TCTAP 2012
Seoul, Korea
April 26, 2012

Deferring AAA Repair: Best Medical Management Based on Evidence-Based Medicine

Michael R. Jaff, DO, FACC

Associate Professor of Medicine

Harvard Medical School

Chair, Massachusetts General Hospital Institute for Heart, Vascular and Stroke Care

Boston, Massachusetts USA

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

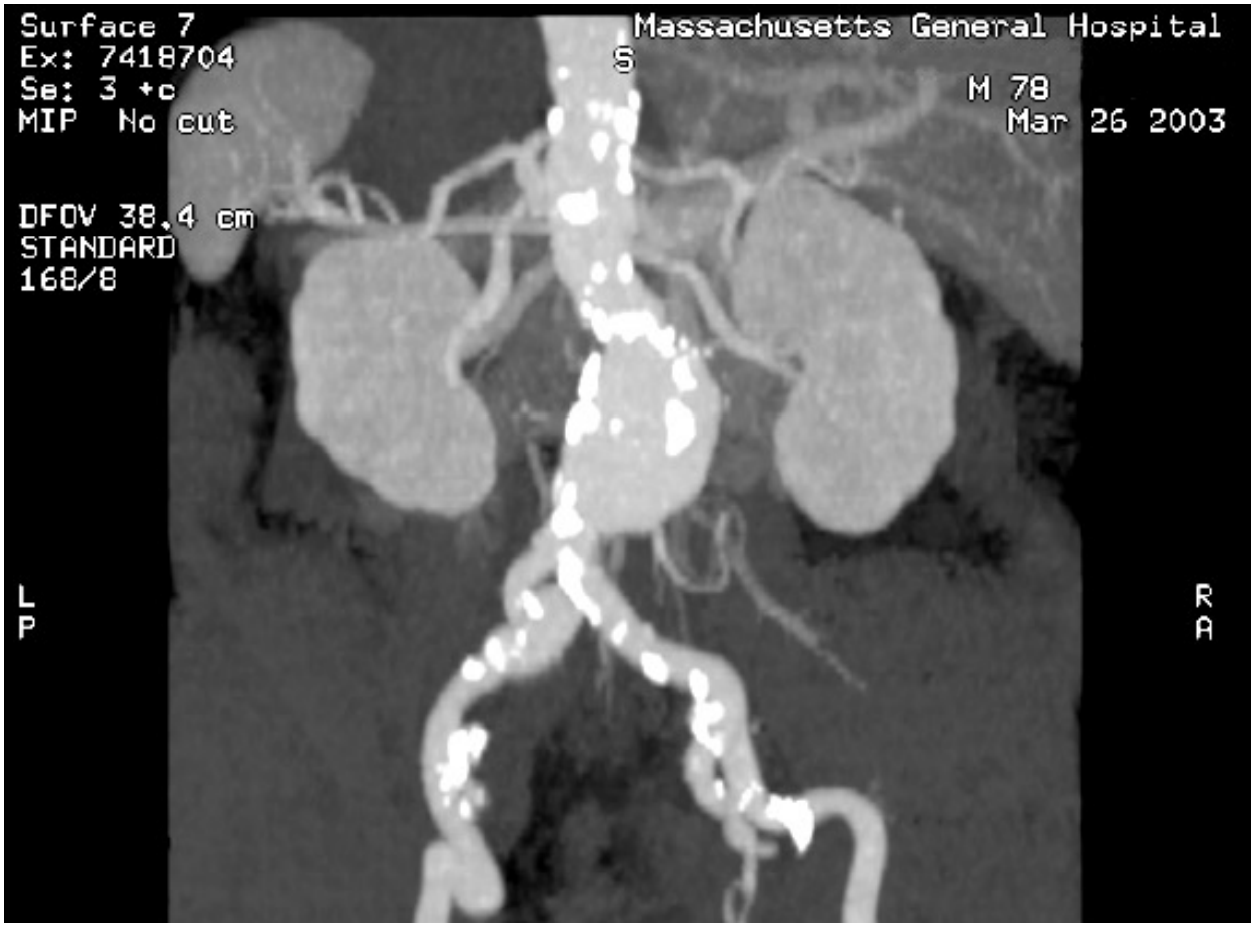
Michael R. Jaff, DO
Conflicts of Interest

