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The Unique Challenges of Developing Novel Therapies for Abdominal Aortic Aneurysms

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ABDOMINAL AORTIC ANEURYSM
N-TACT
noninvasive treatment • clinical trial

Conflicts of Interest

Research Funding

Non-Profit Sources:

National Institutes for Health

American Vascular Association

American College of Surgeons

American Heart Association

Flight Attendants Medical Research Institute

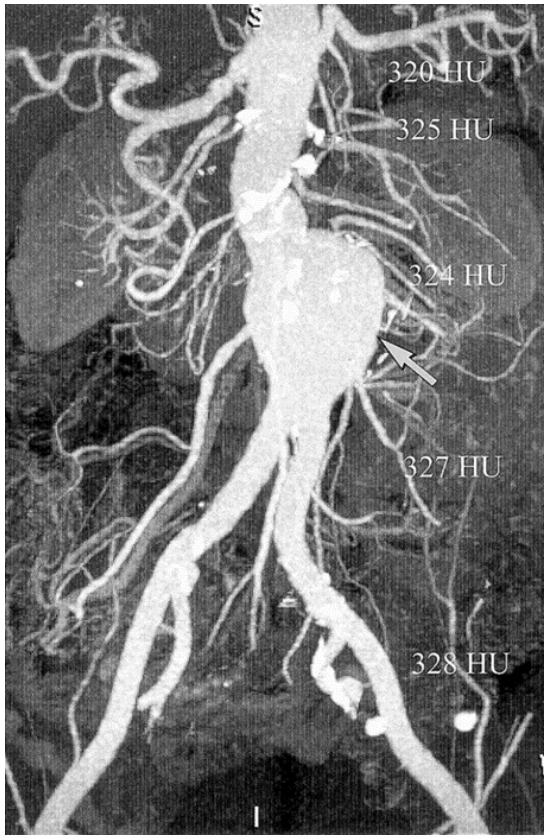
Peripheral Vascular Surgery Society

Off-label indications:

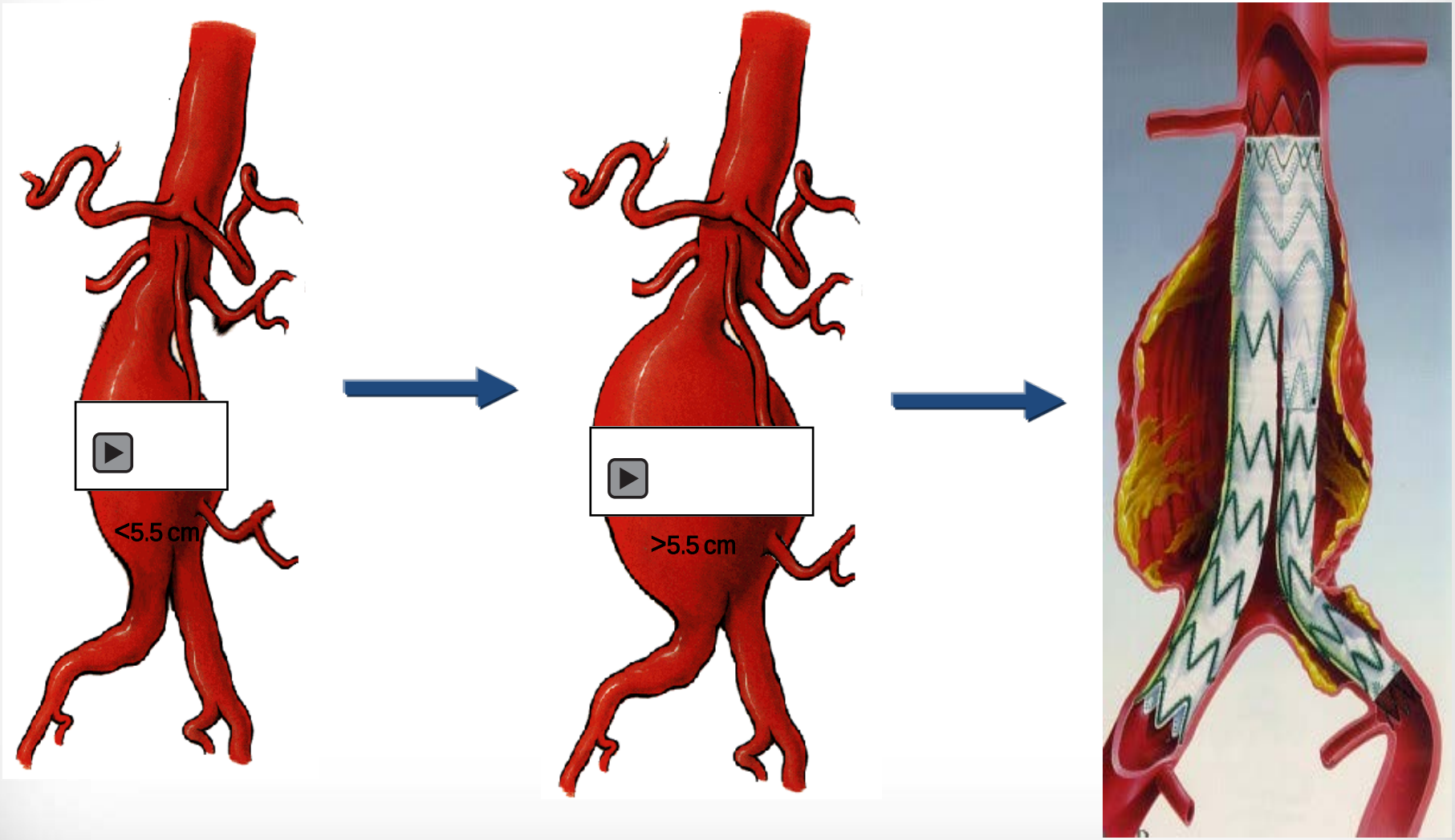
Doxycycline

Disease Modifying Therapy for AAA

- The Practical Clinical Therapeutic Considerations
- Limitations of Clinical Trials for AAA
- Advanced Considerations and Implications for Lab Work



