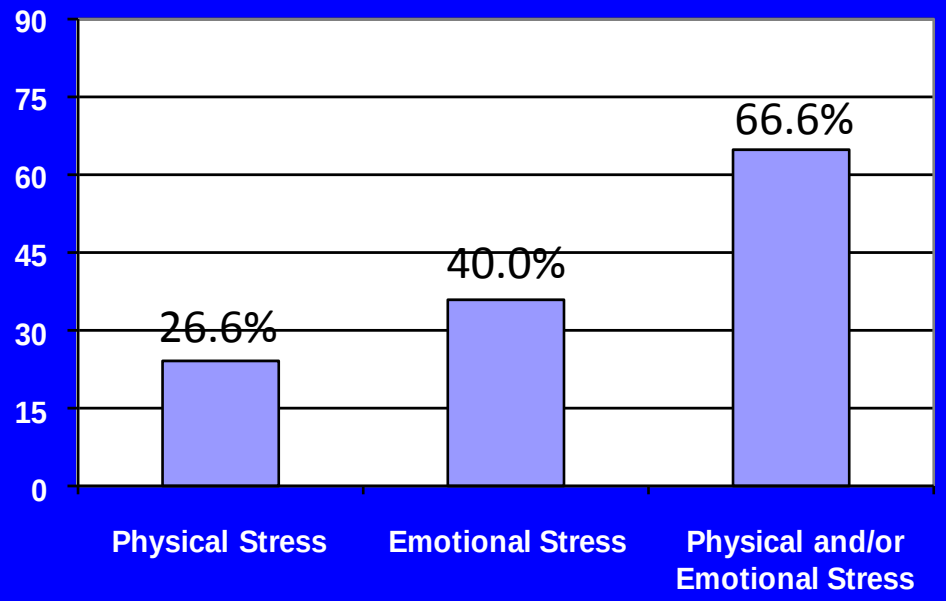
Healthy young men with only moderately enlarged aortas-> Aortic dissection while weightlifting

Elefteriades JA, et al. *JAMA.* Dec 5, 2003.

Inciting Events for Acute Aortic Dissection

65/90 (66.6%) Reported Physical/Emotional inciting events:

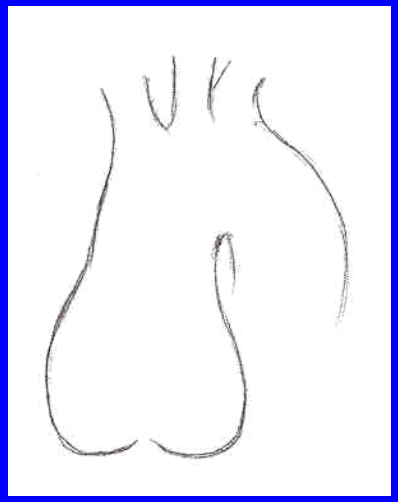
- 24/90 (26.6%) Physical
- 36/90 (40.0%) Emotional



Why does dissection pick one point in time to occur?

MMPs

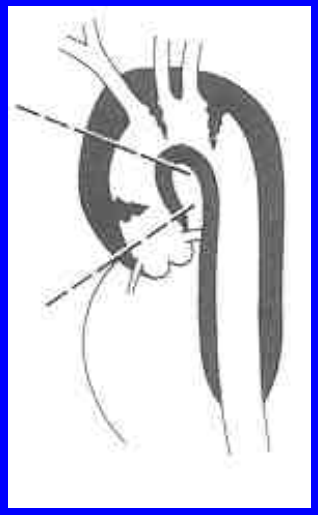
Genetic Predisposition



Aortic Dilatation

Exertion or emotion

Blood Pressure



Acute Aortic Dissection

REVIEW

In Search of Blood Tests for Thoracic Aortic Diseases

Santi Trimarchi, MD, Giuseppe Sangiorgi, MD, Xiangpeng Sang, BS, Vincenzo Rampoldi, MD, Toru Suzuki, MD, Kim A. Eagle, MD, and John A. Elefteriades, MD

Policlinico San Donato IRCCS, Cardiovascular Center "E. Malan," University of Milano, Milan, Department of Cardiology, Cardiac Catheterization Laboratory, University of Modena, Modena, Italy; Department of Internal Medicine, University of Tokyo, Tokyo, Japan; Department of Internal Medicine, University of Michigan Health Systems, Ann Arbor, Michigan; and Yale Thoracic Aortic Center, Yale University School of Medicine, New Haven, Connecticut

A number of new diagnostic screening tools have been developed for the assessment of acute and chronic diseases of the thoracic aorta. Although standardized blood-based tests capable of detecting individuals at risk for aortic aneurysm and dissection disease are not yet available, our current knowledge is expanding at a rapid rate and the future is very promising. In this review, an update of the contemporary knowledge on blood tests for detecting thoracic aortic diseases in both preclinical and clinical settings is provided, offering the potential to predict adverse aortic events, such as enlargement, rupture, and dissection.

(Ann Thorac Surg 2010;90:1735–42)

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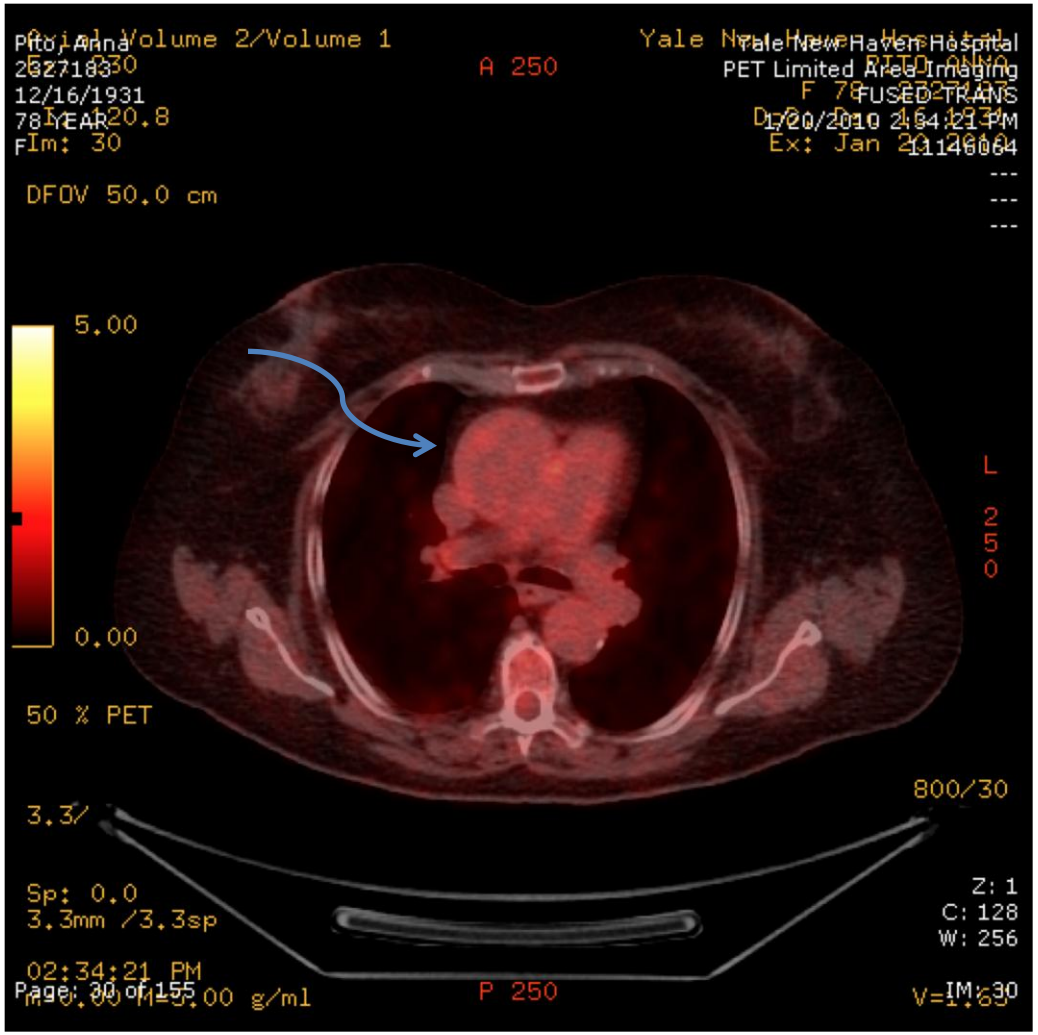
PET?

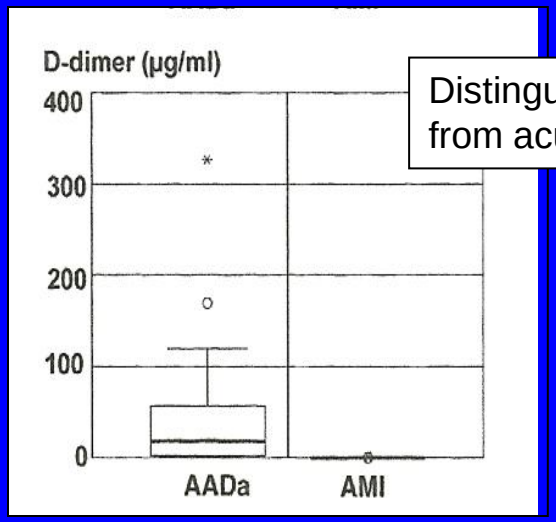


Truijers M. Endovasc Ther 2008;15:462-7.
Reeps C. J Vasc Surg 2008;48:417-23.

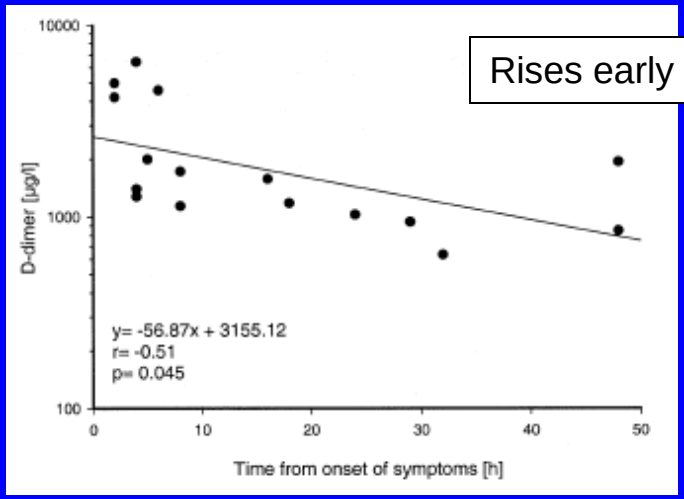
Potential Biomarkers

- D-Dimer
- Markers of inflammation
  - CRP
  - CD4+CD28- T-Cells
- Matrix metalloproteinases
- Markers of collagen turn-over
  - Elastin Peptide (EP)
- Genetic markers
  - “RNA Signature”

