

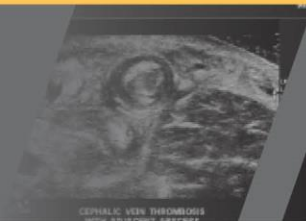
2024 MID-ATLANTIC CONFERENCE  
12th ANNUAL CURRENT CONCEPTS IN  
**VASCULAR THERAPIES**

2024



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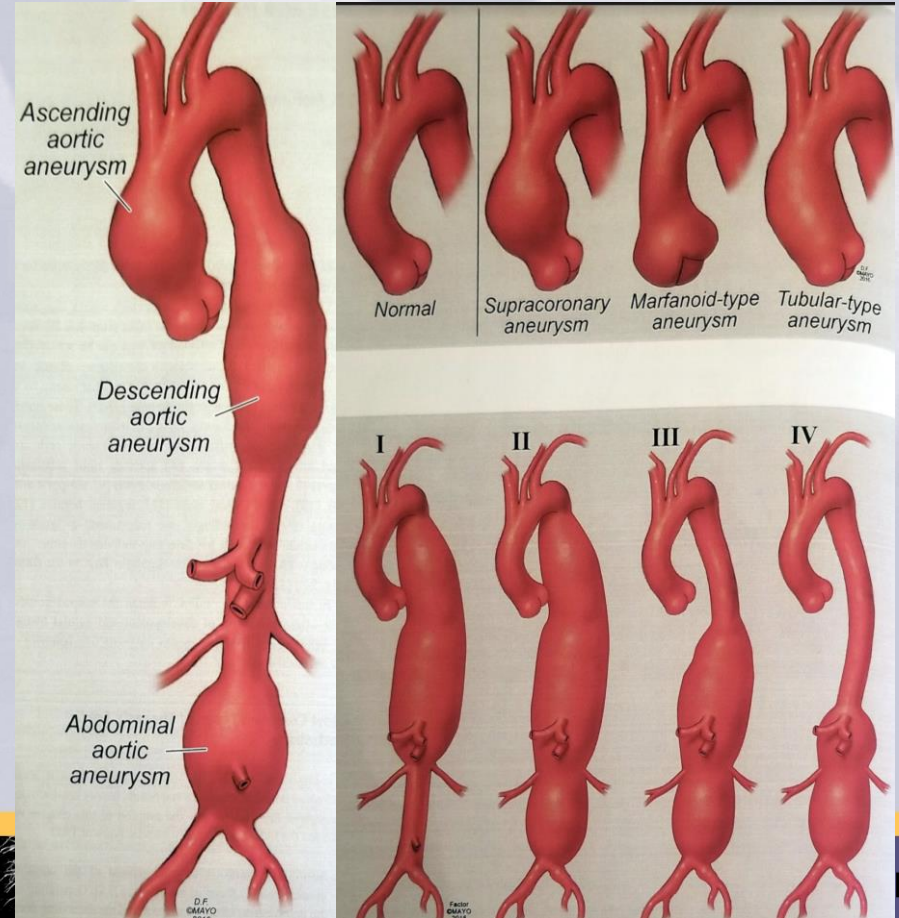


# Medical Management, Inhibiting Aneurysm Growth, What's the Data?

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# Aortic Pathology

- Aortic Aneurysms (ascending, arch, descending, thoracoabdominal, abdominal, aortoiliac)
- Aortitis (mycotic vs large vessel vasculitis)
- Acute aortic syndromes
  - Aortic dissection
  - Penetrating aortic ulcer
  - Intramural hematoma
  - Aortic transection



# Definition

- Increase in diameter of the vessel by  $>50\%$  compared to normal expected diameter.