Contemporary Management of AAA

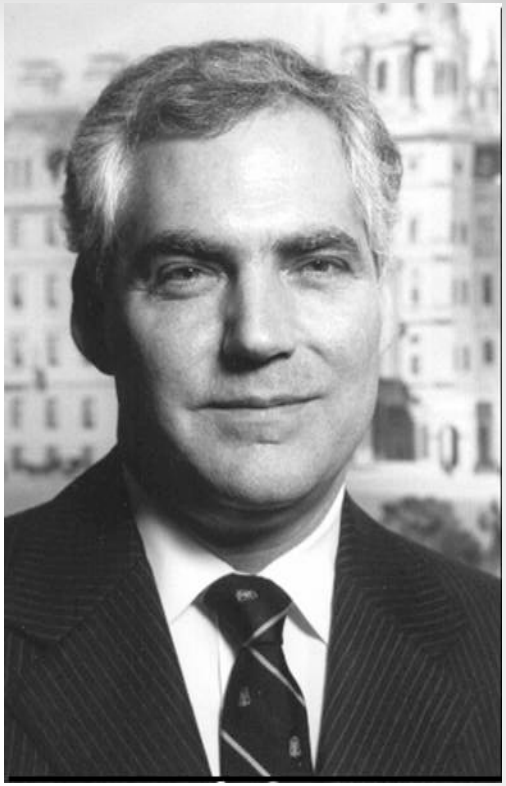


THE AAA AS A UNIQUE VASCULAR DISEASE

A Radical Thought

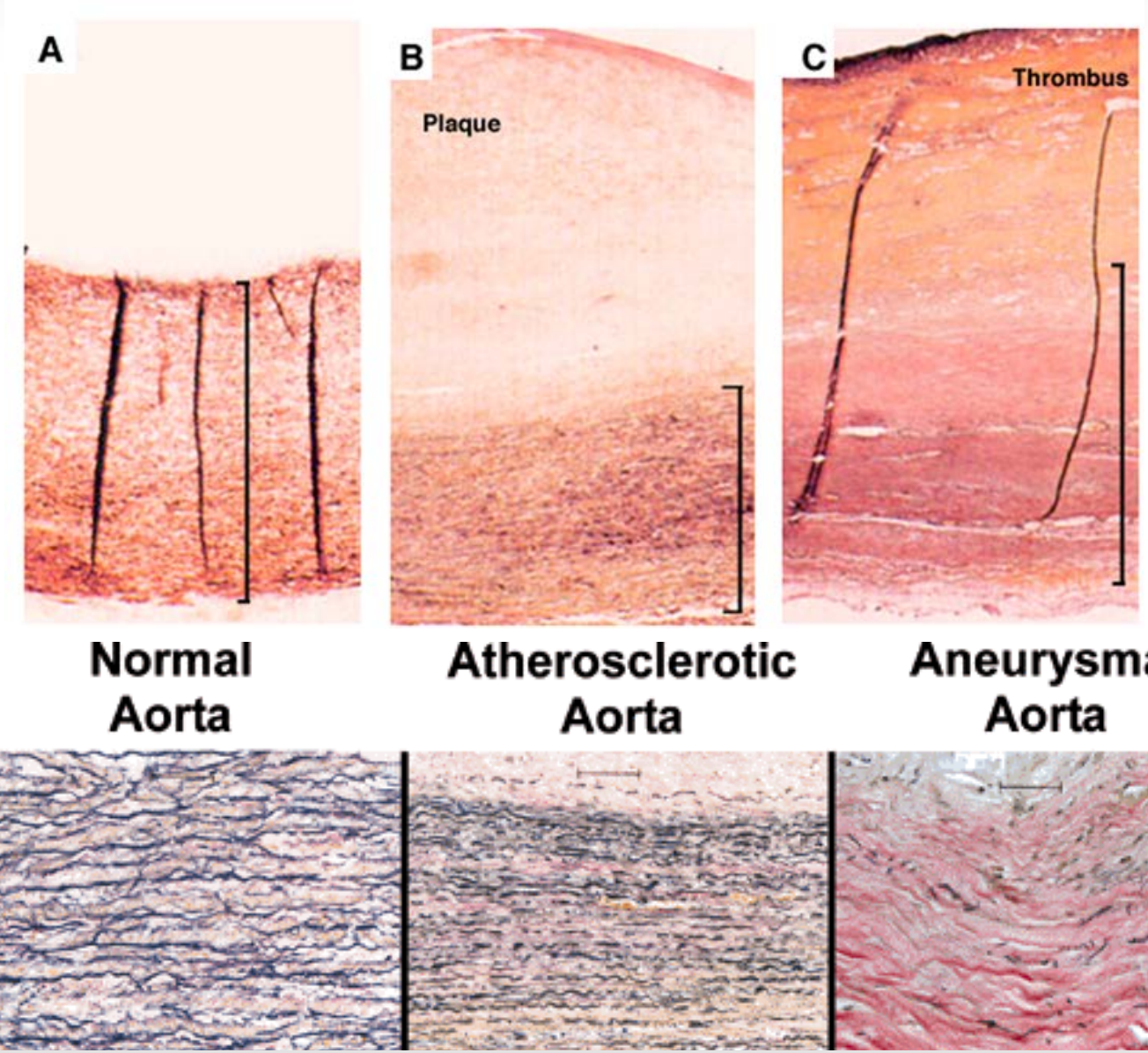
not the answer to the disease in all patients with AAA. In addition, preservation of fluorescent fibers that morphologically resemble elastin in four of the aortas, with only a trace of iron hematoxylin–reactive elastin, suggests that the pathogenetic mechanism is not indiscriminate destruction of the media by atherosclerotic involvement. Instead, there appears to be a specific and perhaps subtle alteration detectable by histochemical techniques. One possibility is that the elastin is really "gone" and that the residual matrix is a scaffolding of collagen, like type III, that codistributes with the elastin. Not enough is known at present about the chemistry of the reaction of elastin with iron hematoxylin to allow a more specific hypothesis about this alteration.