- **Consultant**
  - Abbott Vascular (non-compensated)
  - Becker Venture Services Group
  - Bluegrass Vascular Therapies
  - Cordis Corporation(non-compensated)
  - Covidien (non-compensated)
  - Hansen Medical
  - Medtronic (non-compensated)
  - Micell, Incorporated
  - Primacea
  - Trivascular, Inc.
  - Vortex
- **Equity**
  - Access Closure, Inc
  - Embolitech, Inc
  - Hotspur, Inc
  - Icon Interventional, Inc
  - I.C.Sciences, Inc
  - Janacare, Inc
  - Northwind Medical, Inc.
  - PQ Bypass, Inc
  - Primacea
  - Sadra Medical
  - TMI/Trireme, Inc
  - Vascular Therapies, Inc
- **Board Member**
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
    - www.vivapvd.com

April 2012

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Abdominal Aortic Aneurysms



MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Abdominal Aortic Aneurysm (AAA): Scope of the Problem

- Defined most often as aortic diameter ≥ 3.0 cm
- Occur in 5 % of men ≥ 65 years of age
- Prevalence increasing four-fold over the past 3 decades
  - Aging population
  - Improved and more readily available imaging techniques
- If untreated 1/3 will cause death from rupture
  - Rupture causes 15,000 deaths annually in the US
  - 10th leading cause of death in male Medicare population
- Readily detectable and correctable.

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Abdominal Aortic Aneurysms: Risk Factors

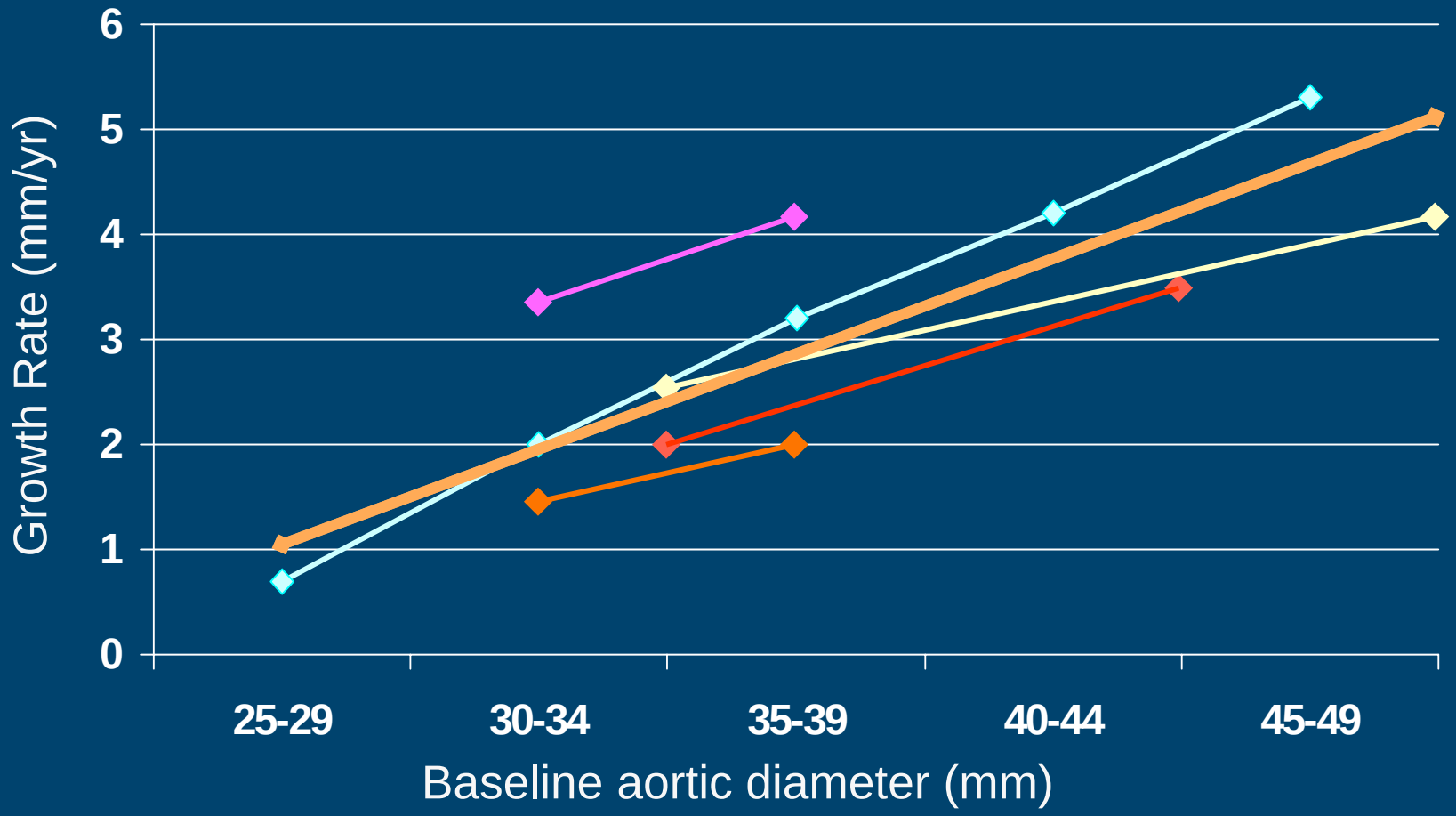
- Major risk factors
  - Age (particularly age > 65)
  - Male gender: Men 4-10 x more likely to have AAA than women
  - Smoking
- Atherosclerosis risk factors
  - Hypertension
  - Hyperlipidemia
  - Atherosclerotic vascular disease (CAD, CVD, PAD)
- Genetic predisposition
  - First-degree relative with AAA = 30% increased risk
  - AAAs tend to occur at a younger age and carry greater risk of rupture than do sporadic aneurysms.