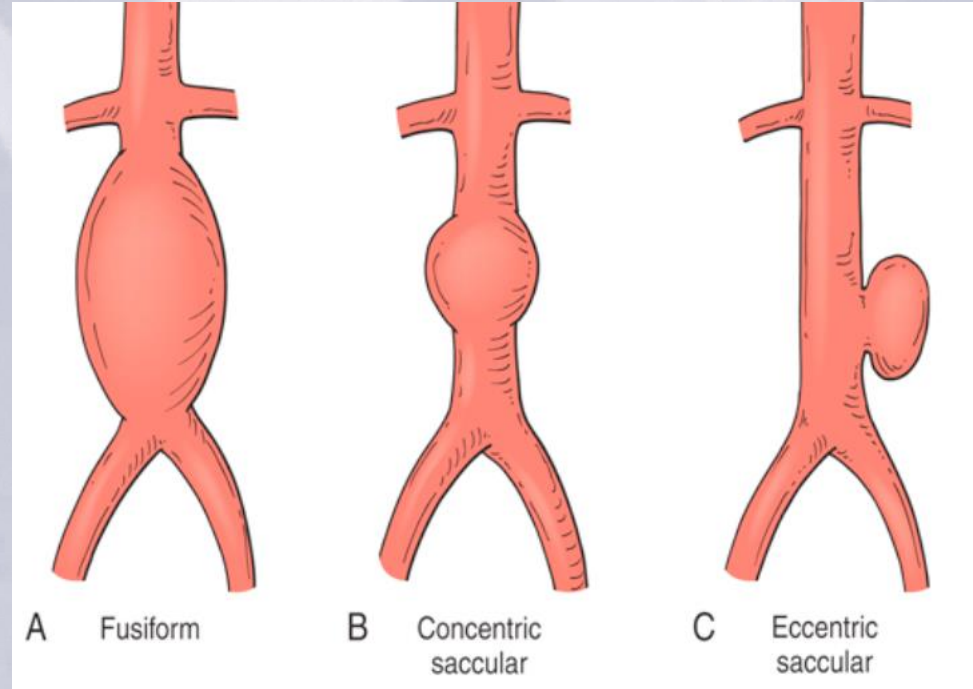
## Definition of Aneurysm at Various Aortic Segments: Size and Ratio to Normal

Aortic Segment	Men		Women	
	Diameter (cm)	Ratio to Normal	Diameter (cm)	Ratio to Normal
Ascending	4.7	1.8	4.2	1.7
Descending	3.7	1.5	3.3	1.3
Infrarenal	3.0	1.1	2.7	1.0



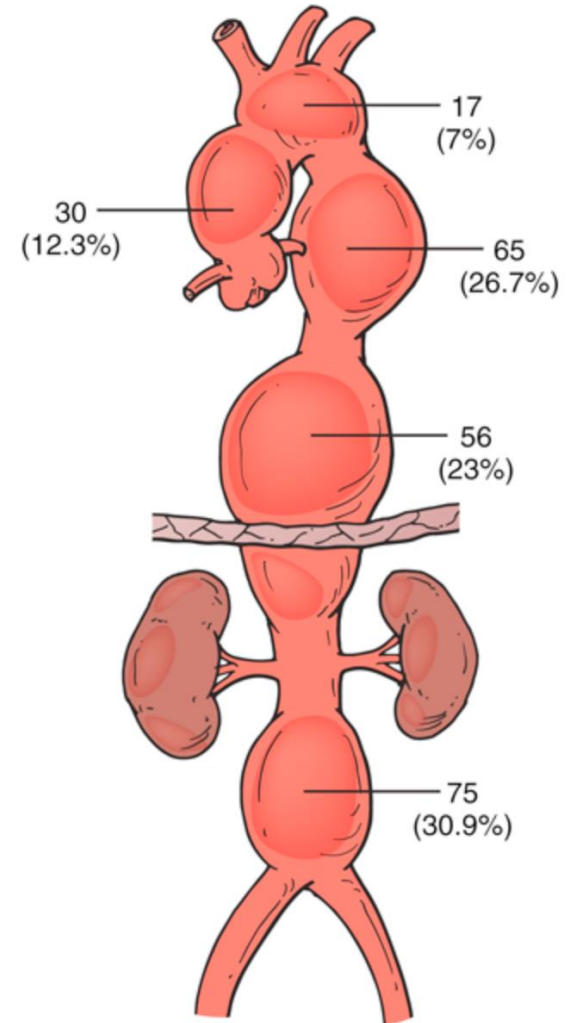
# Definition

- Fusiform versus saccular
- Etiologic classification
  - Degenerative (atherosclerotic)
  - Inflammatory (Takayasu, giant cell, polyarteritis nodosa, Behcet disease, Cogan syndrome, cystic medial necrosis)
  - Familial
  - Dissection
  - Traumatic
  - Developmental/congenital (Kommerrell's diverticulum)
  - Infectious