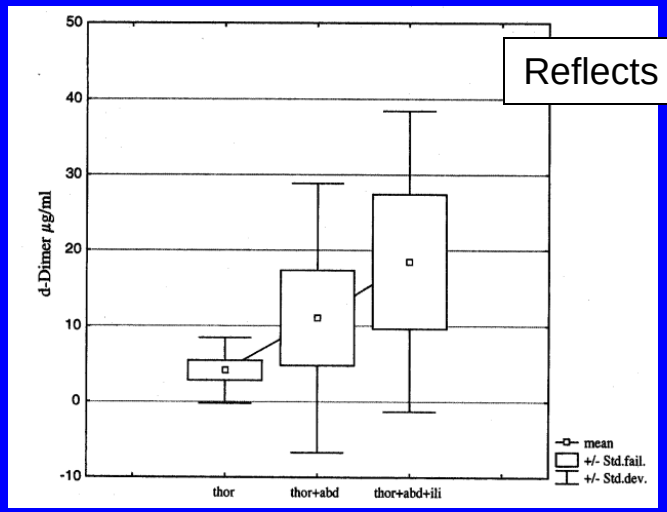
D-Dimer in Aortic Dissection-1



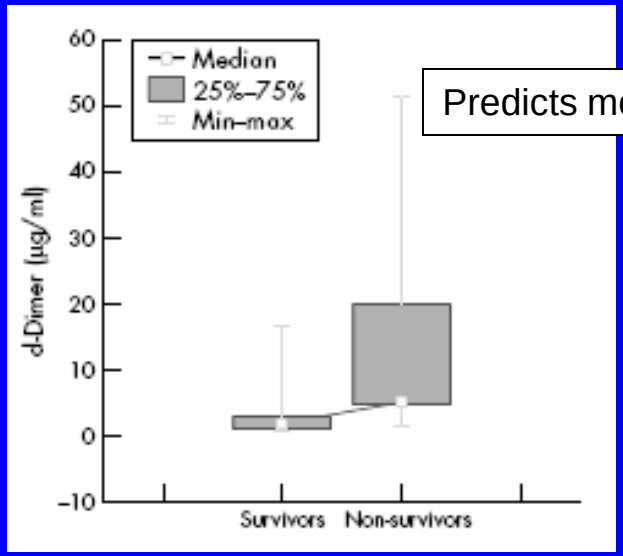
Distinguishes from acute MI



Rises early

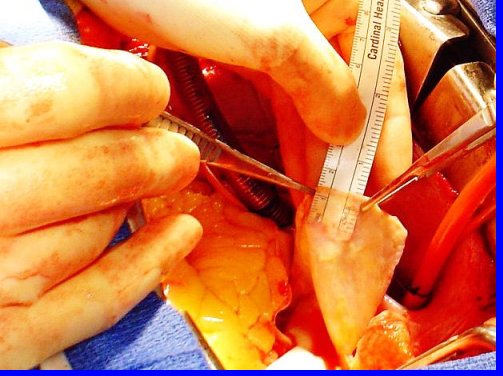


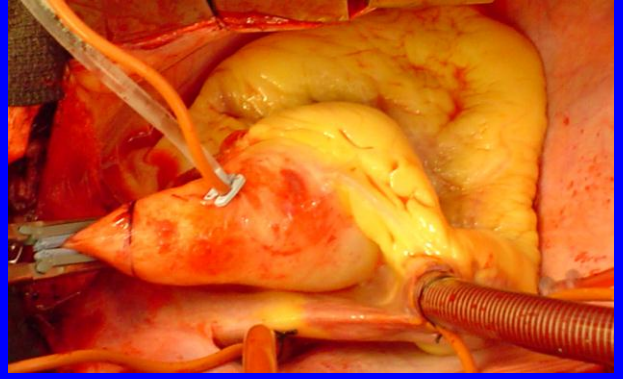
Reflects extent

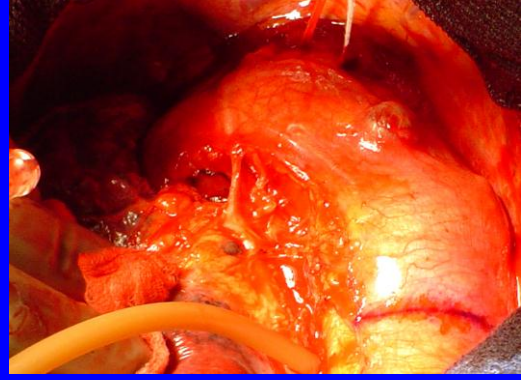


Predicts mortality

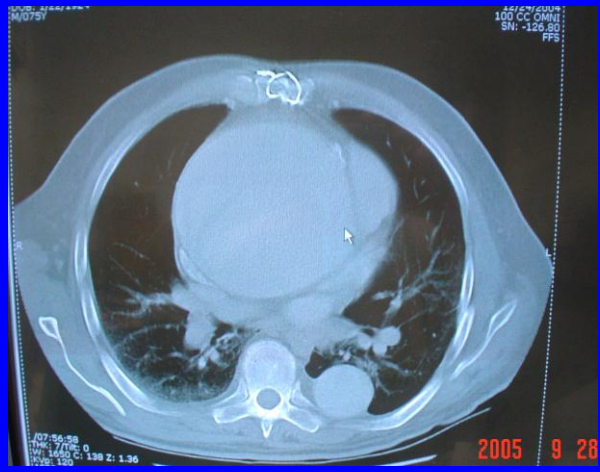
1. Hazui H et al. Circ J 2005;69:677-682.
2. Weber T et al. Chest 2003;123:1375-1378.
3. Eggebrecht H et al. J Am Coll Cardiol 2004;44:804-9
4. Weber T et al. Heart 2006;92:836-837.

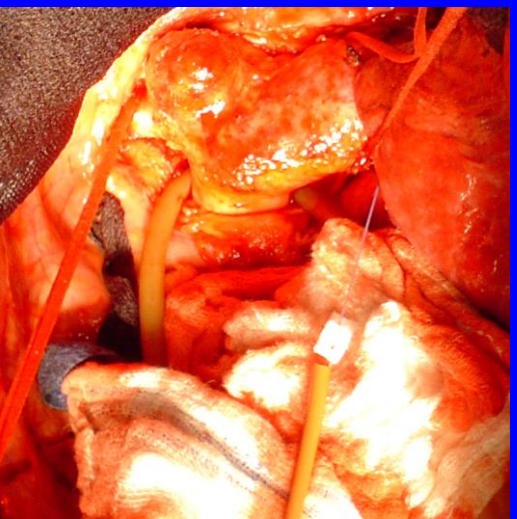


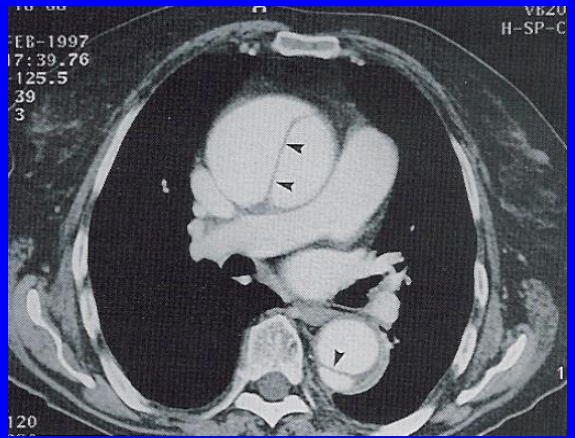


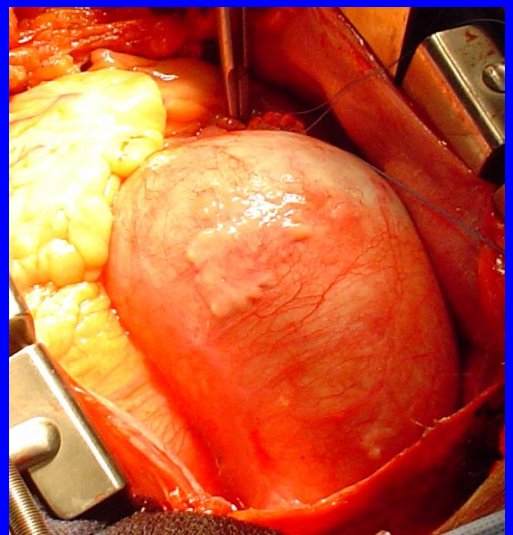


- Research at Yale and other programs indicates an important etiologic role for excess MMP activity in the destruction of the aortic wall underlying thoracic aortic aneurysm disease.