Mechanisms of AAA Formation and Growth

- Genetic
- Environmental
- Hemodynamic
- Immunological
  - Inflammatory infiltrates within the wall of AAAs
  - Matrix metalloproteinases (MMPs) are enzymes produced by smooth muscle and inflammatory cells
  - Certain MMPs can degrade elastin and collagen
  - Levels of some matrix MMPs are significantly elevated in the walls of aneurysms compared with controls
  - So several MMPs are likely to participate in AAA formation.

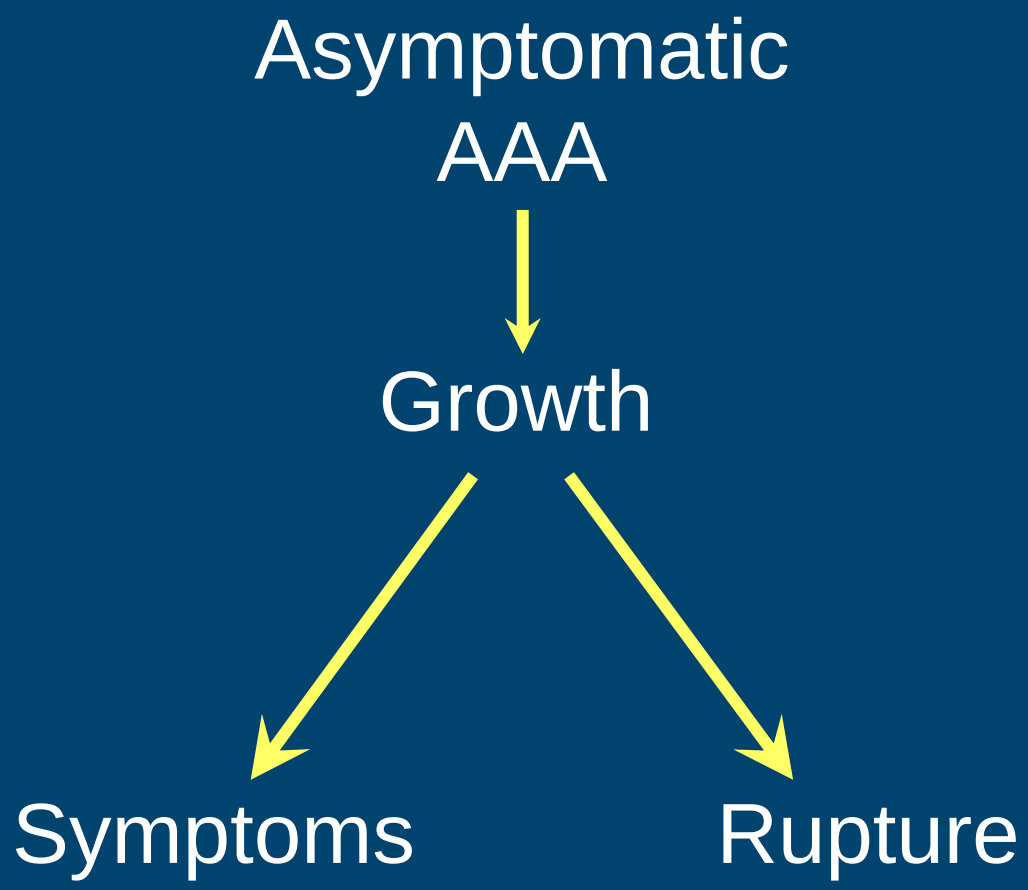
Growth Rate of Small AAAs vs. Baseline Size:

10% per year, but individuals' rates are extremely variable



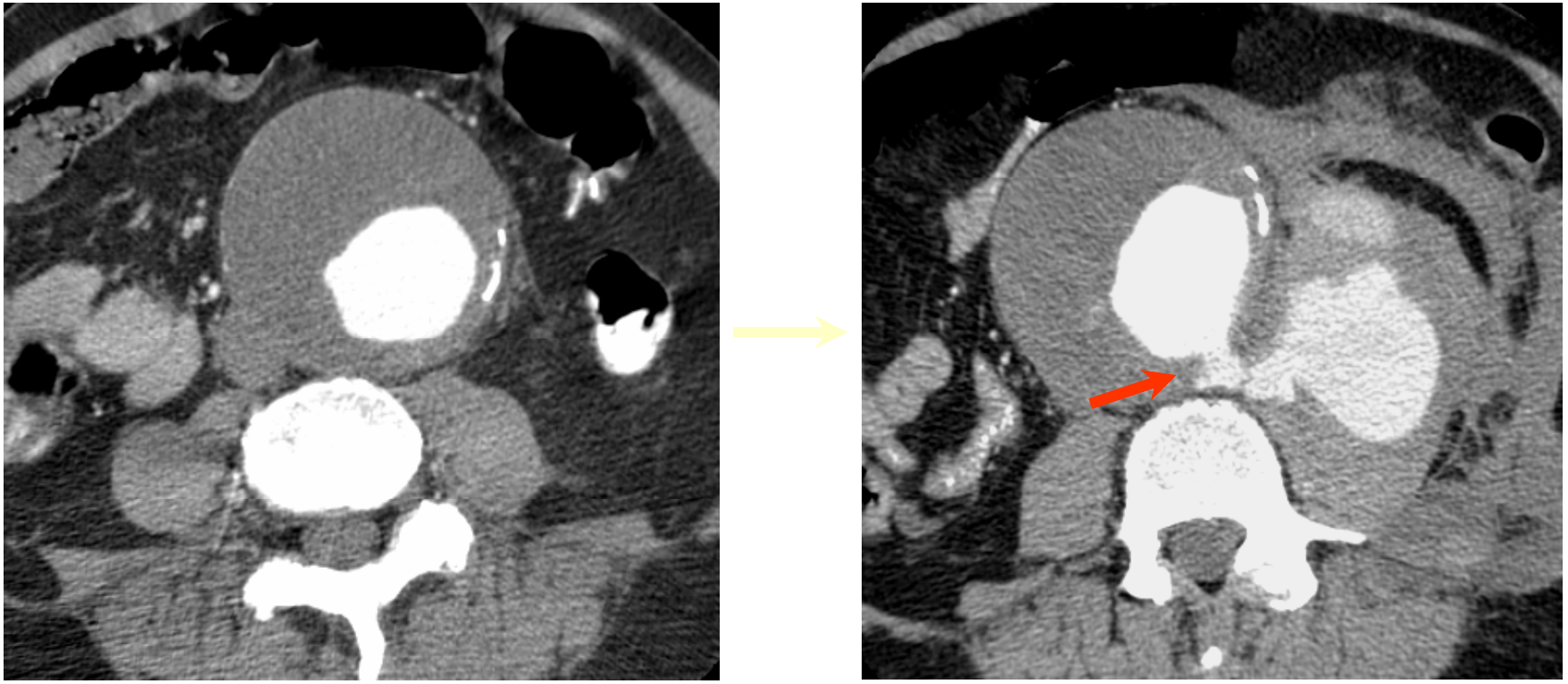
- Lindholt JS. Eur J Vasc Endovasc Surg. 2000;20:369.
- Brown PM. .J Vasc Surg 1996;23:313.
- Vardulaki KA. Br J Surg 1998;85:1674
- Stonebrige PA. Eur J Vasc Endovasc Surg. 1996;11:70
- Santilli SM. J Vasc Surg 2002;35:666-71.