# Location

- Aortic aneurysm
  - Ascending
  - Arch
  - Descending
  - Thoracoabdominal
  - Abdominal
  - Aortoiliac



# Epidemiology

- 10<sup>th</sup> leading cause of mortality in the US
- 120 000 procedures annually in the US to prevent rupture and other complications
- 1.4 % prevalence among 50-84 years with rising incidence with age. Odds ratio 14.5 for age 75 - 69 years
- Caucasian race and male gender additional predictors
- Smoking is the most important modifiable risk factor ( 0.5 pack a day for 10 years increases the risk). 35 pack years increases the odds 14 folds
- Family history
- Other positive risk factors: increased salt intake, atherosclerotic disease, history of myocardial infarction, peripheral vascular disease, cerebrovascular disease and hypertension
- Negative risk factors: female gender, African American race and diabetes

# Risk factors for AAA

- Male gender (OR 5.7)
- Age (OR 20 after age 75). Everyone eventually gets an aneurysm if they live long enough
- Caucasian race
- Uncontrolled BP
- CAD
- Family history
- High cholesterol
- DM protective
- Carotid disease
- Smoking
- BMI >25
- Fruit, vegetables, nuts, exercise > 1 time per week



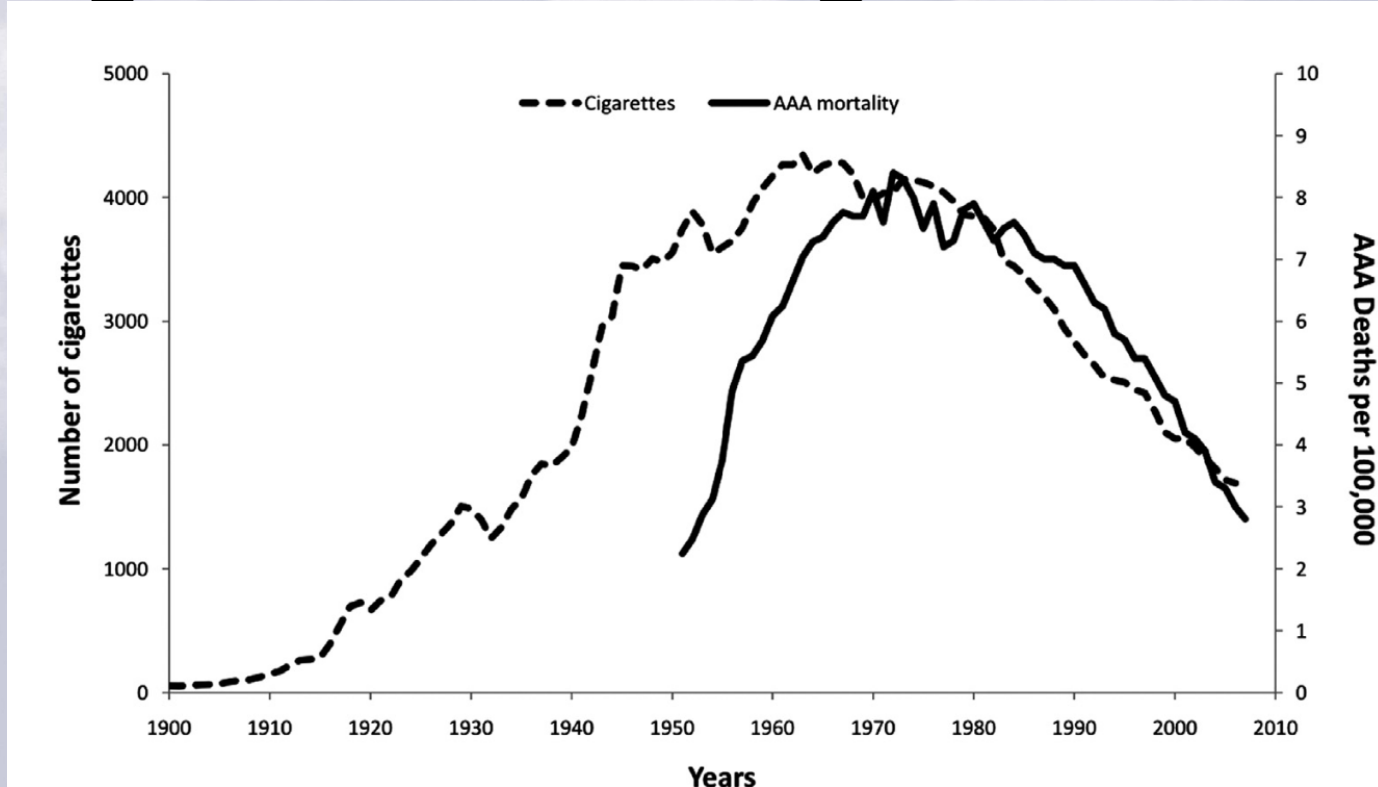
# Rupture risk

- Smoking cessation and HTN control only modifiable risk factors