Arch Surg – Vol 123, April 1988



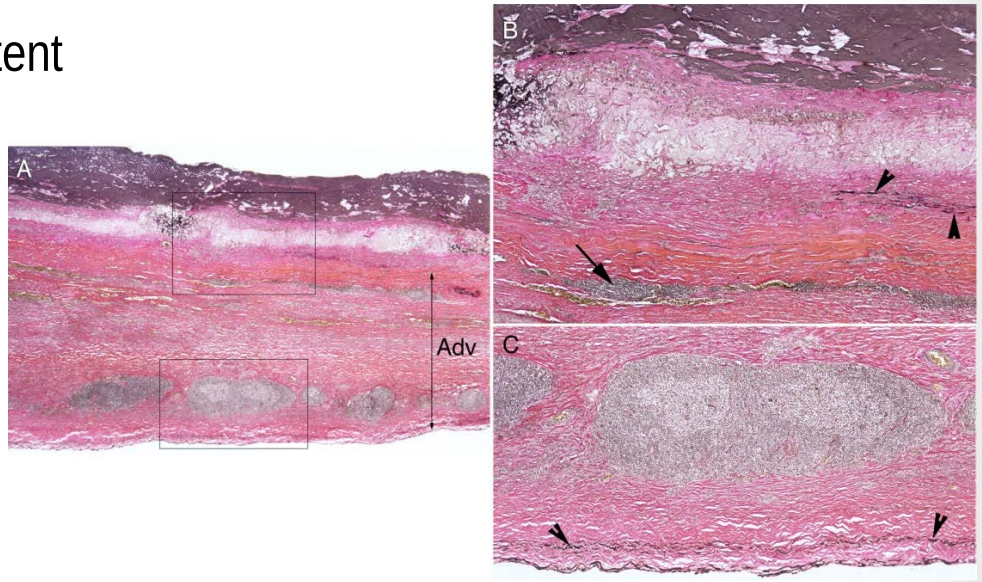
M. David Tilson, MD

Histologic Changes



Initial Focus of Investigation

- Two *shiny* histologic features of the AAA
  - Severely diminished medial elastin content
  - Heavy inflammatory cell infiltration
- Inflammation and Elastin Loss
  - Matrix Proteases
  - Elaboration by activated macrophages
  - Induced by infection/autoimmunity



- Working Hypothesis
  - Inflammation ⟶ Protease ⟶ Thinning of the aortic wall ➞ Relative weakening ➞ "Ballooning" of the aorta ➞ Further weakening ➞ Rupture

Gregory T Jones (2011). The Pathohistology of Abdominal Aortic Aneurysm, Diagnosis, Screening and Treatment of Abdominal, Thoracoabdominal and Thoracic Aortic Aneurysms, Prof. Reinhart Grundmann (Ed.), ISBN: 978-953-307-466-5