Abdominal Aortic Aneurysms: Natural History



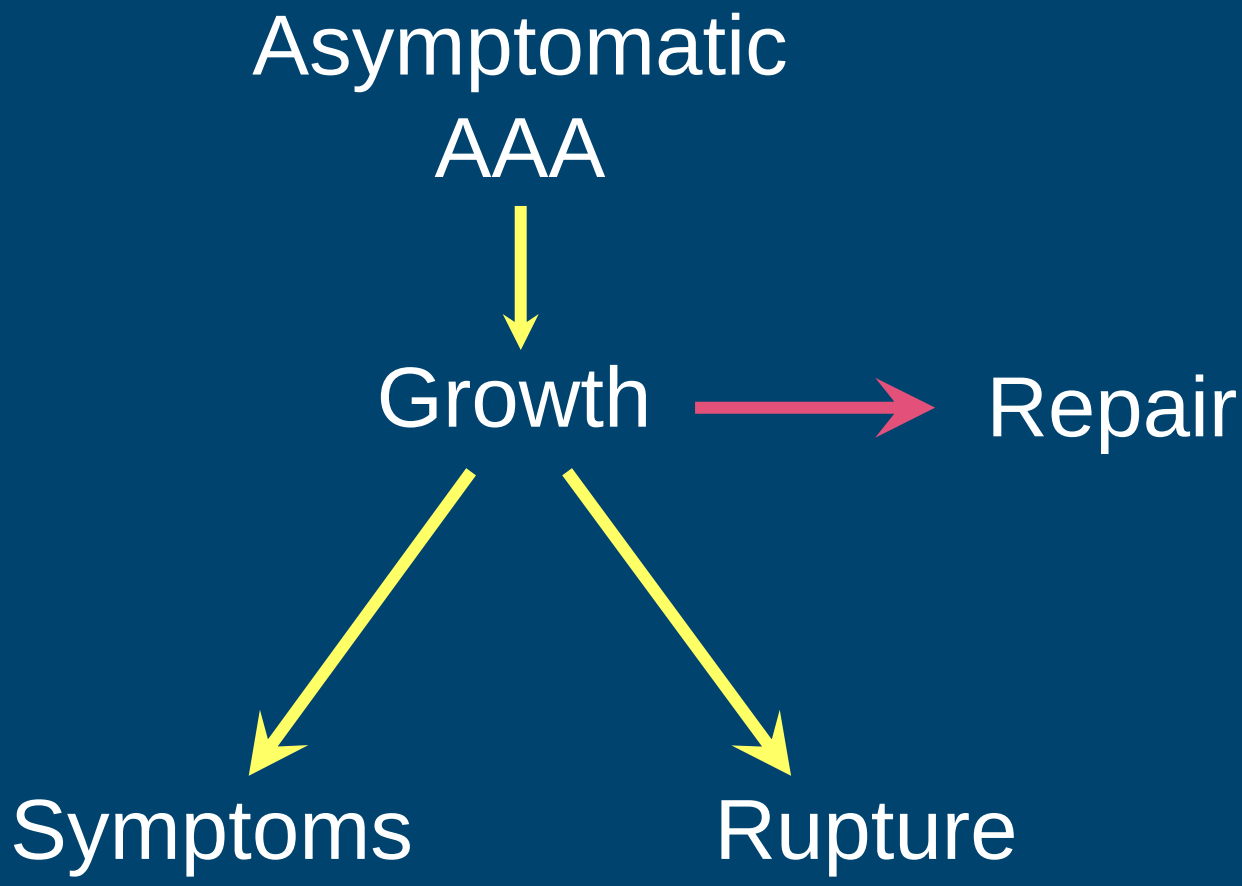
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