- **High risk factors:** female sex (3X), larger AAA diameter at the time of initial diagnosis, smoking, lower FEV1, saccular morphology and higher mean arterial pressure
- Growth rate (>10 mm in 12-month rapid growth)
- DM with reduced growth rate

AAA Diameter (cm)	Rupture Risk (%)
3.0–3.9	0.3
4.0–4.9	0.5–1.5
5.0–5.9	1–11
6.0–6.9	11–22
>7	>30

# Cigarette smoking

- Declining AAA mortality with decreasing smoking prevalence
- Female smokers have combined higher risk than males



# Clinical evaluation

- Pulsatile abdominal mass
- Look for concomitant aneurysm (femoral, popliteal)

# Diagnostic evaluation

- Biomarkers :fibrinogen, D-dimer, Interleukin-6, matrix metalloproteinase 1, tissue inhibitor of matrix metalloproteinase 1, C-reactive protein, alpha 1 antitrypsin, triglycerides, lipoprotein (a), apolipoprotein A.
  - None with sensitivity, specificity or proven clinical validation



# Genetic evaluation

SYNDROMIC (5%)	
Marfan syndrome	FBN1
Ehlers Danlos syndrome	COL 1A1, COL 1A2, COL 3A1, COL5A1, COL 5A2
Loeys-Dietz syndrome	TGFBR1, TGFBR2
TGFB2 related vasculopathy	TGFB2
Aneurysm-osteoarthritis syndrome	SMAD3
Cutis laxa syndrome	FBLN4, ELN
Weil-Marchesani syndrome	ADAMTS10

NON-SYNDROMIC (21%)	
Familial thoracic aortic aneurysm	TGFBR1, TGFBR2, ACTA2, SMAD 2, TGFB2, PRKG1
Familial thoracic aortic aneurysm with patent ductus arteriosus	MYH11
Familial thoracic aortic aneurysm with bicuspid aortic valve	NOTCH1