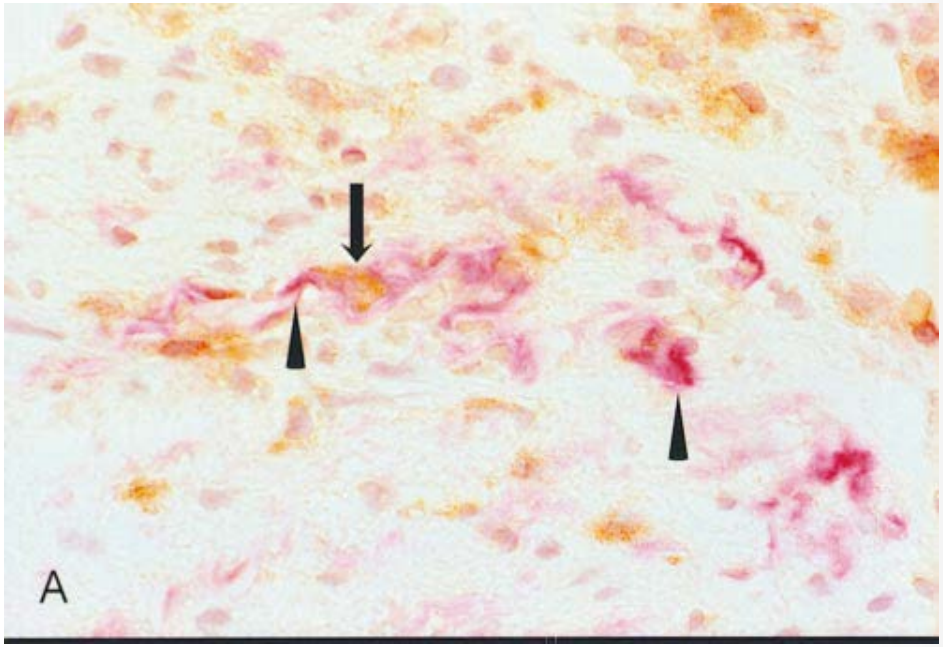
Histology Suggestion Pathophysiology

Arrow: Macrophage

Arrowhead: Elastin Fragments

Pink: MMP-12

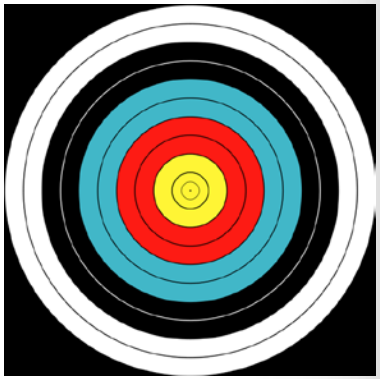
Brown: CD68



Curci, JCI 1998, 102(11)

How do we translate?

- Human Histology
  - Inflammation
  - Protease Activity/Matrix Modification
- Targeting Pathophysiology
  - Need a teleologic understanding
  - Deciphering pathology from response



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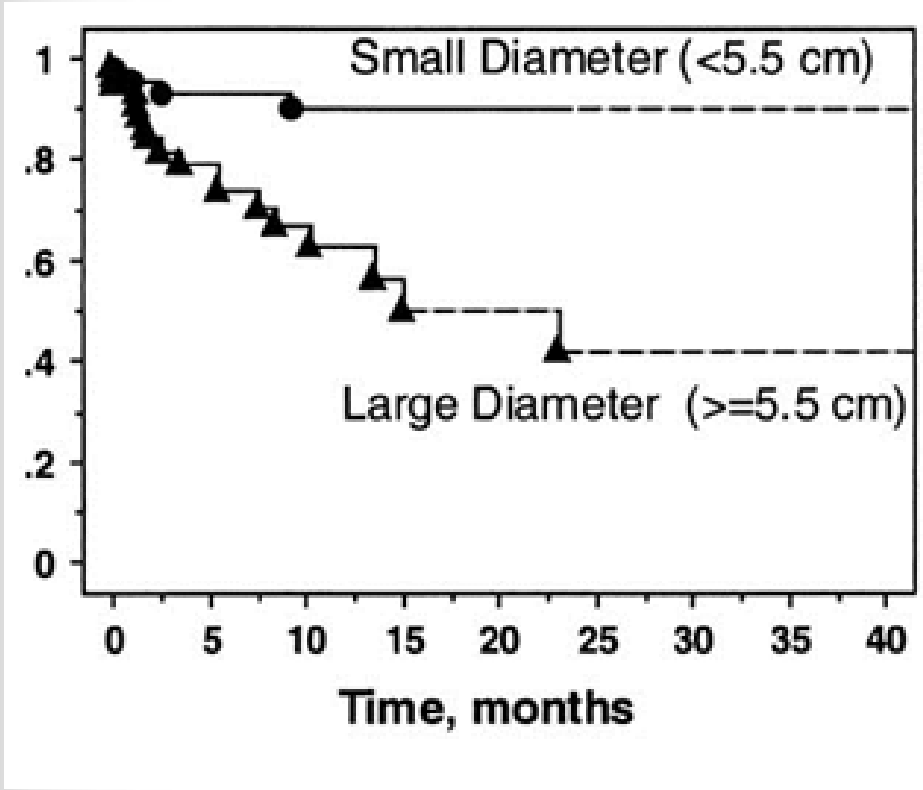
Defining Goals of Medical Therapy

CLINICAL THERAPEUTICS IN THE CONTEXT OF AAA

Looking into the Future

- Natural History of AAA
  - Rupture risk increasing substantially only after 5.5 cm
  - Growth at roughly 10% annually
  - Early surgery no advantage

Size is (really) good at predicting rupture



Fillinger MF, et. Al., J Vasc Surg 2003;37:724-32.