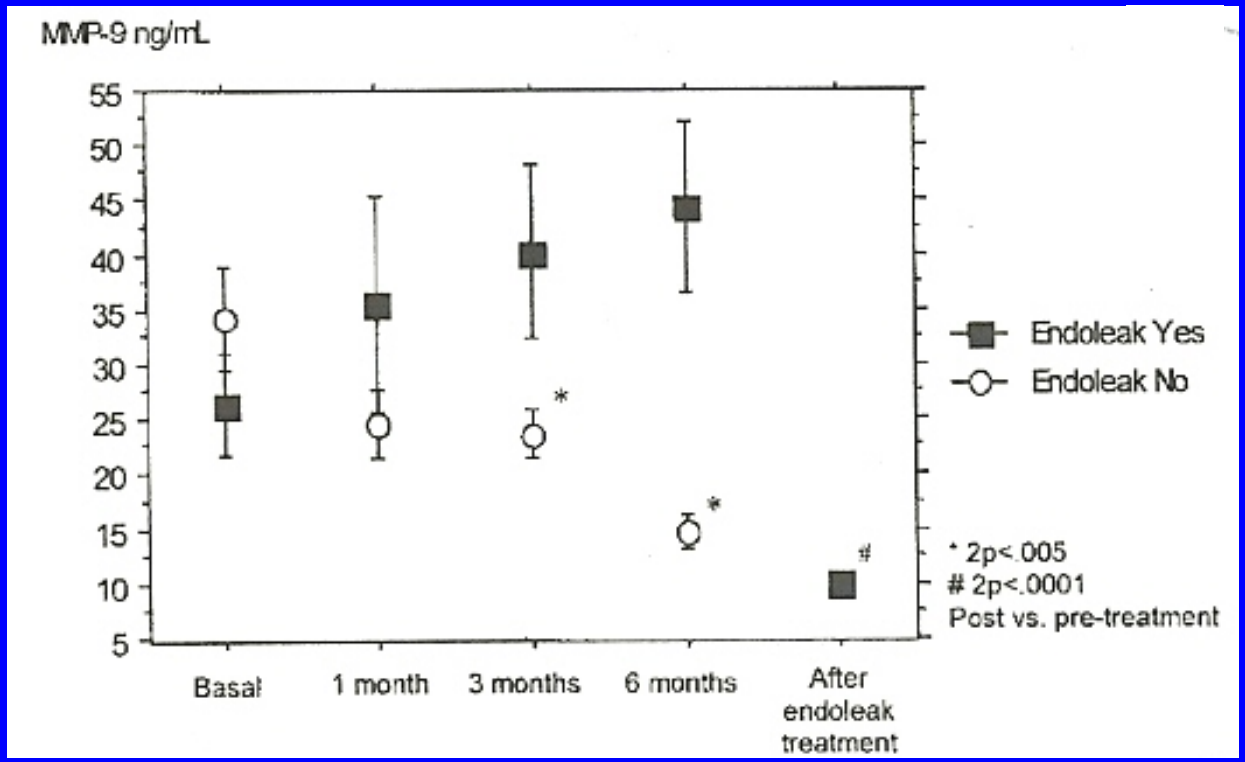






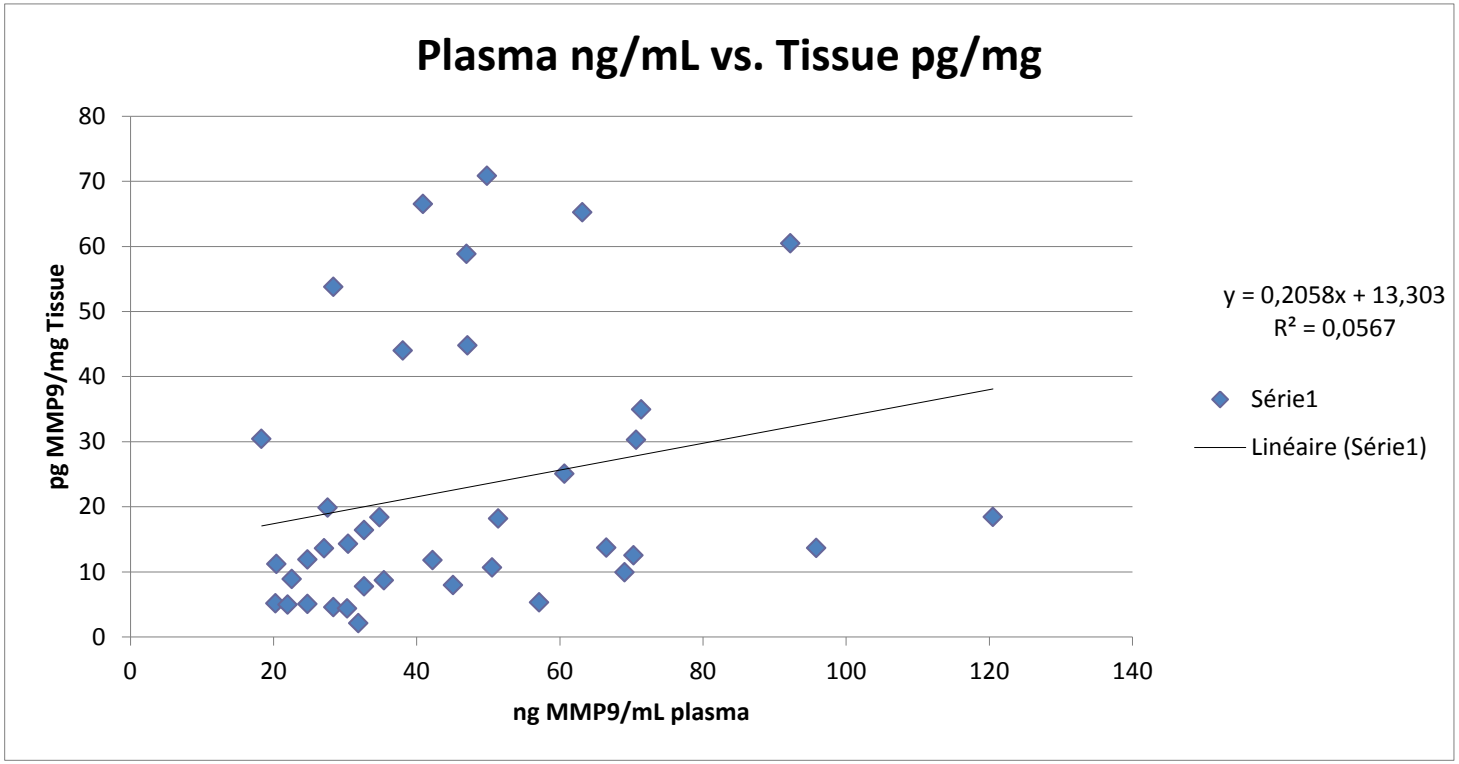


Serum MMP levels successfully predict stent graft failure



Sangiorgi G, et al. *Circulation* 2001;104[suppl I]:I-288-I-295.

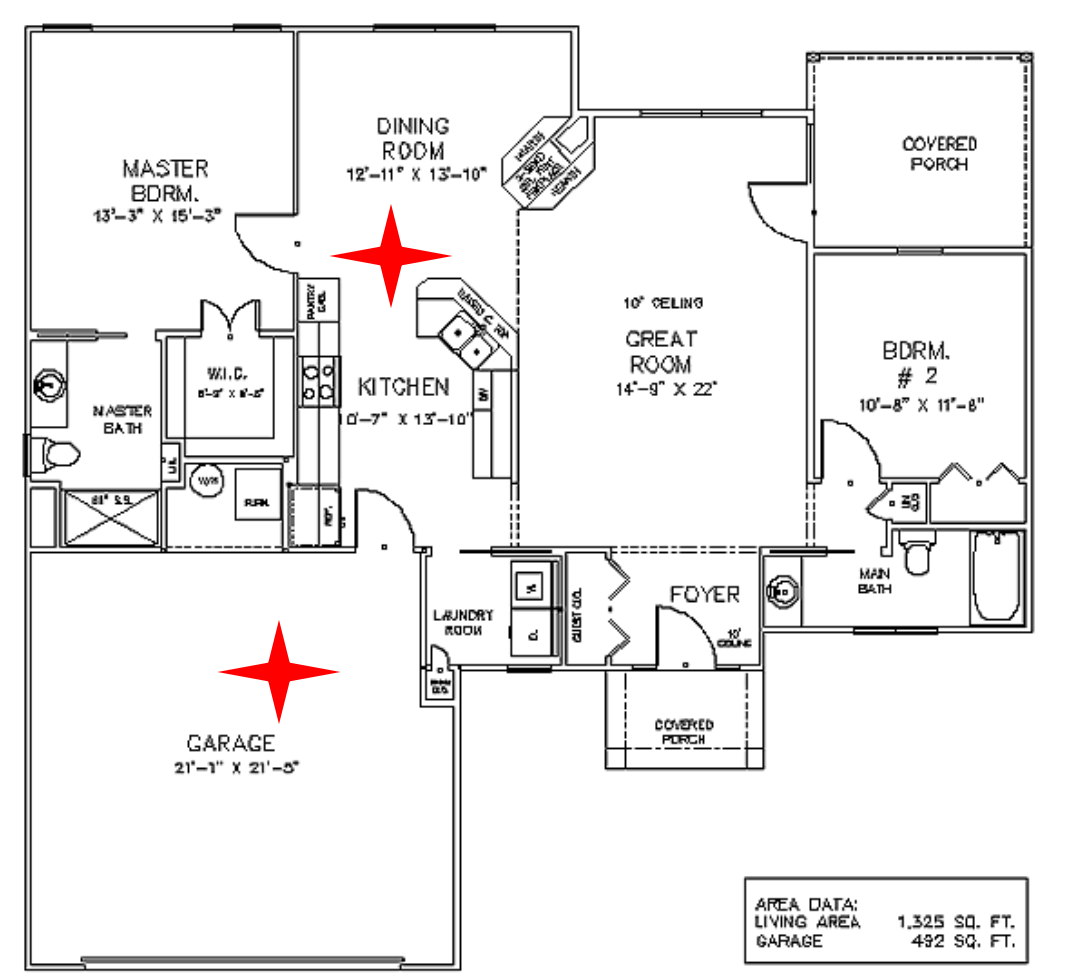
MMPs?



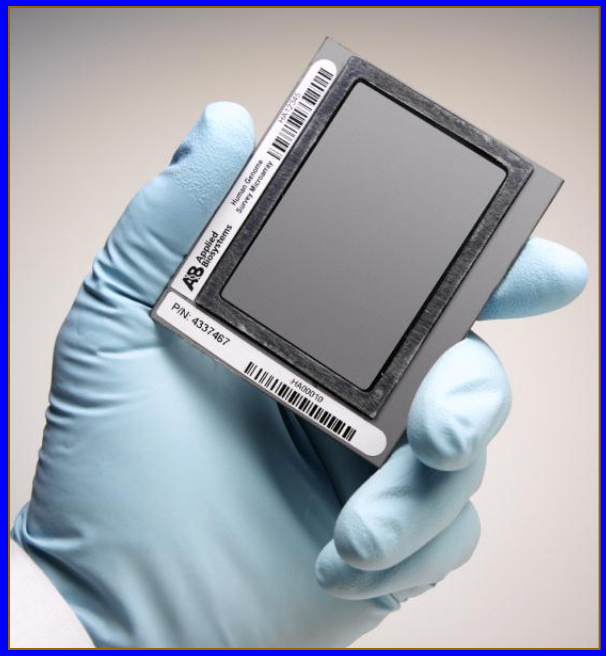
No significant correlations of serum with tissue levels of MMP-9.

“RNA Signature”

- DNA is blueprint
- RNA tells us what rooms (systems) are actively being worked on