# Other factors

- Diameter of normal aorta

  - Ascending:  $3.2 \pm 0.4$  cm

  - DTA: 2-2.3 cm

  - Abdominal: 1.7-1.9 cm

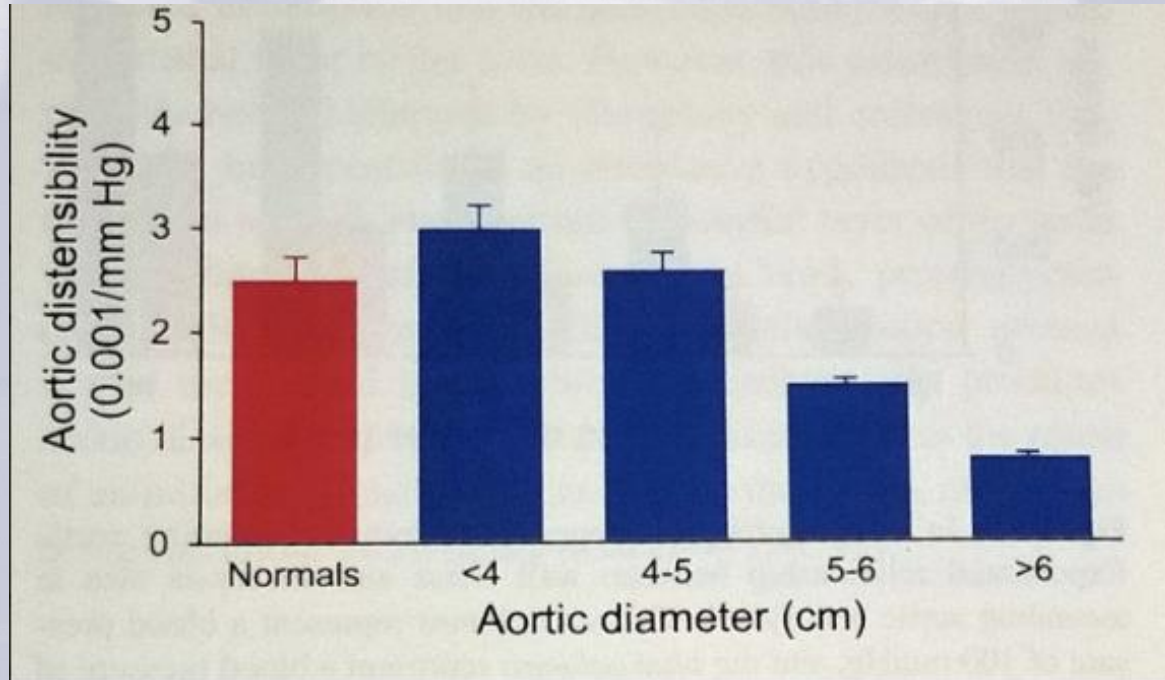
- Growth rate of aneurysm

  - Repair if 0.5-1.0 cm /year

- Body surface area

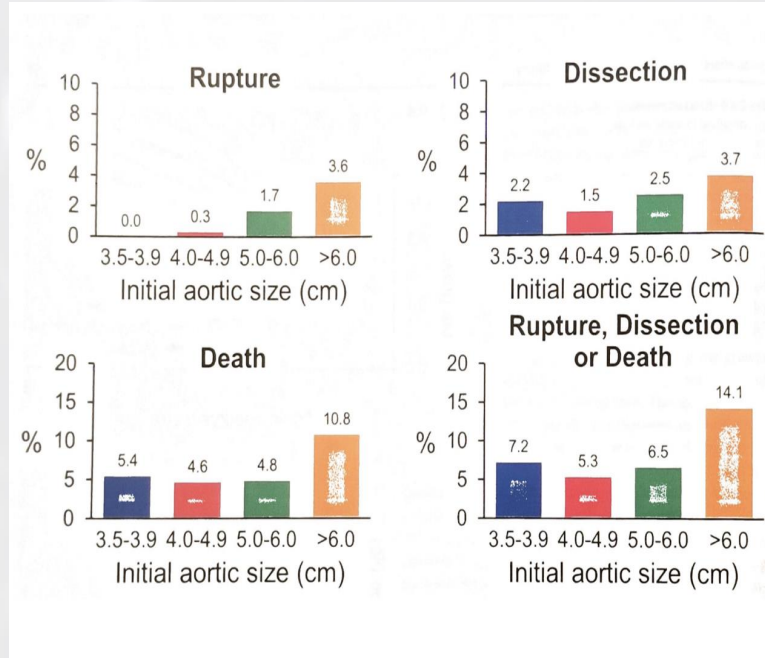
- Maximum diameter of the aneurysmal aorta