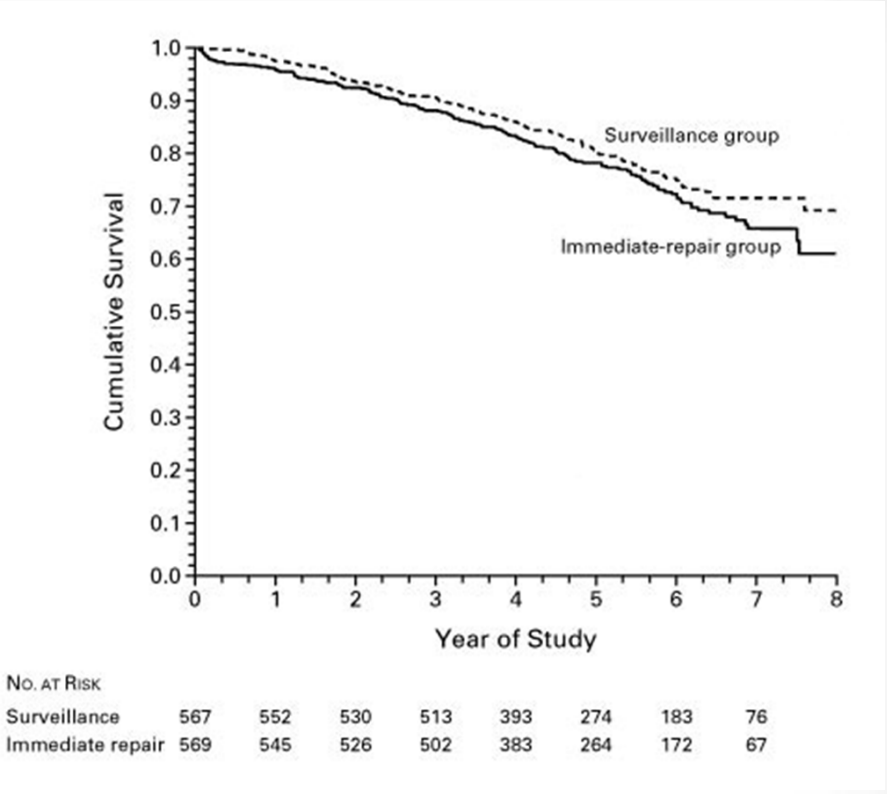
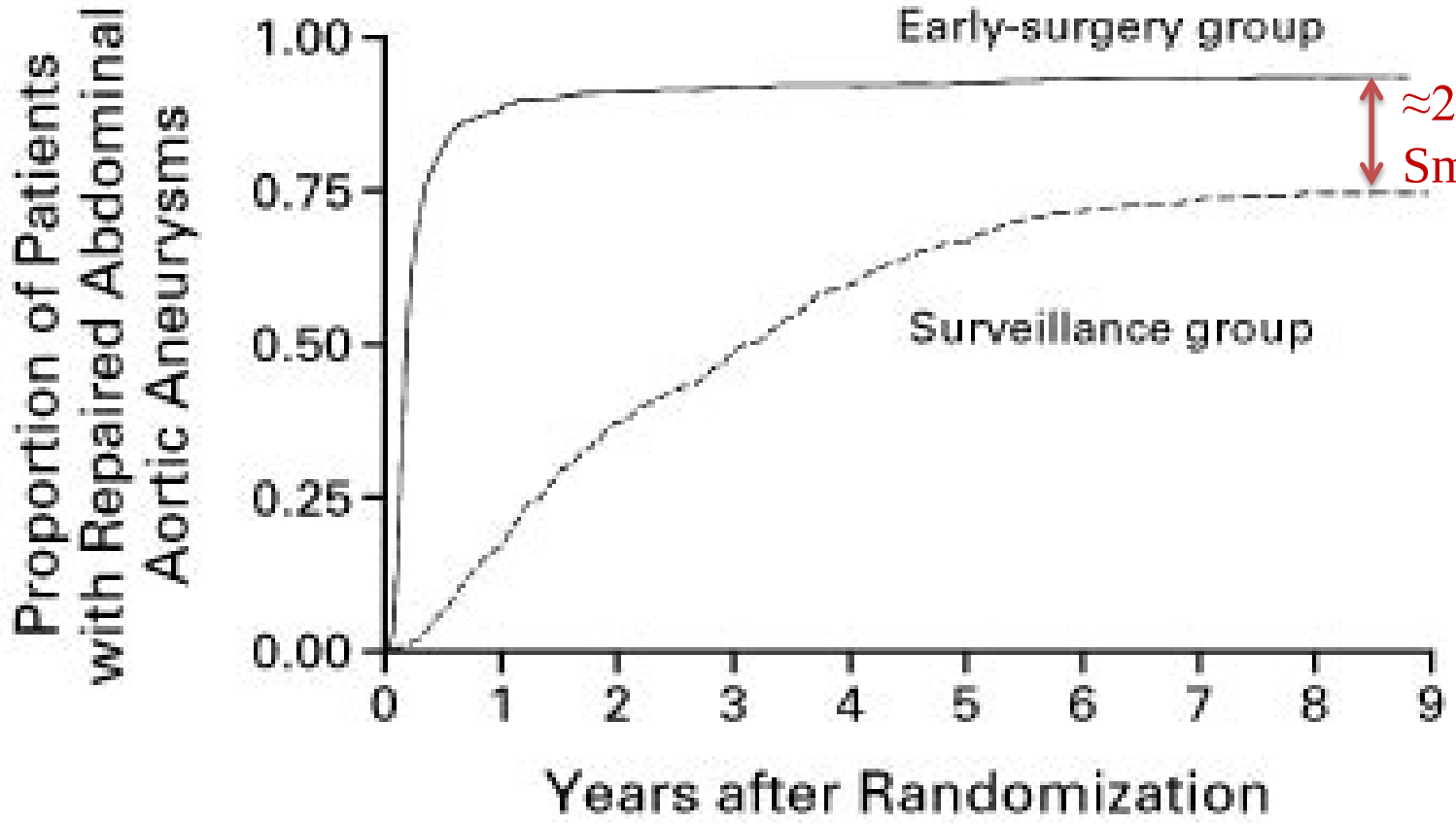