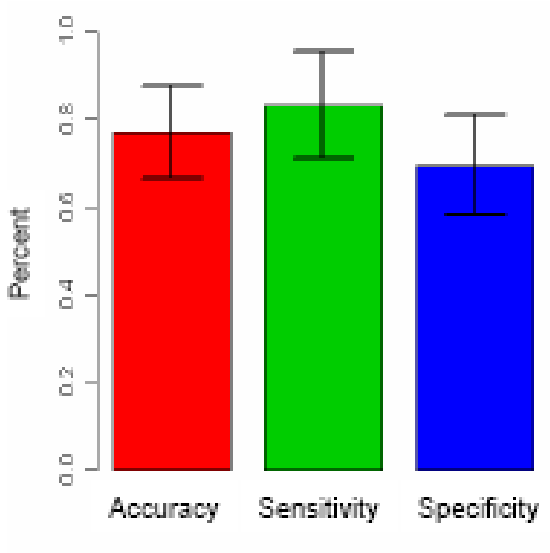


Applied Biosystems Human Whole Genome Survey Microarray

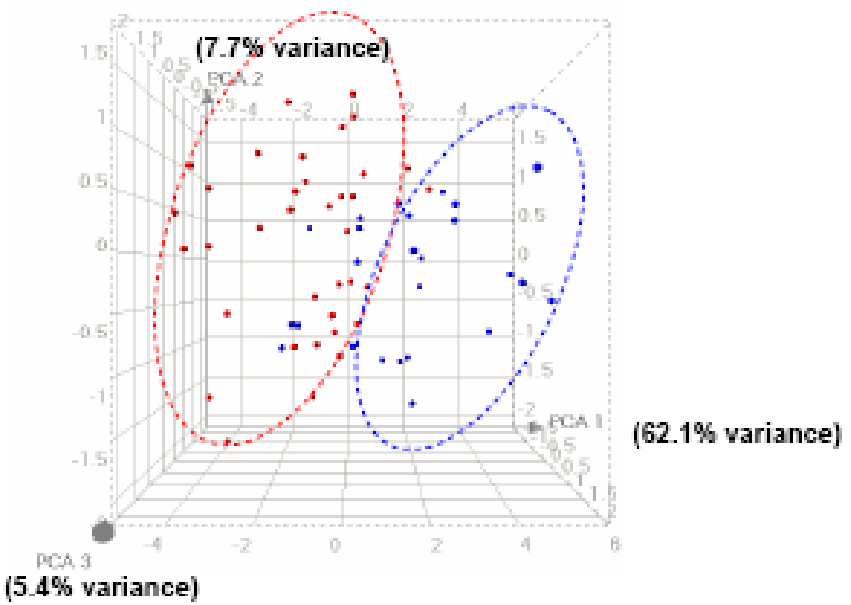


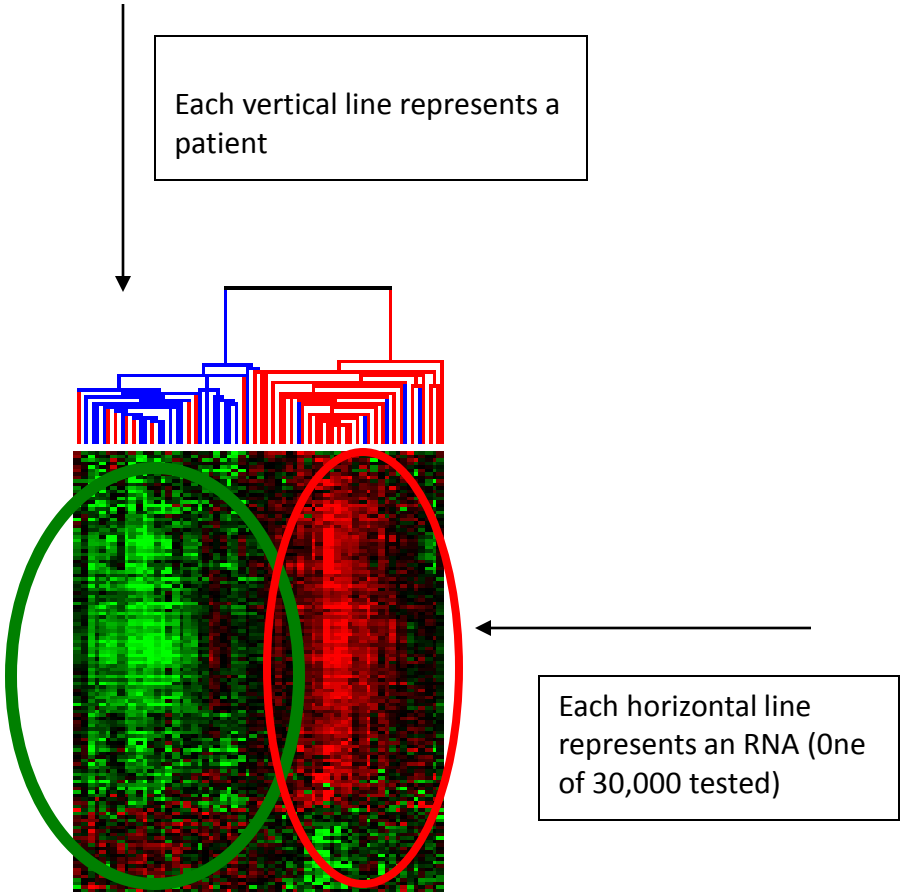
RNA “Signature” in peripheral blood

A.



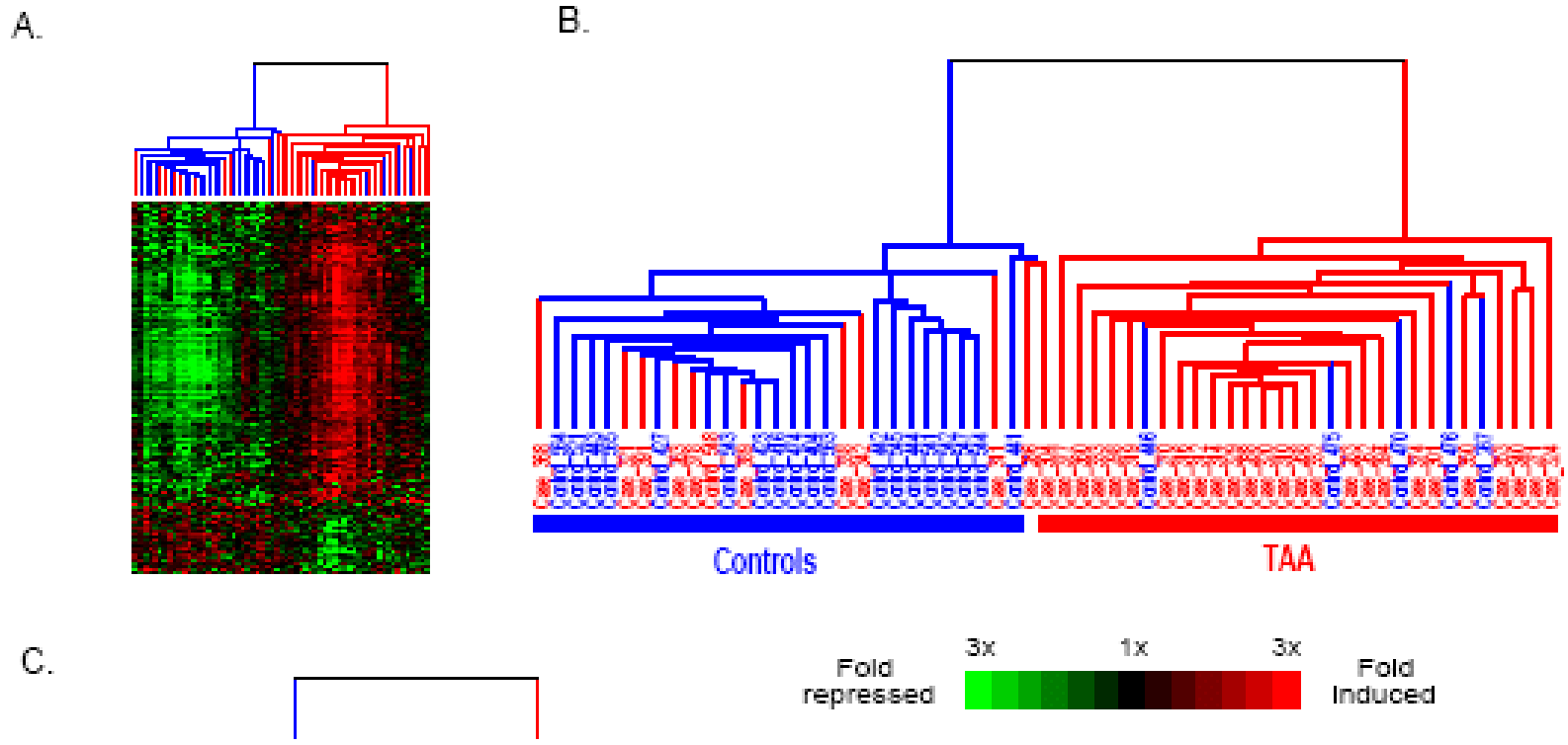
B.





Hierarchical clustering diagrams.

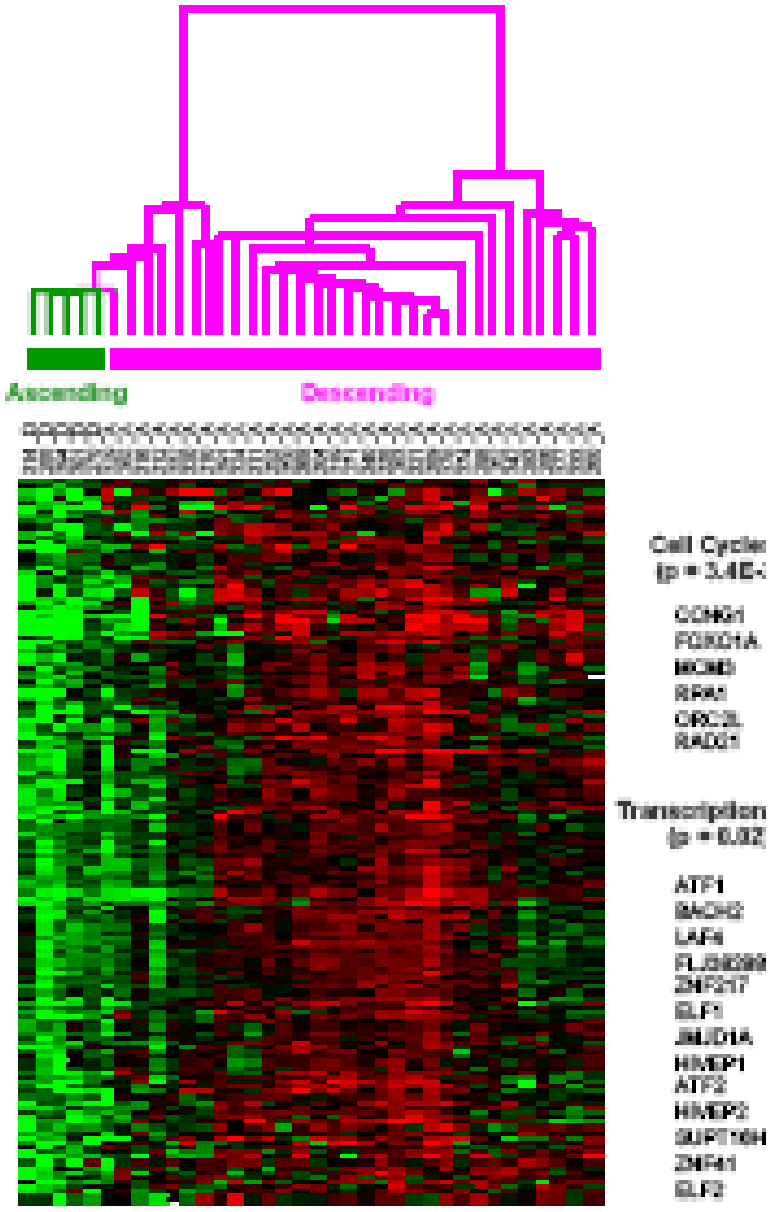
Figure 1



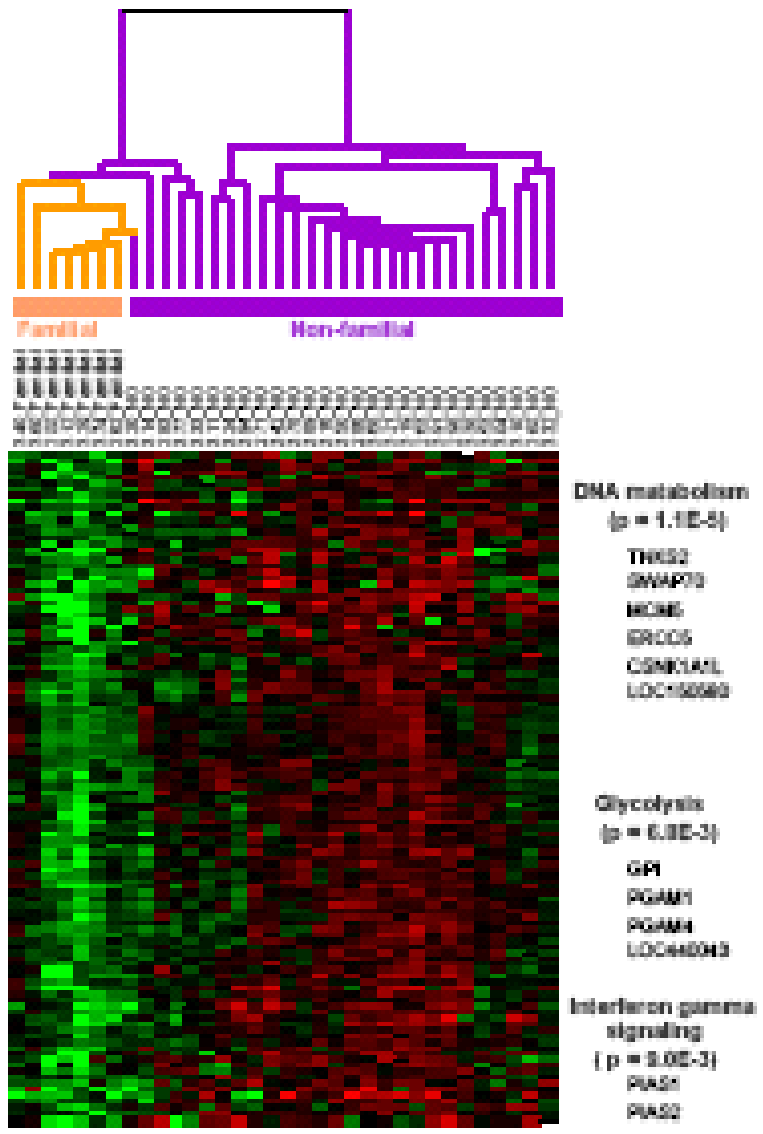
"RNA Signature" genes identified make "physiologic sense": proteolyis, apoptosis, inflammation