  - Loss of distensibility and elasticity

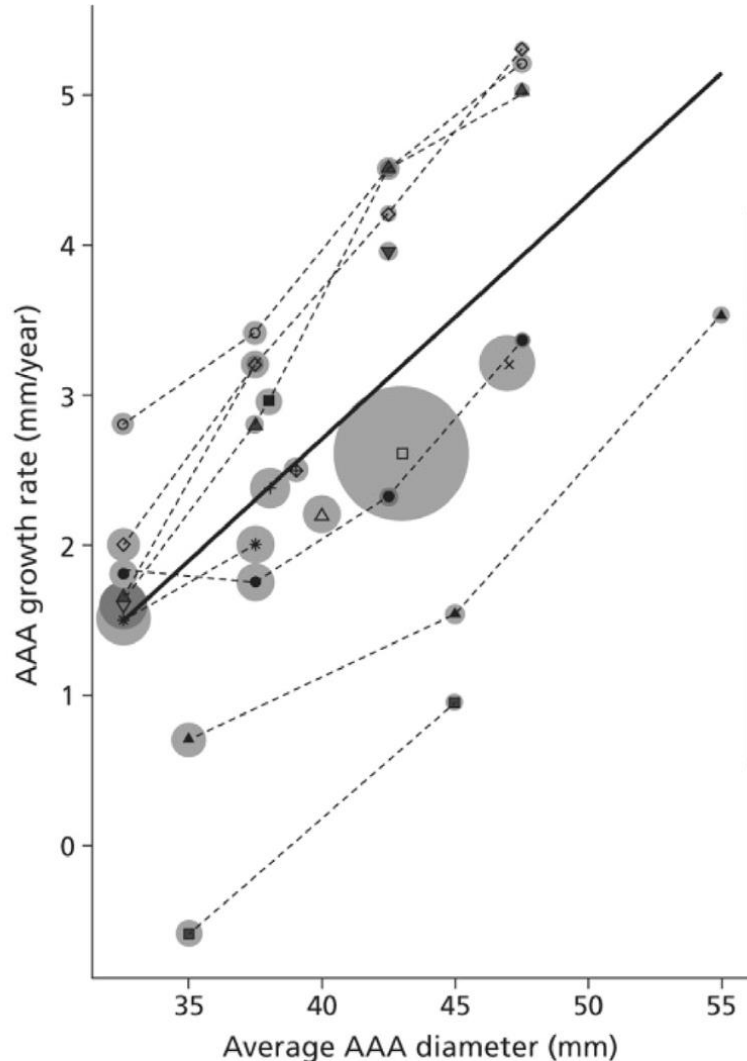


# Other factors

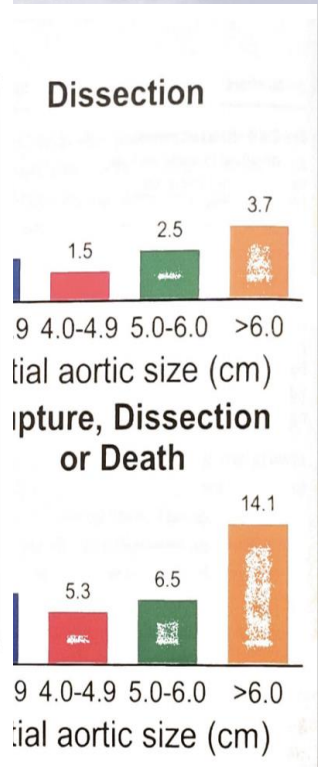
- Maximum diameter of the aneurysm
  - Increased risk for rupture, dissection and death with size
  - Repair indicated for (increase threshold for high operative risk)
    - Ascending aorta: 5.0 cm
    - DTA: 6.0 cm
    - Abdominal: 5.5 cm