AAA Rupture



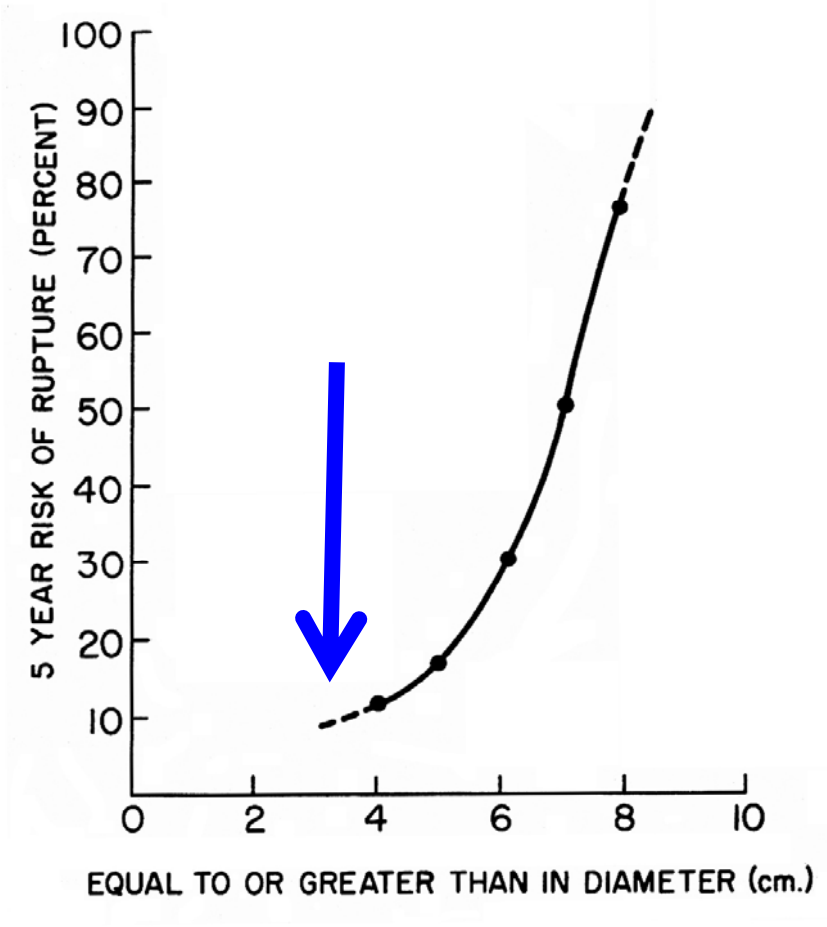
- Overall 30-day survival of 11%

Abdominal Aortic Aneurysms: Natural History



MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

AAA Size Predicts Risk of Rupture



- Risk rises sharply after diameter of 5 cm or larger
- Risk 5.0-5.9 cm = 11 % per year

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Can We Prevent Growth of Small AAAs?

Intervention	Reference(s)	Effect on AAA Growth	Level of Evidence	Class of Recommendation
Propranolol	46, 69	No inhibition	A	III
Macrolides	60	Inhibition	B	IIa
Tetracycline*	67	Inhibition	B	IIa
Statins	38, 39	Inhibition	B	IIb
ACE inhibitors	27, 39, 52, 53	No inhibition	B and C	IIb
AR blockers	48, 50	Animal data	C	IIb

Circulation 2008;117:1883

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Tetracyclines????

- Known inhibitory effects on MMP
  - Suppress aortic wall MMP activity
  - Suppress elastin degradation
  - Prevent aneurysm formation in elastase-induced rat model

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

Clinical Trial of Doxycycline for Matrix Metalloproteinase-9 Inhibition in Patients With an Abdominal Aneurysm : Doxycycline Selectively Depletes Aortic Wall Neutrophils and Cytotoxic T Cells

Jan H.N. Lindeman, Hazem Abdul-Hussien, J. Hajo van Bockel, Ron Wolterbeek and Robert Kleemann

Circulation 2009, 119:2209-2216: originally published online April 13, 2009
doi: 10.1161/CIRCULATIONAHA.108.806505

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Doxycycline in AAA

- 60 patients scheduled for open AAA repair
  - Randomized to two weeks of
    - Doxycycline 50 mg/100 mg/300 mg per day for 2 weeks pre-op OR
    - Placebo
- Aortic wall samples collected at time of surgery
- Assessed aortic wall inflammation

Circulation 2009;119:2209

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

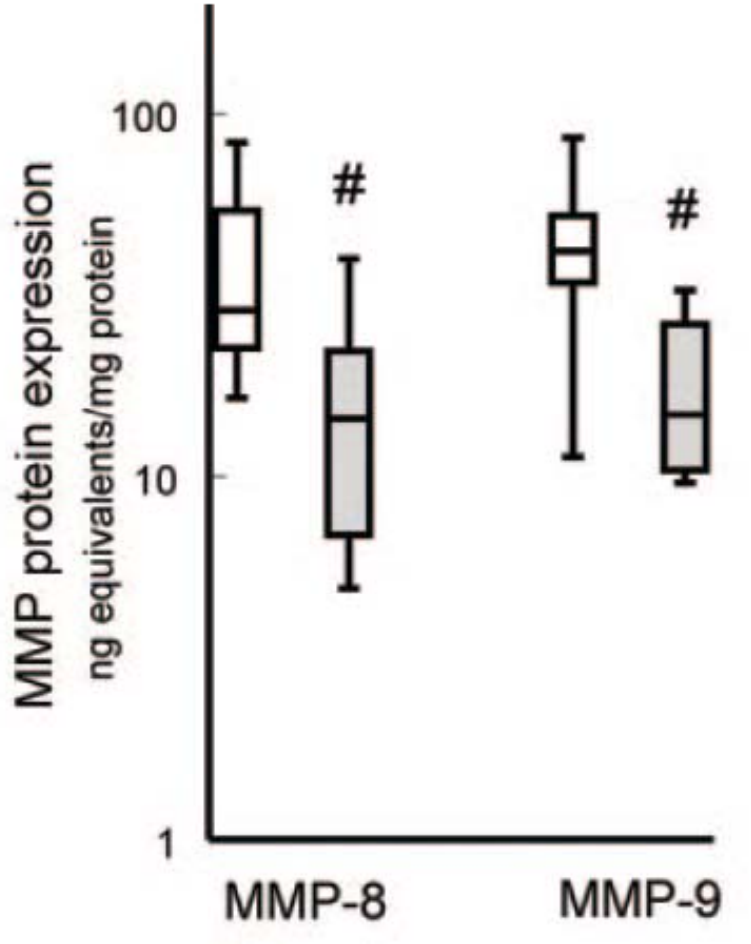
Doxycycline in AAA

	Control AAA	Doxycycline, mg			*P*
		50	100	300	
Evaluable patients, n	15	13	15	15	NS
Mean age (range), y	74.8 (69–84)	72.7 (62–85)	74.1 (50–88)	72.1 (58–87)	NS
Mean AAA diameter, cm	6.7	6.5	6.3	6.7	NS
Mean time between diagnosis and surgery, mo	6	7	5	4	
Female sex, n	1	2	2	3	NS
Current smoker, n	6	6	7	5	NS
Statin use, n	1	1	1	2	NS
Antihypertensives, n	8	7	8	7	NS
Antiplatelet therapy, n	10	8	8	8	NS