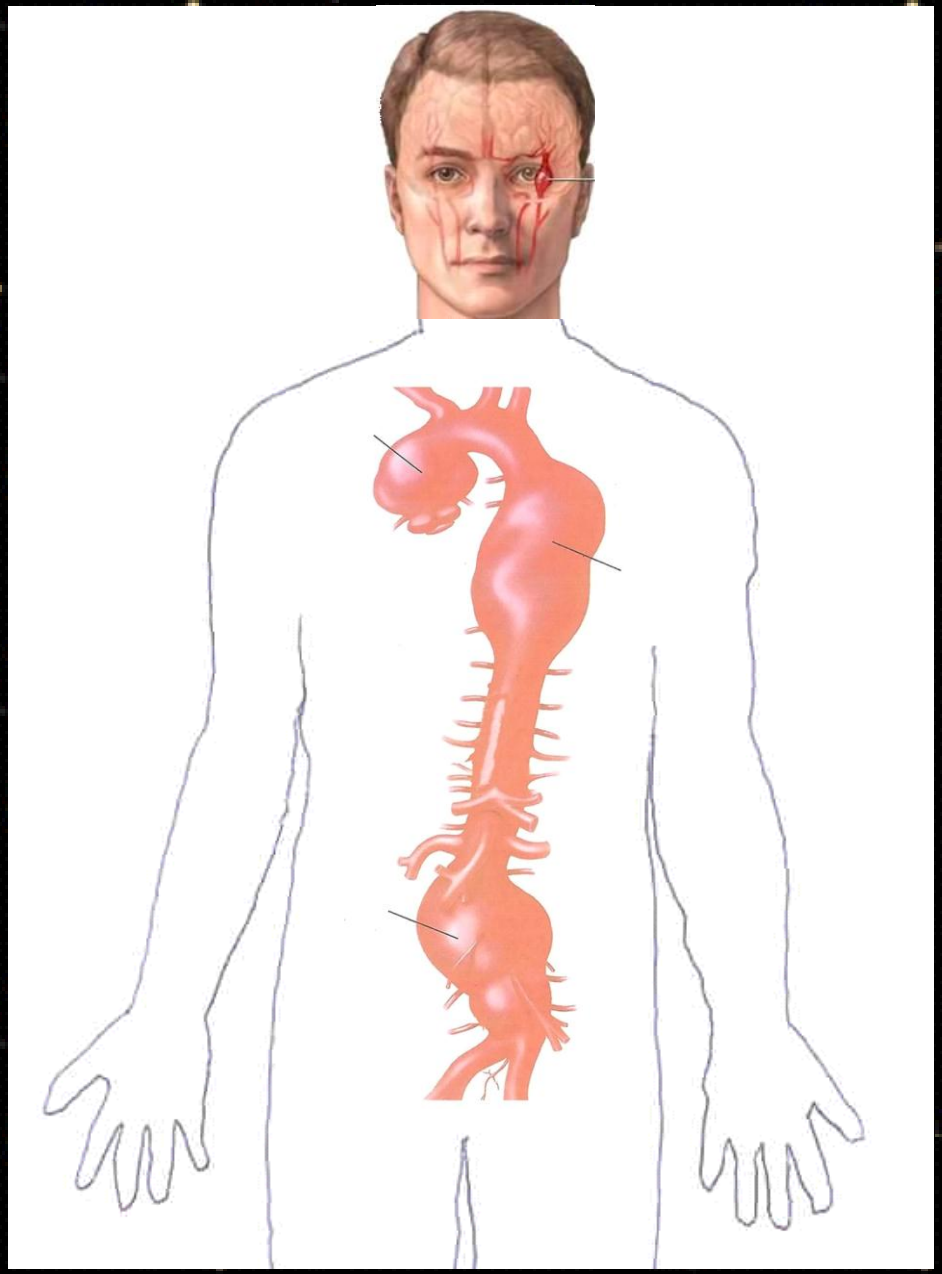
Gene Symbol	Gene_Name	Target RefSeqs	Asc/Desc Ratio (array)	Asc/Desc Ratio (TaqMan)
AFF3	AF4/FMR2 family, member 3	NM_002285	2.79	2.27
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	NM_021813	2.38	2.22
ZNF41	zinc finger protein 41	null	2.33	1.53
ATF2	activating transcription factor 2	NM_001880	2.20	1.58
HIVEP2	human immunodeficiency virus type I enhancer binding protein 2	NM_006734	2.08	1.53
HIVEP1	human immunodeficiency virus type I enhancer binding protein 1	NM_002114	2.00	1.44
ATF1	activating transcription factor 1	NM_005171	1.78	1.33
ORC2L	origin recognition complex, subunit 2-like (yeast)	NM_006190	1.66	1.55
FOXO1A	forkhead box O1A (rhabdomyosarcoma)	NM_002015	1.63	1.48
RAD21	RAD21 homolog (S. pombe)	NM_006265	1.62	1.29
ELF1	E74-like factor 1 (ets domain transcription factor)	NM_172373	1.61	1.35
ELF2	E74-like factor 2 (ets domain transcription factor)	NM_006874	1.59	1.35
MCM3	MCM3 minichromosome maintenance deficient 3 (S. cerevisiae)	NM_002388	1.57	1.45
RPA1	replication protein A1, 70kDa	NM_002945	1.52	1.53
ZNF217	zinc finger protein 217	NM_006526	1.46	2.02
JMJD1A	jumonji domain containing 1A	NM_018433	1.44	1.55
SUPT16H	suppressor of Ty 16 homolog (S. cerevisiae)	NM_007192	1.43	1.63
CCNG1	cyclin G1	NM_004060	1.39	1.53

A.


Ascending
Descending
Cell Cycle
(p = 3.4E-
CDNG1
FOXO1A
MCM5
RPA1
ORC3L
RAD21
Transcription
(p = 6.02
ATF1
BACH2
LAF4
FLJ10289
ZNF217
ELF1
JMJD1A
HMEP1
ATF2
HMEP2
SUPT16H
ZNF41
ELF2

B.


Familial
Non-familial
DNA metabolism
(p = 1.1E-5)
THOC2
SNAP29
MCM5
ERCC5
CSNK1A1L
LOC150580
Glycolysis
(p = 6.3E-3)
GPI
PGAM1
PGAM4
LOC440043
Interferon gamma
signaling
(p = 9.0E-3)
PIAS1
PIAS2



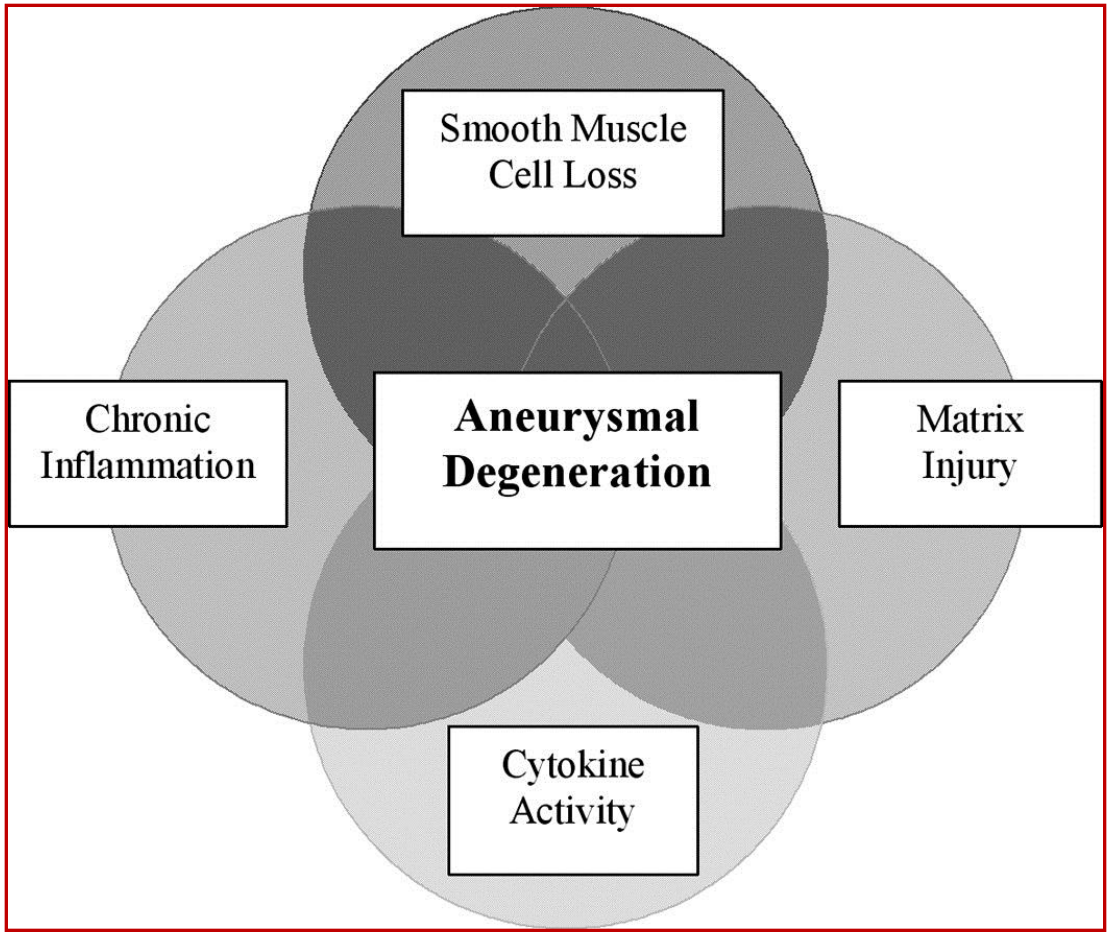
FUTURE: Biomarkers for Aortic Disease?????…

- Urgently needed.
- Not a reality yet.
- Considerable promise for the future.
- RNA Signature promising
- Radiographic biomarkers ready to be applied.

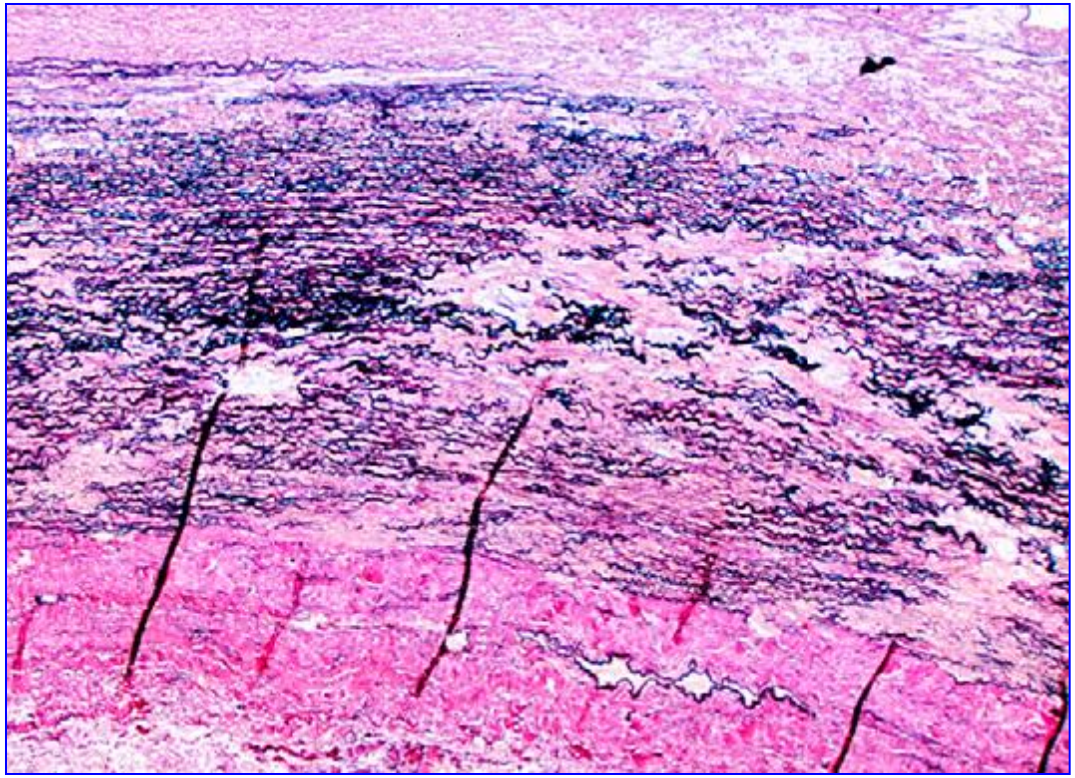
THERE *IS* AN EFFECTIVE MEDICAL TREATMENT FOR THORACIC AORTIC ANEURYSM

John A. Elefteriades, MD
William W.L. Glenn Professor of Cardiothoracic Surgery
Director, Aortic Institute at Yale-New Haven

Pathogenesis of Aortic Aneurysms



One would think that there would be multiple opportunities for drug Rx to stop this process!