Figure 2: There was no significant difference between the two groups in the primary outcome of the rate of death from any cause (relative risk, 1.21 for repair vs. surveillance; 95 percent confidence interval, 0.95 to 1.54)

Lederle FA et al. N Engl J Med 2002;346:1437-1444

Growth is Nearly Inevitable



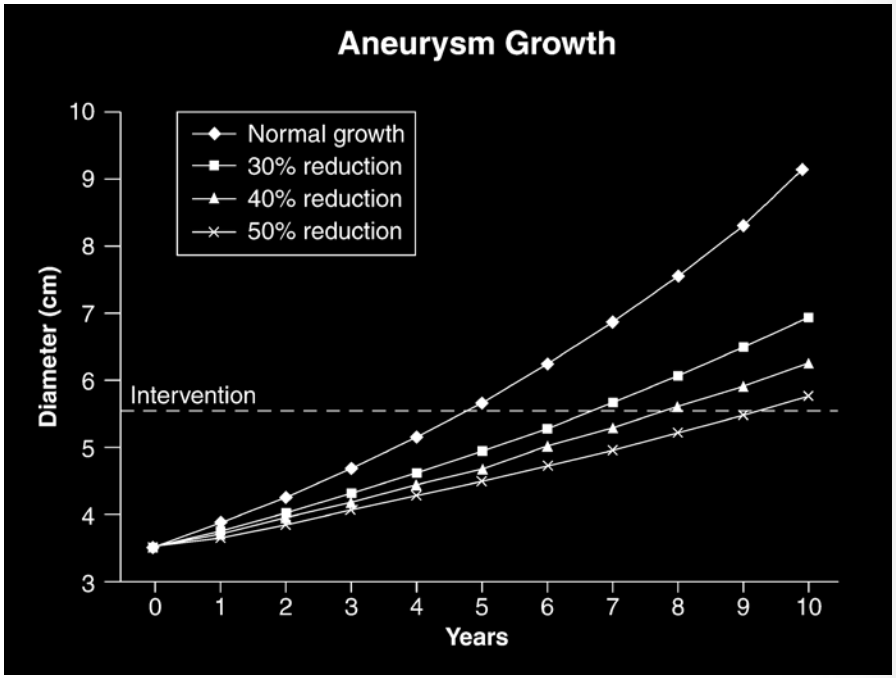
The United Kingdom Small Aneurysm Trial Participants. N Engl J Med 2002;346:1445-1452.

Stabilizing the Aneurysm

- Prevent AAA reaching threshold for repair
  - Slow the growth
  - Stop the growth

A Crude Estimation

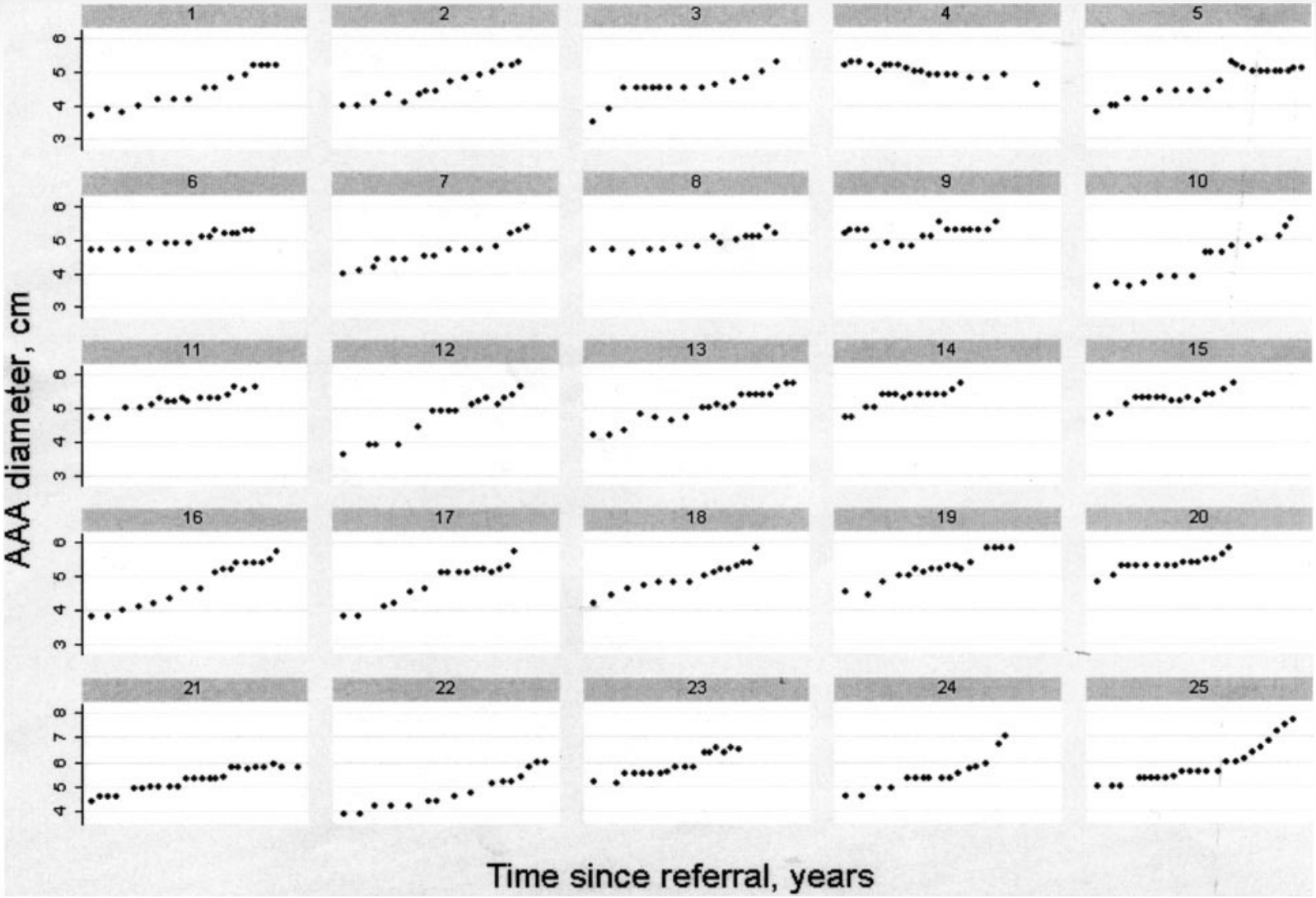
- For very small AAA, A 50% reduction in growth rate may extend need for intervention about 5 years.
- Larger “small AAA” will have appreciably less benefit.