- Maximum aneurysm growth rate
- Increased dissection risk
- Repair threshold (risk)
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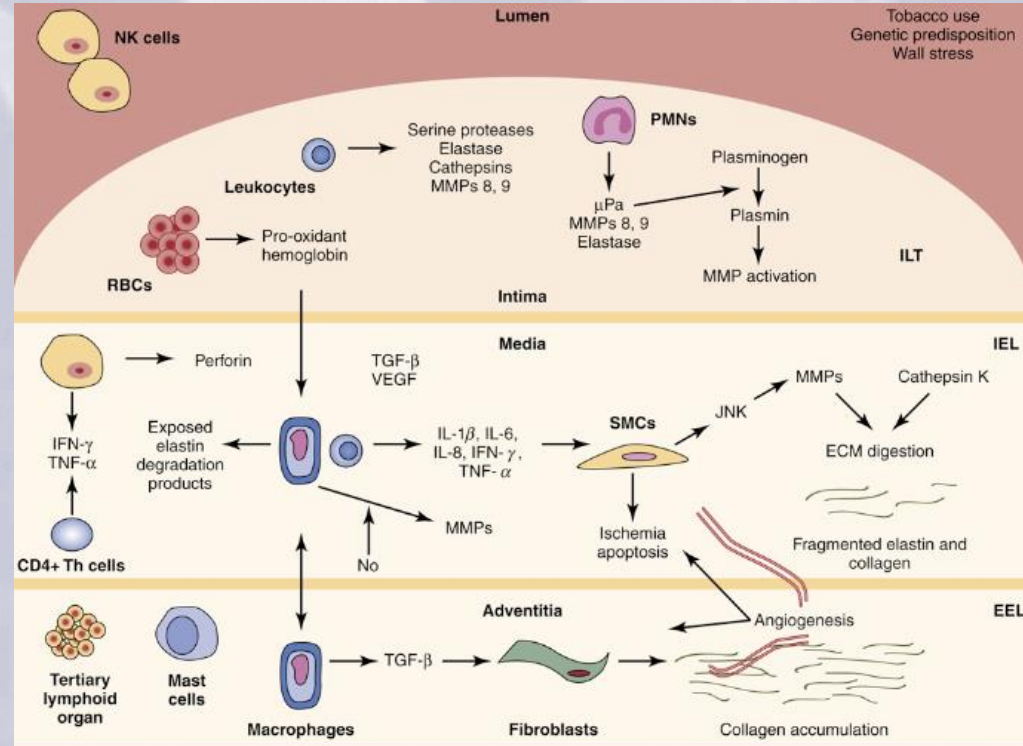
- Author**
- Brady 2004
  - Brown 2003
  - △ Karlsson 2009
  - + Propranolol 2002
  - × Lederle 2002
  - ◇ Lindholt 2000
  - ▽ McCarthy 2003
  - \* Santilli 2002
  - ◆ Schlosser 2008
  - Schouten 2006
  - Solberg 2005
  - ▲ Vardulaki 1998 Chichester
  - Vardulaki 1998 Huntingdon
  - ▲ Vega de Céniga 2006
  - ▼ Vega de Céniga 2008





# Pathophysiology

- Heterogeneity of different segments of aorta.
- Thoracic aorta with adventitial vasa vasorum and 50-60 lamellar units in media compared to 28-32 in abdominal aorta.
- CRP has direct correlation to aortic diameter: role of inflammation
- Hypothesis of aortic wall hypoxia from Intra-luminal thrombus: Fibrinolysis → plasmin induced activation of TGF-beta and MMP (2, 9, 12) → medial degeneration, elastic degradation, adventitial inflammation → AAA



# Diagnostic evaluation

- Clinical exam: also include femoral an
- Imaging
  - Ultrasound: good screening
  - CT scan: highly sensitive and
  - MRI
- Screening recommendation with
  - Men and women with smoking history and age 65 and above.
- Surveillance: Every 3 years for 3.0-3.9 cm, annual for 4.0-4.9 cm, 6 monthly for > 5 cm
- Aortic size index (maximum diameter/BSA): superior rupture prediction model for rupture in females

Screening Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) amendment in 2006 one-time screening by ultrasound for men aged 65 to 75 years if they had smoked > 100 cigarettes in their lifetime and for men and women with a family history of AAA disease as part of their Welcome to Medicare physical examination.

# Diagnostic evaluation

- Future directions: genomic sequencing to determine the patients at risk for AAA development and rupture.
- ‘Crescent sign’ disruption of intraluminal thrombus (ILT) by plaque hemorrhage as a predictor for rupture
- Calcification of media ? Protective effect against rupture
- ILT and wall inflammatory activity by MRI, scintigraphy or radionuclide scans
- Promising current targets include:
  - interruption of the inflammatory cascade leading to the degeneration of medial smooth muscle and ECM through MMPs 2, 8, and 9 as well as inflammatory cytokines, including TNFs and interleukins IL-1 $\beta$ , IL-4, IL-6, and IL-8;
  - suppressing neoangiogenesis, which characterizes adventitial changes
  - minimizing the oxidative injury associated with ILT.