β-Blockers

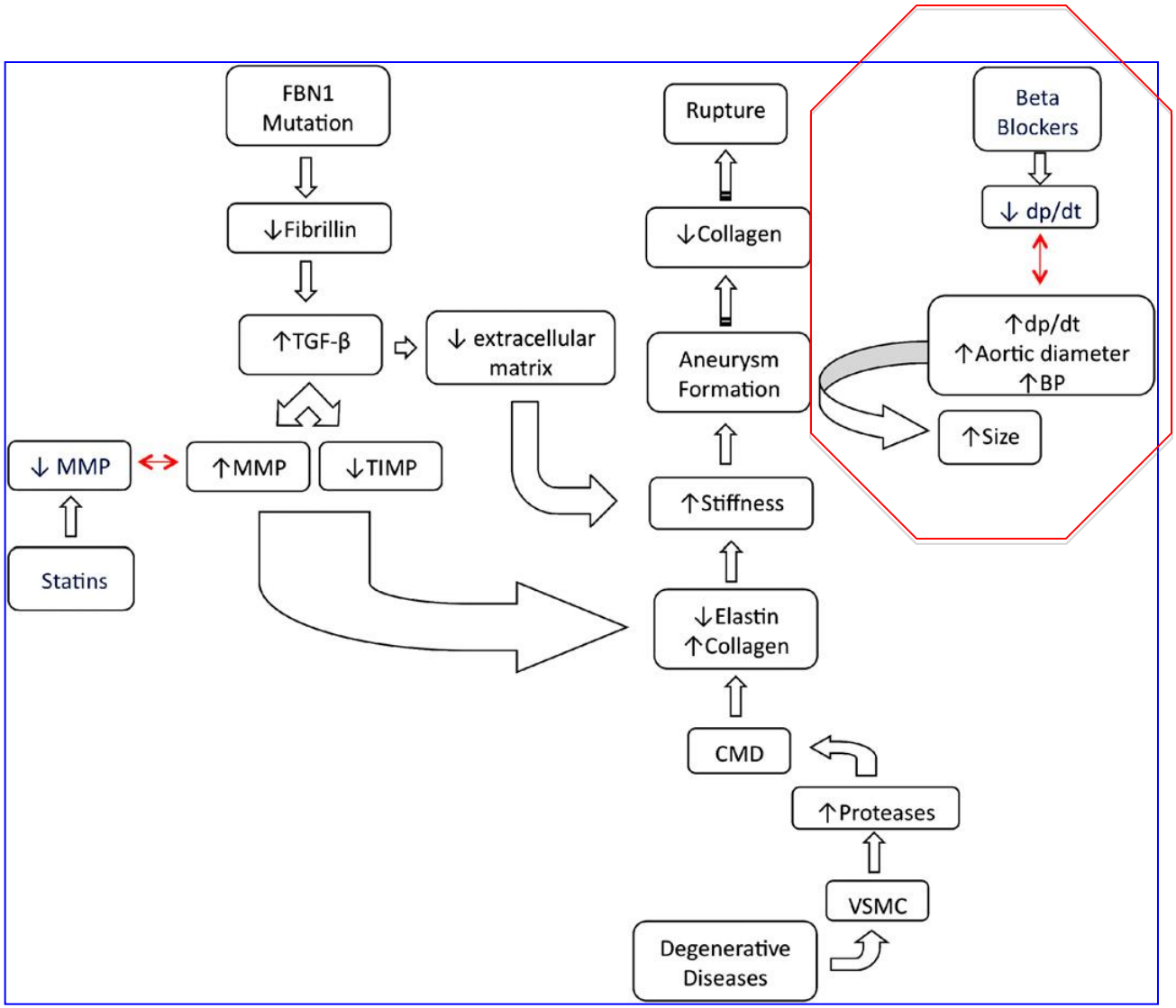
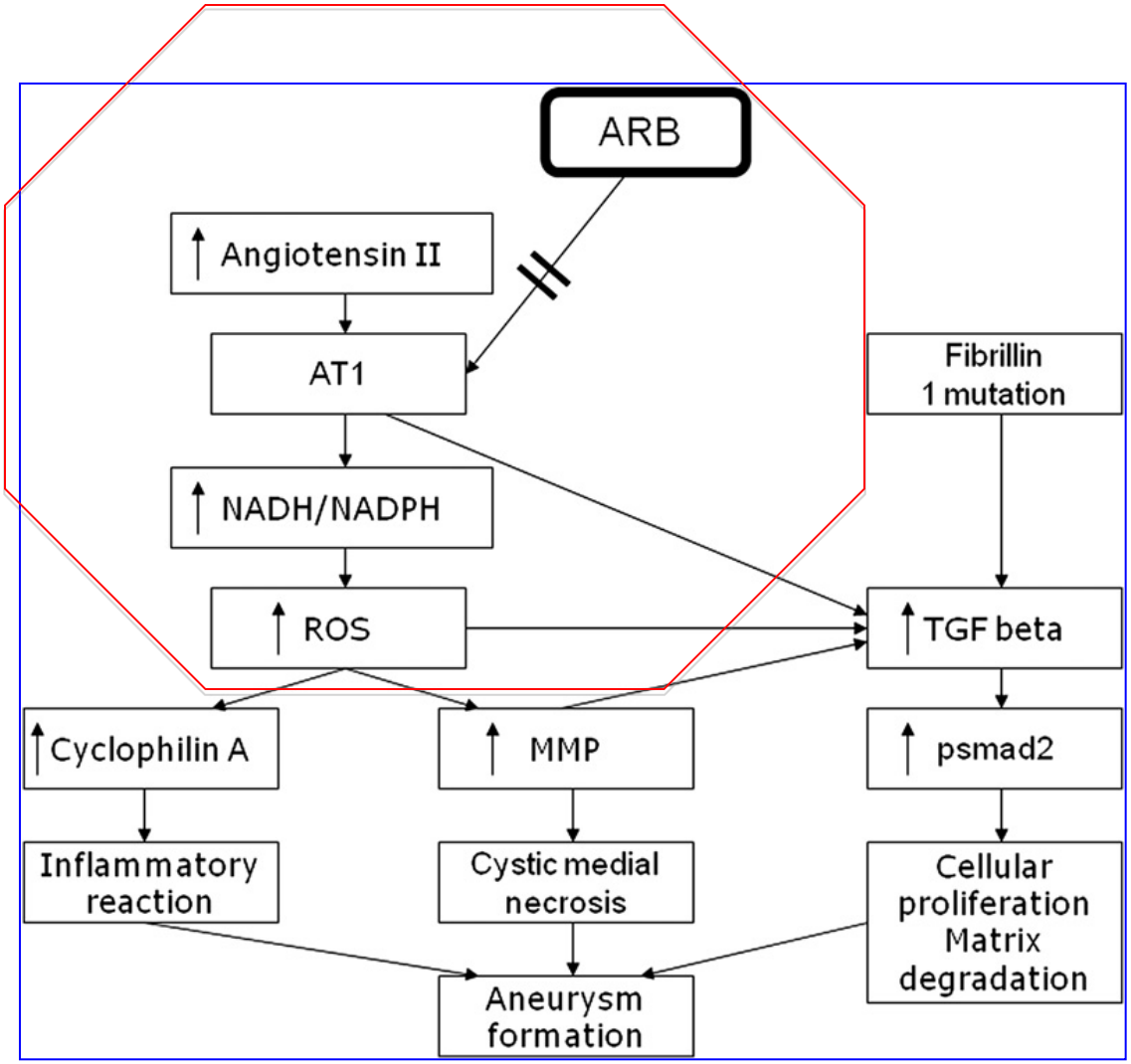

FBN1 Mutation
↓Fibrillin
↑TGF-β
↓ extracellular matrix
↓ MMP
↑MMP
↓TIMP
Statins
Rupture
↓Collagen
Aneurysm Formation
↑Stiffness
↓Elastin ↑Collagen
CMD
↑Proteases
VSMC
Degenerative Diseases
Beta Blockers
↓ dp/dt
↑dp/dt ↑Aortic diameter ↑BP
↑Size

Table: Clinical trials of β-blockers in management of aneurysms

Aneurysm Type	Author, Year Medicatio	Study Design		Results
TAA	No clinical trials available			
AAA	Lindholt, 1999 Propranolol	RCT of 54 asymptomatic patients with small AAA	(-)	Only 22% were treatable with propranolol for 2 years; increased mortality in β- blocker group
AAA	Propranolol Aneurysm Trial Investigators, CANADA, 2002 Propranolol	Three nonrandomized trials	(-)	Patients with AAAs did not tolerate propranolol well; no significant effect on the growth rate of small AAAs
AAA	Cronenwett; Gadowski; Leach, 1990, 1994, 2005 Propranolol	RCT of asymptomatic AAA (3.0-5.0 cm)	(+)	Decreased rate of AAA expansion in β-blocker group
Marfan syndrome	Shores, 1994 Propranolol	RCT of 70 patients	(+)	Decreased rate of aortic root dilatation and fewer aortic complications in β-blocker group
Marfan syndrome	Gersony, 2007 β-Blockers	Meta-analysis: 9 studies (5 nonrandomized; 1 was a prospective RCT with 802 patients)	(-)	No change in risk of aortic dissection or rupture, cardiovascular surgery, or death
Marfan syndrome	Gambarin, 2009 Losartan vs nebivolol	Open-label phase 3 study will include 291 patients	Ongoing	Primary end point: effect on the progression of aortic root growth

ARBs


ARB
Angiotensin II
AT1
NADH/NADPH
ROS
Fibrillin
1 mutation
TGF beta
Cyclophilin A
MMP
psmad2
Inflammatory
reaction
Cystic medial
necrosis
Cellular
proliferation
Matrix
degradation
Aneurysm
formation

Preclinical and clinical studies of angiotensin receptor blockers in aortic aneurysms