Rentschler M and Baxter BT, Ann NYAS, Volume 1085, pages 39–46, November 2006

Looking into the Future

- Natural History of the Patient with AAA
  - Life expectancy -- not AAA related
    - Other CV disease
    - Malignancy
    - Etc
- Improvements in the treatment of other cardiovascular disease may be at odds with the medical treatment of AAA which delays natural progression of disease.



Brady, Circulation. 2004;110:16-21

Calculating the Effect of Growth Inhibition

- What is the minimum inhibition of growth?
  - Delay/Obviate need for surgical intervention
  - Improve the quality of life
- Monte Carlo simulations
  - Utilize known vital statistics
  - In silico estimate the effects of a new treatment

Predicted Lifetime Effects of Slowed AAA Growth

	Simulation Results			
	% Operated			
% Reduction with Arbitrary Rx	Placebo	Treatment	Absolute Difference	Relative Reduction
40	78%	65%	13%	16%
30	78%	70%	8%	11%
20	78%	73%	5%	7%

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Non-invasive Treatment of Abdominal Aortic Aneurysms Clinical Trial

THE N-TA³CT STUDY

NIH National Institutes of Health
Office of Extramural Research

N-TA^{3}CT RCT Study Design

- Doxycycline 200 mg daily (100 mg bid)
- Include Small AAA at risk for growth
  - 3.5 to 5.0 cm in men
  - 3.5 to 4.5 cm in women
- All treated for 2 years
- CT imaging every 6 months
- Sophisticated pre-specified statistics to evaluate growth
  - Based on rank order
  - Includes effect of death or AAA repair in primary outcome
- Biorepository (imaging and serum/plasma/DNA)

ABDOMINAL AORTIC ANEURYSM
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Powering the Study

			Simulation Results			
	Study Design		% Operated			
% Reduction with Doxycycline	N (per treatment)	Power	Placebo	Doxycycline	Absolute Difference	Relative Reduction
40	**85**	**0.90**	78%	65%	13%	16%
	124	0.98				
30	124	0.84	78%	70%	8%	11%
20	124	0.70	78%	73%	5%	7%

Propanolol Aneurysm Trial Investigators. J Vasc Surg. 2002;35(1):72.
Int J Numer Method Biomed Eng. 2014 Feb;30(2):280-95.
Ann Intern Med. 2013 Dec 17;159(12):815-23.
Br J Surg. 2015 Jul;102(8):894-901.

Table 3. Adjusted Differences in Expansion Rate by Suspected Predictor

Characteristic	Adjusted Difference (95% CI), cm/y	*P* Value
Smoking factors		
Smokers vs nonsmokers	−0.08 (−0.22 to 0.05)	.24
Years of smoking, per 1-y increase	0.00001 (−0.001 to 0.001)	.99
Pack-years, per 1-pack-year increase	0.0001 (0.000 to 0.001)	.64
Ye		
Hype		
Hi		
Sy		
Athe		
Hi		
To		
HI		
LD		
BM		
Medi		
My		
An		
En		
Stroke or TIA	0.04 (−0.004 to 0.08)	.08
Deep-vein thrombosis	0.004 (−0.06 to 0.06)	.88
Claudication	−0.01 (−0.06 to 0.03)	.52
CABG or PTCA	0.002 (−0.03 to 0.03)	.92
Cancer	0.02 (−0.02 to 0.05)	.40
Pulmonary emboli	0.02 (−0.08 to 0.12)	.69
Medication		
β-blocker	0.009 (−0.02 to 0.04)	.51
Cholesterol-lowering medication	−0.02 (−0.05 to 0.01)	.18
Antihypertensive	−0.001 (−0.04 to 0.03)	.78
Daily aspirin	−0.01 (−0.05 to 0.02)	.48
Antiarrhythmic	0.000 (−0.03 to 0.03)	.98
Anticoagulant	0.001 (−0.03 to 0.03)	.94

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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

JAMA Surg. 2015;150(1):44-50.

Table 2 Propensity analysis of factors potentially affecting abdominal aortic aneurysm enlargement rate

	No. of matched pairs	Enlargement rate without factor (mm/year)	Change in rate with factor (mm/year)	*P*
Age > 72 years*	459	2·1	0·0 (–0·7, 0·7)	0·934
After 2000	310	1·9	–1·1 (–2·0, –0·2)	0·016
Current smoking	639	2·1	– 0·2 (–0·6, 0·2)	0·358
After 2000	461	2·0	–0·2 (–0·7, 0·2)	0·338
Coronary artery disease	894	2·1	–0·3 (–0·8, 0·2)	0·198
After 2000	561	2·1	–0·5 (–1·2, 0·2)	0·154
Chronic obstructive pulmonary disease	671	1·7	0·5 (0·0, 1·0)	0·050
After 2000	430	1·7	0·7 (–0·1, 1·6)	0·109
Diabetes	263	2·4	–1·2 (–2·0, –0·3)	0·008
After 2000	185	2·1	–1·1 (–2·0, –0·2)	0·020
Statins	1013	2·1	0·1 (–0·2, 0·5)	0·510
After 2000	538	1·8	0·4 (0·3, 1·1)	0·290
Beta-blockers	828	2·1	–0·5 (–1·2, 0·3)	0·242
After 2000	605	2·0	0·0 (–0·6, 0·6)	0·997
Angiotensin-converting enzyme inhibitors	994	2·0	0·1 (–0·3, 0·4)	0·656
After 2000	669	2·0	0·1 (–0·4, 0·7)	0·613
Angiotensin II receptor blockers	115	1·8	–0·2 (–1·3, 0·9)	0·608
After 2000	107	1·8	0·1 (–1·3, 1·1)	0·823

Values in parentheses are 95 per cent c.i. *Age at first measurement; other factors could be present at any time during follow-up. After 2000 refers to measurements after 1 January 2000.

British Journal of Surgery Volume 102, Issue 12, pages 1480–1487, November 2015

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Finding effective therapy

SORTING THE WHEAT FROM THE CHAFF

Potential Goals of Medical Therapy

- Alter the natural history of an established AAA
  - Only large AAA pose clinical danger
  - Small AAA are asymptomatic and do not rupture
- Prevent AAA development
  - No way to identify aorta with nascent AAA.

Stabilizing the Aneurysm

- Prevent AAA reaching threshold for repair
  - Slow the growth
  - Stop the growth
  - Reverse the growth
- Delay repair beyond 5.5 cm
  - Reduce risk of rupture at a given diameter

Novel Research Goals

- Develop Biomarkers
  - Only opportunity to identify “pre-clinical” disease
  - Understand longitudinal progression of disease
  - Needed to allow screening of therapeutics before moving to expensive randomized clinical trials.
- Hi Fidelity Models of AAA
  - Understand contextual value of current models
  - Develop novel models that better represent the clinical condition

Novel Research Goals

- Recognize Heterogeneity of AAA
  - TAAD is not AAA
  - Not all AAA may be homogeneous.
  - Aortic vs. Aortoiliac involvement
  - Infrarenal vs. Pararenal/Visceral
  - “Inflammatory” vs. ?
  - AAA in Diabetics
  - AAA in non-Smokers

Considerations for Aortic Wall Stabilization

- Production of matrix proteins
- Integration of matrix proteins in a functionally relevant manner
- **Appropriate active cellular machinery**
- Role of MMP may be beneficial when properly regulated

"It's fine to discover cures, but, remember, chronic conditions are our bread and butter."

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Trouble in Paradise

BEYOND N-TA^{3}CT

- Propranolol for small abdominal aortic aneurysms: results of a randomized trial. Propanolol Aneurysm Trial Investigators. J Vasc Surg. 2002;35(1):72.
- ACZ885 for the Treatment of Abdominal Aortic Aneurysm (AAA). IL-1beta monoclonal antibody. Terminated 2015
- Study of the Effectiveness of Telmisartan in Slowing the Progression of Abdominal Aortic Aneurysms (TEDY). Stopped Recruitment in US
- Eplerenone in the Management of Abdominal Aortic Aneurysms (Adosterone inhibition). Just started recruiting
- The Efficacy of Ticagrelor on Abdominal Aortic Aneurysm (AAA) Expansion (TicAAA). Started recruiting in 2014.
- Comparison of Beta-blocker Versus Angiotensin Receptor Blocker for Suppression of Aneurysm Expansion in Patients With Small Abdominal Aortic Aneurysm and Hypertension (BASE Trial). Recruiting. Estimated completion October 2016
- AORTA Trial: Pemirolast (CRD007) (mast cell inhibitor). Br J Surg. 2015 Jul;102(8):894-901. Epub 2015 May 12. No effect.
- Cyclosporine A in Patients With Small Diameter Abdominal Aortic Aneurysms (ACA4). Recruiting since 2014
- Study on Anti-inflammatory Effect of Anti-hypertensive Treatment in Patients With Small AAA's and Mild Hypertension (PISA) (Amlodipine Aliskiren)
- Exercise Therapy to Treat Adults With Abdominal Aortic Aneurysms (AAA:STOP): No Effect on AAA growth: Int J Numer Method Biomed Eng. 2014 Feb;30(2):280-95.
- PHAST
- N-TA^{3}CT
- rterioscler Thromb Vasc Biol. 2016;36:236-244, published online before print December 29 2015, Surrogate Markers of Abdominal Aortic Aneurysm Progression
- Lederle

rterioscler Thromb Vasc Biol.2016;36:236-244, published online before print December 29 2015,