# Diagnostic evaluation

- Other rupture prediction tools
  - AAA expansion rate
  - AAA shape affects wall stress more than the diameter alone
  - Wall stiffness
  - Peak wall stress assessment based on ultrasound
  - Peak wall rupture index based on peak wall stress and residual wall strength (CT based ILT volume, PET imaging)
  - Computational fluid dynamics and its impact on AAA growth, remodeling and rupture
  - Molecular imaging of angiogenesis, matrix disruption, activated macrophage localization, proteolysis



# Management

- Only proven intervention to reduce progression as smoking cessation and HTN control
- Potential target to reduce progression are inhibition of immune function, dyslipidemia, hypertension, connective tissue degradation, oxidative stress, and vascular smooth muscle degradation
- EXERCISE IF SAFE, SO IS MODERATE ACTIVITY
- Increased blood flow through exercise, might reduce intraluminal thrombus (in interval enlargement over 3 years)

Myers J, et al. A randomized trial of exercise training in abdominal aortic aneurysm disease. Med Sci Sports Exerc. 2014;46:2–9. PMID: 23793234

# Medical therapy

- Animal studies with reduced progression with statins, angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, and antibiotics including tetracycline and doxycycline
- Multiple trials: none of the human trials have shown reversal of progression so far
- **$\beta$ -blockers:** earlier trial with some impact, not noted in larger studies.

1. Wilmink A.B.M, Hubbard C.S.F.F, Day N.E, Quick C.R.G. Effect of propranolol on the expansion of abdominal aortic aneurysms: a randomized study. Br J Surg. 2000;87 499–499.
2. Gadowski G.R, Pilcher D.B, Ricci M.A. Burlington F. University of Vermont College of Medicine. Abdominal aortic aneurysm expansion rate: effect of size and beta-adrenergic blockade. J Vasc Surg. 1994;19:727–731

# Medical therapy

- **Anti-HTN therapy**
- **ACE inhibitors** with earlier studies with some improvement
  - Not proven on larger studies
  - UK Small aneurysm trial with trend towards increased growth rate of AAA
  - HTN control and statin have led to improved perioperative outcomes
  - Increased risk of rupture in those who discontinued ACE inhibitors
- **Doxycycline** (Inhibits MMP). Multiple animal studies with slower AAA growth rate. Not seen in human trial
  1. The UK Small Aneurysm Trial Participants, . Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet*. 1998;352:1649–1655. PMID: 9853436
  2. Baxter B.T, et al. Effect of doxycycline on aneurysm growth among patients with small infrarenal abdominal aortic aneurysms. *JAMA*. 2020;323:2029–2038. PMID: 32453369

# Medical therapy

- **Statin:** Animal studies. But not proved in human trials. (UK Heart Protection Study). But showed 22% reduction in MACE.
- **Anti-platelet therapy** causes thrombus reduction and AAA growth reduction in mouse model. But not in human studies.
- **Metformin:** ongoing trial Limiting AAA with Metformin (LIMIT)

1. Heart Protection Study Collaborative Group, . Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007;45:645–654.e1. PMID: 17398372



# StAAAble trial



- Nectero EAST system: single use endovascular system 14 or 16 Fr with dual balloon delivery catheter and stabilizer mixer containing pentagalloyl glucose (PGG), delivered over 3 minutes via 'weeping' balloon
- Binds elastin and collagen and potentially strengthen the aortic wall and reduce further degradation. **Decrease AAA growth and rupture**
- Early study with 20 patients
- The average changes in maximum aneurysm diameter from baseline to 6, 12, 24, and 36 months were 0.2 mm, 1.1 mm, 1.2 mm, and 0.8 mm, respectively, and the average changes in volume were 2.0%, 9.6%, 18.1%, and 11.6%, respectively. At 12 months, none of the aneurysms showed growth >5.0 mm, and three had volume growth >10%.

A pilot study to evaluate a novel localized treatment to stabilize small- to medium-sized infrarenal abdominal aortic aneurysms Cheng, Stephen W.K. et al. Journal of Vascular Surgery, Volume 78, Issue 4, 929 - 935.e1

# Conclusion

- **Aortic aneurysm represents pathology with focal increase in diameter of aorta by >50%**
- **Multiple classification schemes are available based on morphology, location and etiology**
- **Pathophysiology remains poorly understood but multiple risk factors are identified, age being the strongest**
- **Aneurysm size is the strongest predictor for rupture, while aortic size index might be more reliable**
- **Smoking cessation and HTN control are the only modifiable risk factors with proven effect on aneurysm enlargement**
- **Antiplatelet therapy and statin are reasonable first line agents to help with overall risk profile.**
- **Results awaited on Nectero EAST system and LIMIT trial (metformin)**



# Thank you

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