First Author [Ref]	Model/Population	Subject Number	Findings
Habashi [15]	Mouse, Marfan	10	ARB prevented aneurysm formation
Daugherty [49]	Mouse, apoE deficient, AAA	15	AT1 blockade (losartan) prevented aneurysm formation, AT2 blockade promoted it
Nagashima[50]	Rat, β-aminopropionitrile monofumarate-induced cystic medial degeneration and aortic dissection	15	ACEI but not ARB prevented cystic medial degeneration and aortic dissection
Liao[51]	Rat, elastase-induced, AAA	9	ACEIs but not ARB suppressed AAA formation
Brooke[52]	Human, Marfan (retrospective)	18	ARB significantly slowed aortic root dilatation
Hackam[53]	Human, AAA (retrospective)	15326	ACEIs were, but ARBs not protective against aortic aneurysm rupture

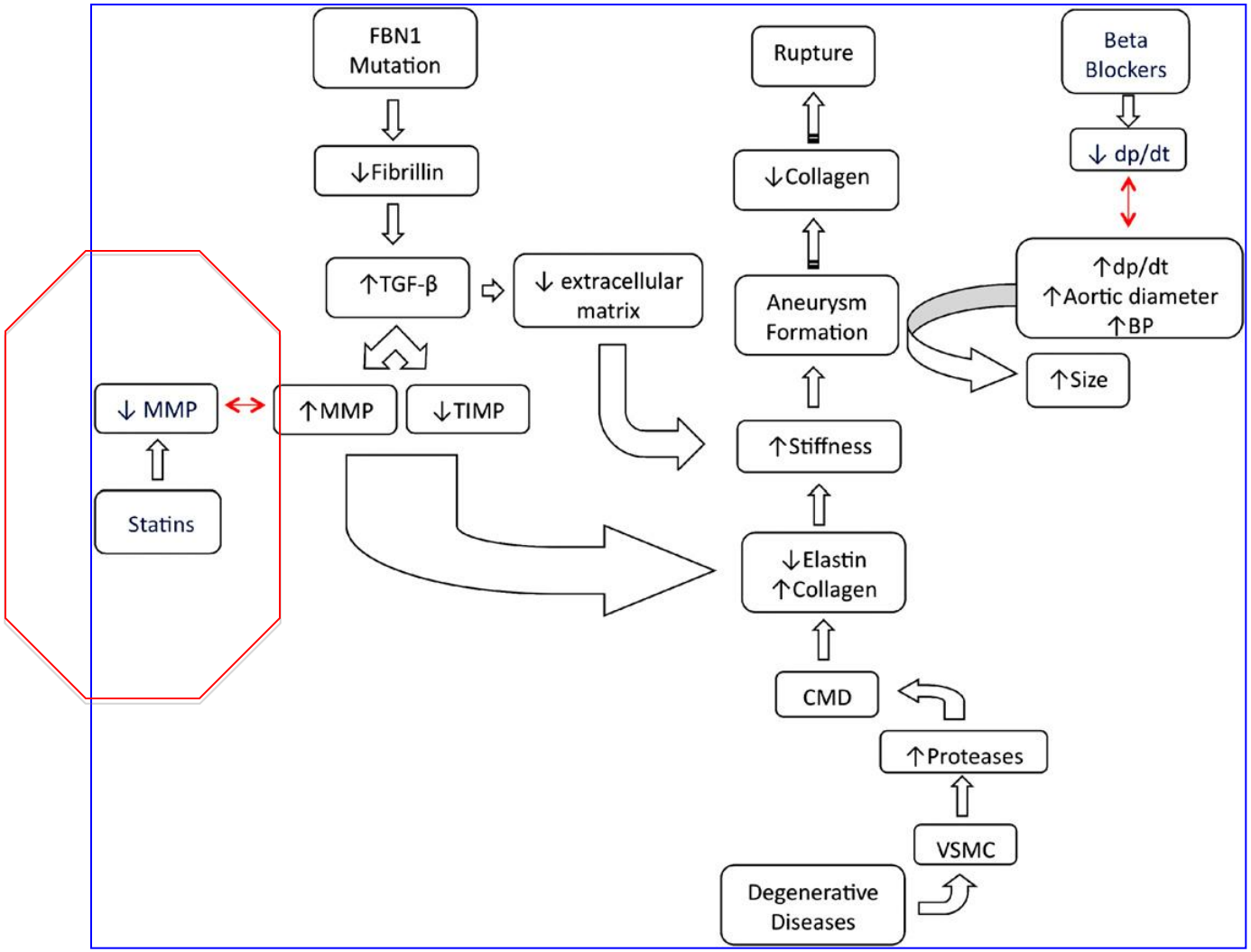
Other: Doxycycline, etc.

Table. Clinical Studies of Medical Therapy for Aortic Aneurysms

Authors	Study Design	Intervention	Patients, n	Findings
Shores et al[59]	Marfan syndrome; randomized, prospective study; ~10-y mean follow-up	Propranolol	32 Treated, 38 control subjects	Propranolol caused significantly reduced aortic root dilatation
Gadowski et al[57]	Infrarenal AAA; observational, prospective study; 43-mo mean follow-up	β-blocker	38 Treated, 83 control subjects	Patients with large aneurysms on β-blockers had significantly lower AAA expansion rate
Leach et al[58]	AAA; observational, retrospective study; 34-mo mean follow-up	β-blocker	12 on β-blocker, 15 not on β-blocker	Patients on β-blocker had significantly lower AAA expansion rate
Propranolol Aneurysm Trial Investigators[61]	AAA; prospective, randomized, double-blind study; 2.5-y mean follow-up	Propranolol	276 on propranolol, 272 on placebo	Propranolol did not significantly affect small AAA growth; high discontinuation rate of propranolol
Lindholt et al[60]	AAA; randomized, controlled study; 2-y follow-up	Propranolol	54 Asymptomatic patients	Increased mortality in propranolol group; only 22% could be treated
Baxter et al[66]	AAA; prospective, observational study; 6-mo phase II study	Doxycycline	36 Patients	Doxycycline was safe and caused MMP-9 level decrease
Mosorin et al[67]	AAA; randomized, placebo controlled, double-blind study; 18-mo follow-up	Doxycycline	17 on doxycycline, 15 on placebo	Aneurysm expansion rate was significantly lower in the doxycycline group
Vammen et al[68]	AAA; randomized, double-blind study; 1.5-y mean follow-up	Roxithromycin	43 on roxithromycin, 49 on placebo	4 wk of therapy reduced AAA expansion rate
Sweeting et al[75]	AAA; prospective, observational study; 1.9-y mean follow-up	ACEI	169 on ACEI, 1532 not on ACEI	Patients on ACEI had a faster AAA growth rate than patients not on ACEI
Ferguson et al[70]	AAA; observational, prospective study; 5-y median follow-up	Statins	394 on statins, 258 not on statins	Statins were not associated with reduced AAA growth rate
Gambarin[62]	Marfan syndrome; open-label phase III study	Losartan, nebivolol	291 patients	Ongoing

AAA indicates abdominal aortic aneurysm; MMP, matrix metalloproteinase; and ACEI, angiotensin-converting enzyme inhibitor.

STATINS


FBN1 Mutation
↓Fibrillin
↑TGF-β
↓ extracellular matrix
↓ MMP
↑MMP
↓TIMP
Statins
Rupture
↓Collagen
Aneurysm Formation
↑Stiffness
↓Elastin ↑Collagen
CMD
↑Proteases
VSMC
Degenerative Diseases
Beta Blockers
↓ dp/dt
↑dp/dt ↑Aortic diameter ↑BP
↑Size

Statin Pleiotrophy		
Effect	**Benefit**	
Increased synthesis of nitric oxide	Improvement of endothelial dysfunction	
Inhibition of free radical release		
Decreased synthesis of endothelin-1		
Inhibition of LDL-C oxidation		
Upregulation of endothelial progenitor cells		
Reduced number and activity of inflammatory cells	**Reduced inflammatory response**	
Reduced levels of C-reactive protein		
Reduced macrophage cholesterol accumulation	Stabilization of atherosclerotic plaques	
Reduced production of metalloproteinases		
Inhibition of platelet adhesion/aggregation	Reduced thrombogenic response	
Reduced fibrinogen concentration		
Reduced blood viscosity		

Comparison of the Effect on Long-Term Outcomes in Patients With Thoracic Aortic Aneurysms of Taking Versus Not Taking a Statin Drug

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The potential of medical therapy to influence the courses and outcomes of patients with thoracic aortic aneurysms is not known. The aim of this study was to determine whether statin intake is associated with improved long-term outcomes in these patients. A total of 649 patients with thoracic aortic aneurysms were studied, of whom 147 were taking statins at their first presentation and 502 were not. After a median follow-up period of 3.6 years, 30 patients (20%) taking statins had died, compared with 167 patients (33%) not taking statins (hazard ratio 0.68, 95% confidence interval 0.46 to 1, p = 0.049); 87 patients (59%) taking statins reached the composite end point of death, rupture, dissection, or repair compared with 378 patients (75%) not taking statins (hazard ratio 0.72, 95% confidence interval 0.57 to 0.91, p = 0.006). After adjustments for co-morbidities, the association between statin therapy and the composite end point was driven mainly by a reduction in aneurysm repairs (hazard ratio 0.57 95% confidence interval 0.4 to 0.83, p = 0.003). On Kaplan-Meier analysis, the survival rate of patients taking statins was significantly better (p = 0.047). In conclusion, the intake of stains was associated with an improvement in long-term outcomes in this cohort of patients with thoracic aortic aneurysms. This was driven mainly by a reduction in aneurysm repairs. **© 2012 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2012;109:1050–1054)**

Yale Statin Study

- 649 patients
  - 147 on statins
  - 502 not on statins
- Median f/u 3.6 yrs (range 1 to 10)

- Survival
- Composite end-point (death, rupture, dissection, surgery)

Table: Aneurysm locations

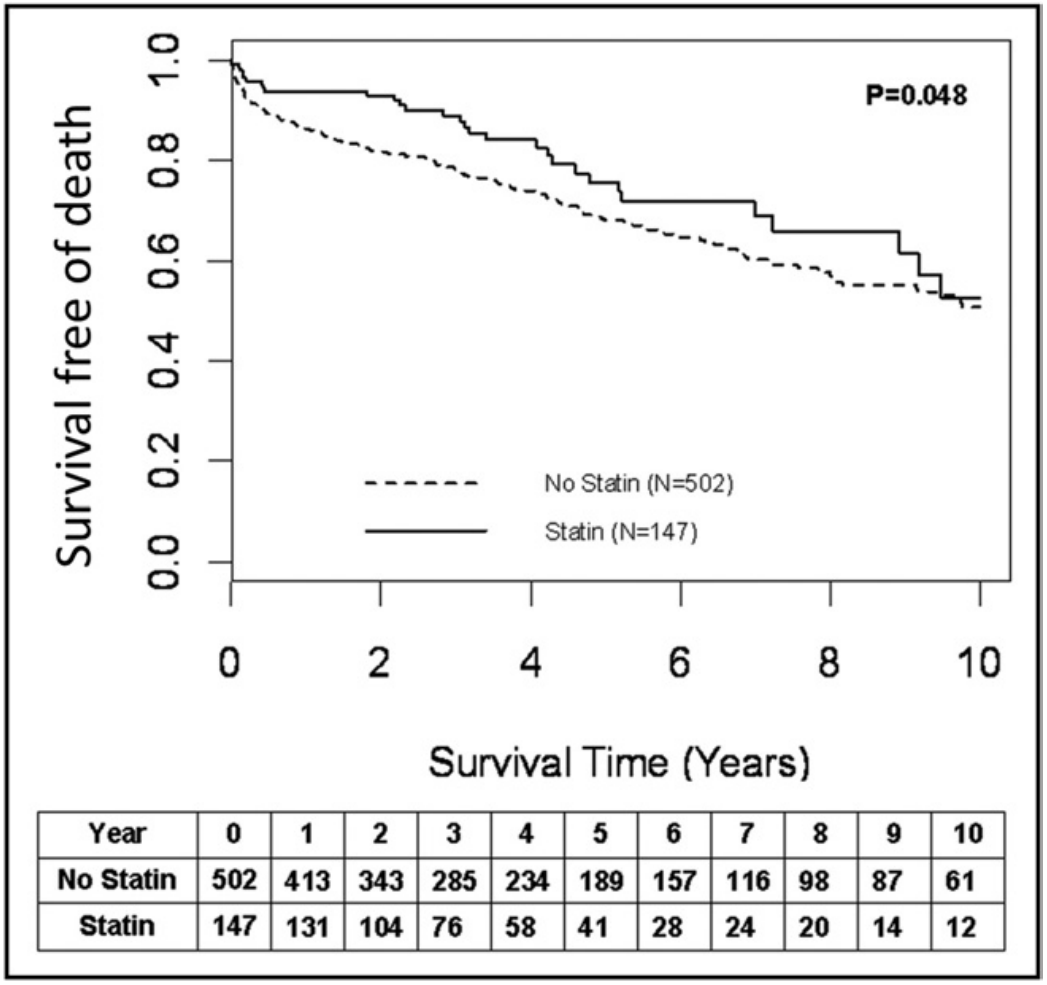
Location	All (n = 649)	Statin (n = 147)	No Statin (n = 502)	p Value*
Ascending	425 (65.4%)	101 (68.7%)	324 (64.5%)	0.35
Aortic arch	60 (9.2%)	13 (8.8%)	47 (9.3%)	0.84
Descending	129 (19.8%)	26 (17.6%)	103 (20.5%)	0.44
Thoracoabdominal	61 (9.4%)	16 (10.8%)	45 (8.9%)	0.48

*Statin vs no statin.

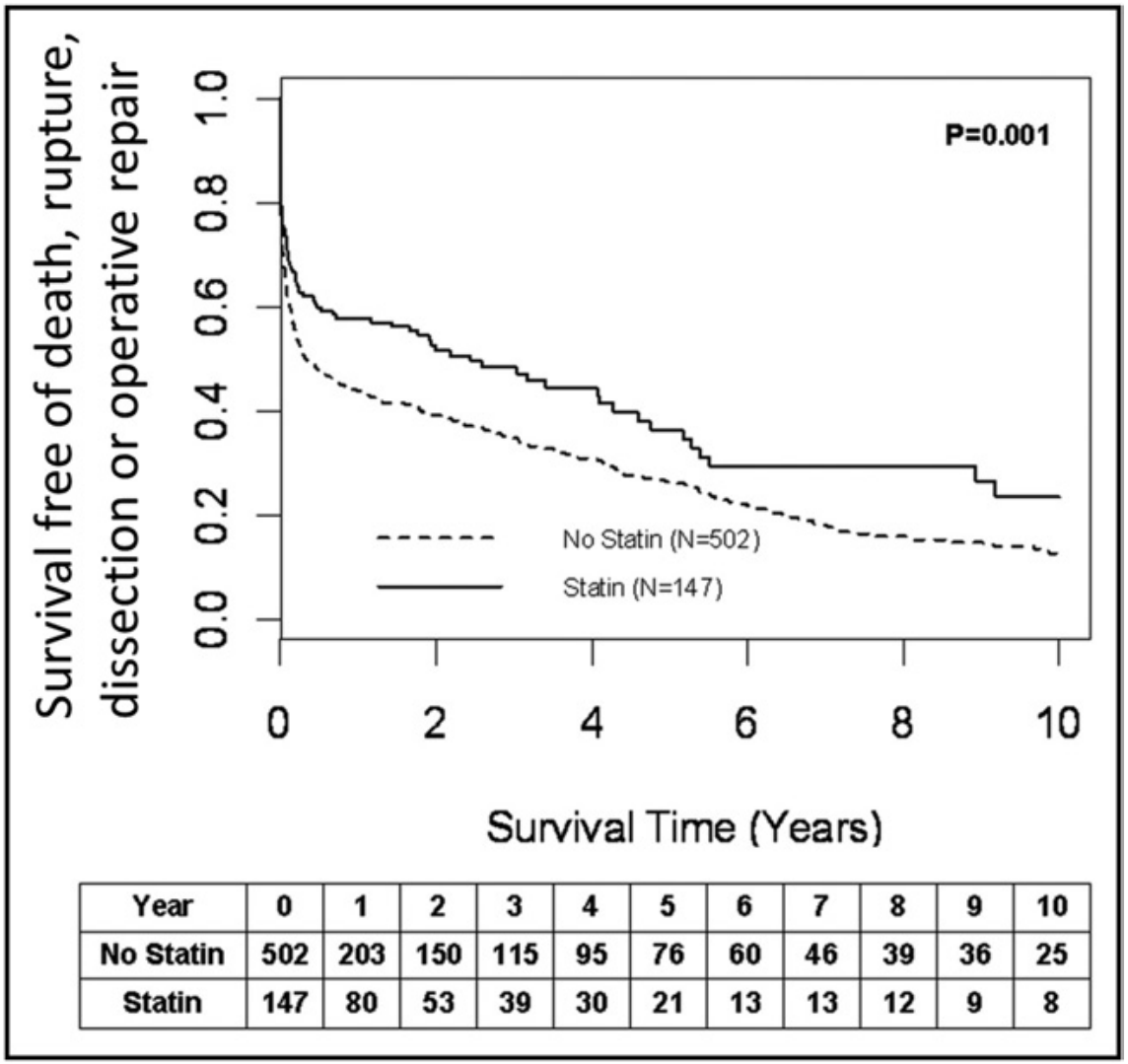
Mortality

	No Statins	Statins	Total
Number	502	147	649
Death	167 (33%)	30 (20%)	
			p=0.006 OR 0.72

Mean f/u 3.6 years



Year	0	1	2	3	4	5	6	7	8	9	10
No Statin	502	413	343	285	234	189	157	116	98	87	61
Statin	147	131	104	76	58	41	28	24	20	14	12



Year	0	1	2	3	4	5	6	7	8	9	10
No Statin	502	203	150	115	95	76	60	46	39	36	25
Statin	147	80	53	39	30	21	13	13	12	9	8

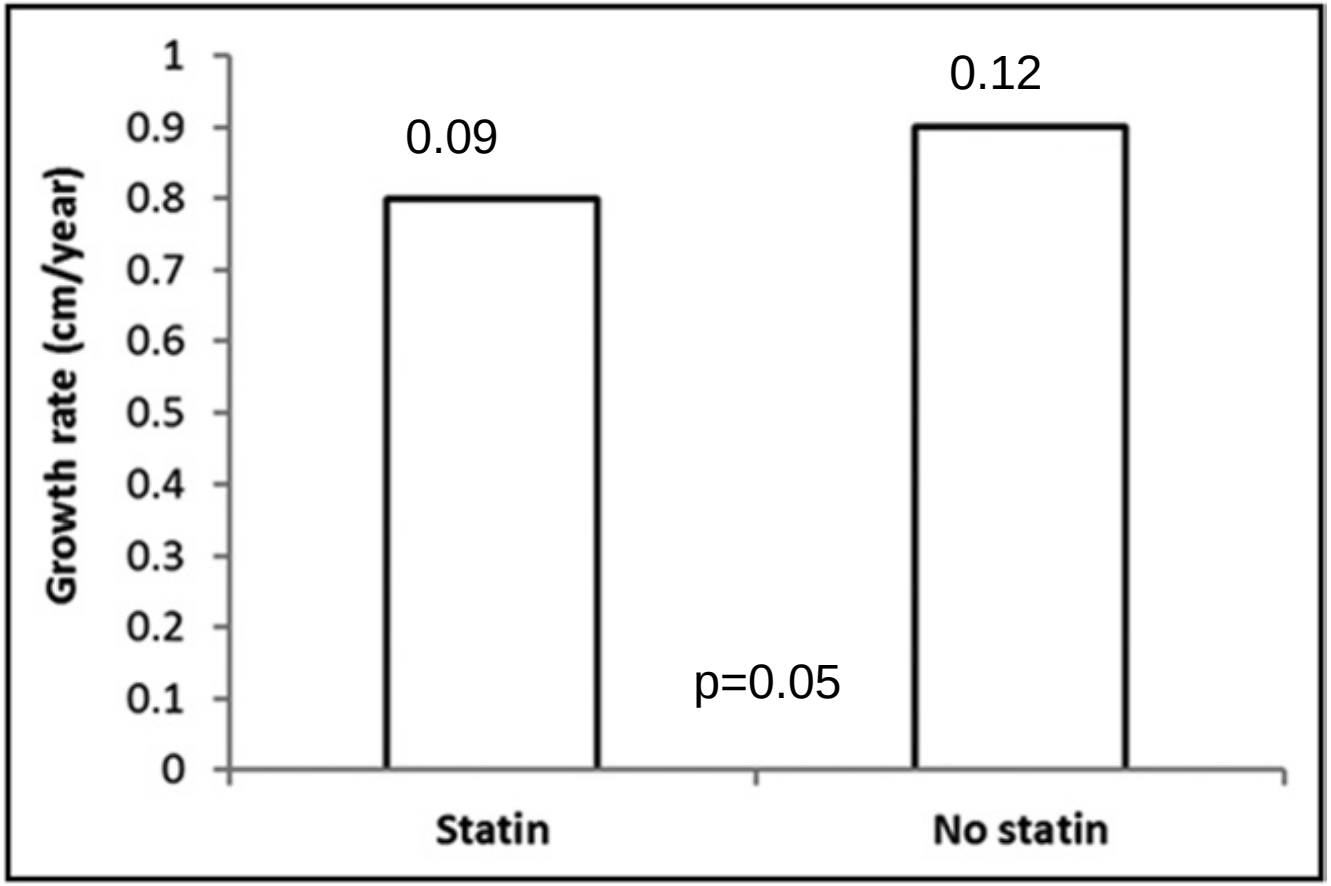

Growth rate (cm/year)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.09
0.12
p=0.05
Statin
No statin

Table: Variables included in the multivariate analysis of outcomes of patients with thoracic aortic aneurysms

Variable	Effect Size for Death (95% CI)	p Value	Effect Size for Death, Dissection, Rupture, or Repair (95% CI)	p Value
Age	1.005 (0.99–1.01)	0.48	0.99 (0.98–1.001)	0.11
Male gender	0.68 (0.48–0.94)	0.02	0.81 (0.66–1.01)	0.06
β blockers	0.86 (0.62–1.2)	0.39	0.99 (0.80–1.23)	0.96
Aspirin	1.07 (0.57–2.03)	0.81	1.69 (1.13–2.52)	0.01
ARBs	0.85 (0.36–1.98)	0.71	0.60 (0.33–1.08)	0.09
Hypertension	1.09 (0.75–1.57)	0.64	0.99 (0.78–1.25)	0.96
PVD/CAD	1.21 (0.84–1.75)	0.29	0.96 (0.76–1.23)	0.78
Diabetes	1.73 (1.01–2.95)	0.04	1.03 (0.68–1.55)	0.88

Statins are effective in combating TAA

- **Lower mortality**
- **Lower combined end-point**
  - **Death**
  - **Rupture**
  - **Dissection**
  - **Operative repair**
- **Slower growth rate**