Circulation 2009;119:2209

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Doxycycline in AAA



Placebo

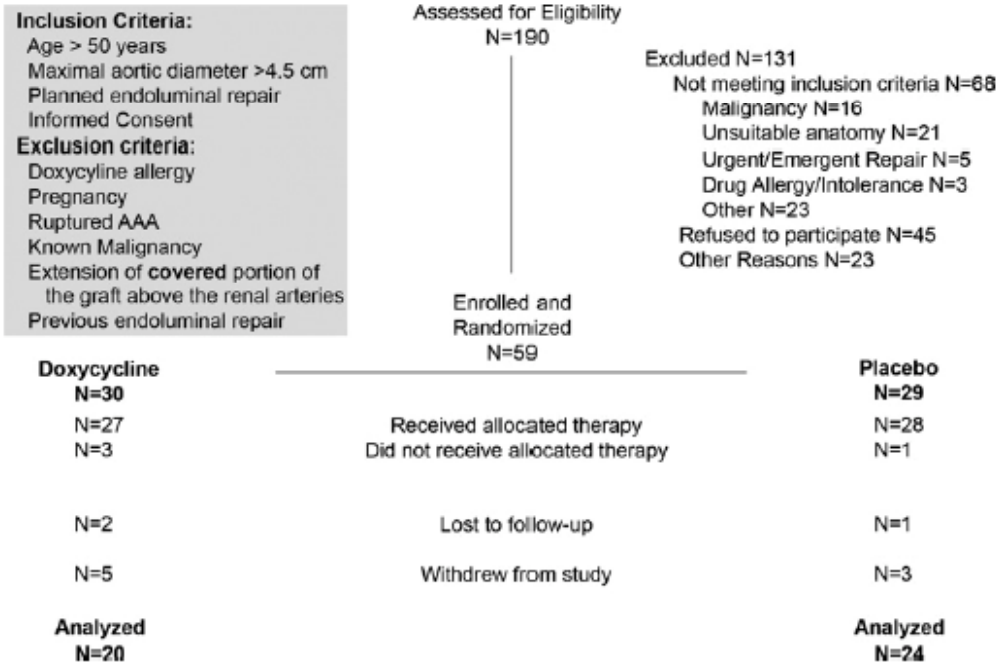
Doxy

Circulation 2009;119:2209

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Doxycycline After Aortic Endograft

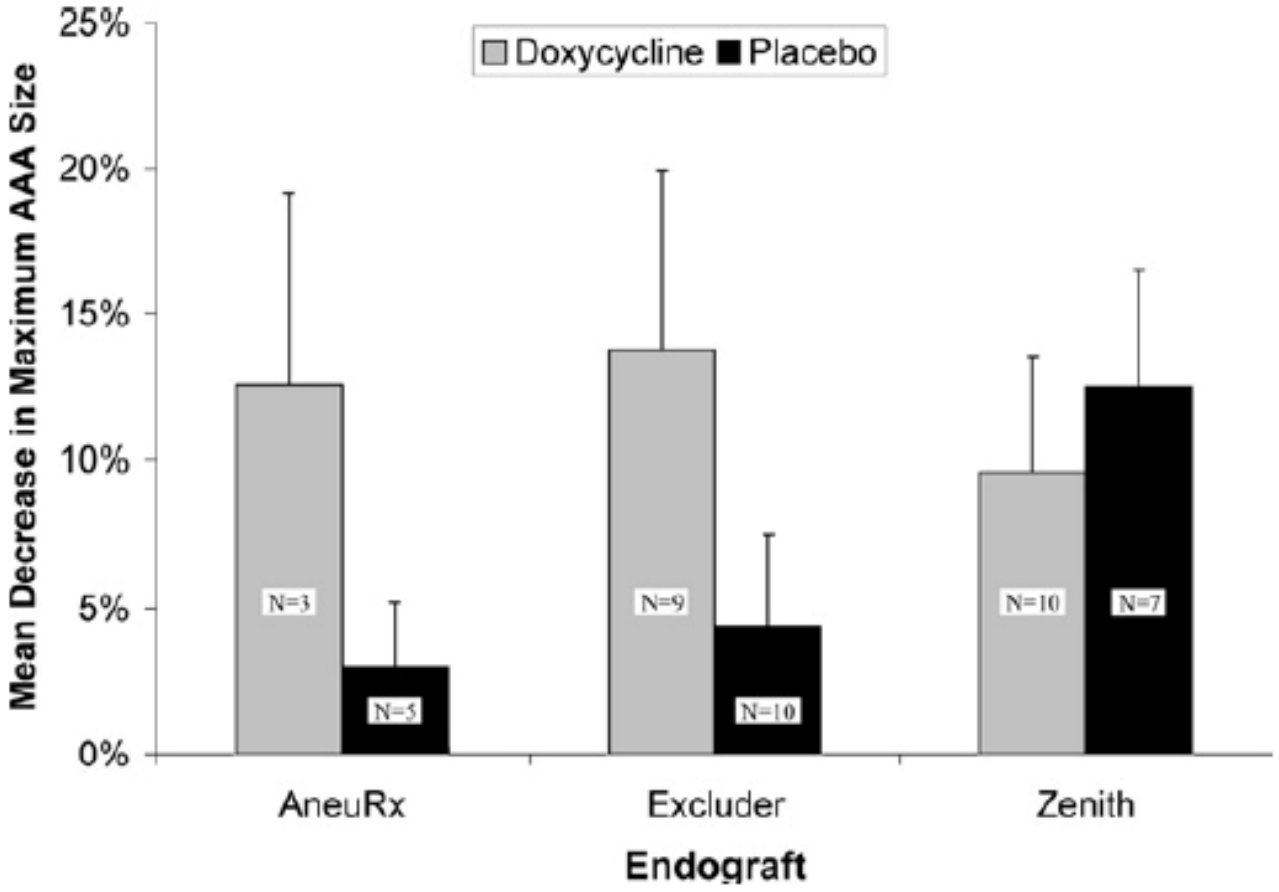
- Randomized, placebo controlled trial
- Doxycycline 100 mg BID or placebo for 6 months following EVAR



J Vasc Surg 2008;48:519

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Doxycycline After Aortic Endograft



J Vasc Surg 2008;48:519

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Statin Therapy Induces Regression of Aneurysm Sac After EVAR

- Retrospective analysis of 166 patients who underwent successful EVAR
  - 120 were taking statins
  - 46 were not on statins

Statins	*No. (%)*
Fluvastatin	
80 mg	4 (3.3)
Simvastatin	
20 mg	19 (15.9)
40 mg	3 (2.5)
Atorvastatin	
10 mg	15 (12.5)
20 mg	12 (10)
40 mg	10 (8.3)
80 mg	1 (0.8)
Rosuvastatin	
5 mg	18 (15)
10 mg	12 (10)
Pravastatin	
10 mg	3 (2.5)
20 mg	17 (14.2)
40 mg	6 (5)

J Vasc Surg 2012

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Statin Therapy Induces Regression of Aneurysm Sac After EVAR

Pre-Procedure Measurements

Variables	*Total, mm* *Mean ± SD mm*	*Nonstatin* *Mean ± SD mm*	*Statin* *Mean ± SD mm*	P
Max transverse diameter	53.15 ± 8.6	53.8 ± 10.6	52.9 ± 7.8	.54
Proximal neck				
Max diameter	23.5 ± 4.3	22.74 ± 4.9	23.8 ± 4.1	.24
Length	26.2 ± 12.9	27.4 ± 17.9	25.76 ± 10.4	.46
Max common iliac artery diameter	18.2 ± 9.1	18 ± 8.1	18.25 ± 9.5	.86

J Vasc Surg 2012

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Statin Therapy Induces Regression of Aneurysm Sac After EVAR

Multivariate Analysis: Statin Use and Sac Measurements

Variable	*5-mm regression OR (95% CI)*	*10-mm regression OR (95% CI)*
Statin use	9.39 (3.45-25.56)	4.35 (1.99-9.5)
Max external diameter	1.08 (1.1-1.15)	1.07 (1.02-1.12)
Proximal neck		
Max diameter	0.97 (0.85-1.11)	0.94 (0.87-1.02)
Length	0.99 (0.95-1.02)	1.03 (1-1.06)
Max common iliac artery diameter	1.03 (0.96-1.11)	0.99 (0.95-1.03)

J Vasc Surg 2012

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

What is Medical Therapy in Small AAA?

- Tobacco Cessation
- Statins (potential role in AAA; useful in CAD)
- Beta Blockers (useful following MI; not useful in AAA)
- ARB (?)
- Tetracyclines (?)

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE