
1

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# SEX DIFFERENCES IN THORACIC AORTIC ANEURYSMS

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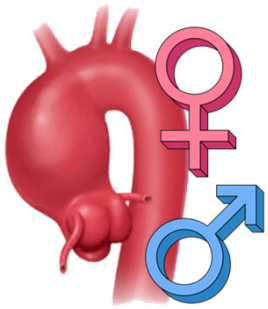
MHI Grant Rounds
September 23rd, 2024





2

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## DISCLOSURES

- **None**



3

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## OBJECTIVES:

- **Identify how thoracic aortic aneurysms (TAA) affect males and females differently**
- **Outline biological and hemodynamic mechanisms underlying sex differences in TAA**
- **Adapt clinical practice to maximize quality of care for males and females with TAA**



4

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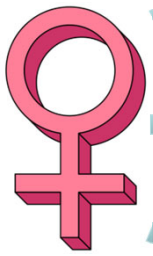
## TAA AND DISSECTIONS – SEX DIFFERENCES IN EPIDEMIOLOGY

~30%

~70%



**3x ↑risk of dissection compared to men**

**40% ↑ risk of death compared to men**

81% ↑ Death

90% ↑ Stroke

40% ↑ Complications

Boczar K and Coutinho T. *Can J Cardiol* 2018
Chung J, Coutinho T, Chu M and Ouzonian M. J Thorac Cardiovasc Surg 2020



5

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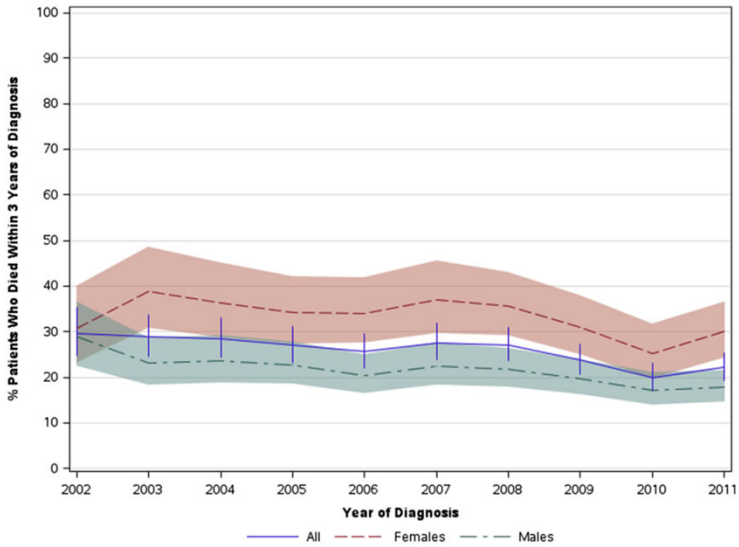
## TEMPORAL TRENDS - 3-YEAR TAA MORTALITY




In Canada, 5-year mortality rates for all cancers: **37%**

3-year TAA mortality rate in women: 30%

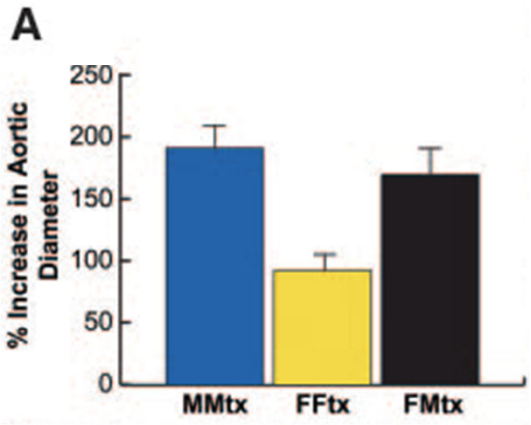
The Journal of Thoracic and Cardiovascular Surgery · June 2018



6

## Why are women protected against TAA?

Sex hormones (and their removal) may partially mediate sex differences




**MMTx and FMTx aortas had more MMP-9 than FFTx aortas**

Ailawadi G et al. *Atherosc Thromb Vasc Biol* 2004

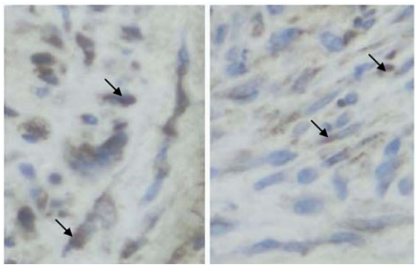


7

## Why are women protected against TAA?

Estrogen (and its removal) may partially mediate sex differences

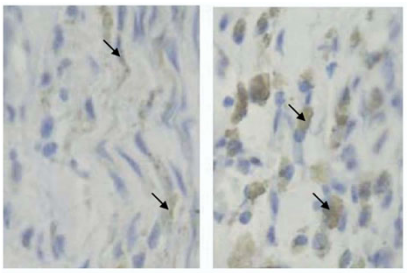
Ovariectomized F rats n=10 | Sham surgery F rats n=10



MMP-2 in AAA (same for MMP-9)

AAA expansion was 58% greater among the ovariectomized rats than sham surgery female rats

M rats treated with E2 n=10 | M rats treated with saline n=10



MMP-9 in AAA (same for MMP-2)

AAA expansion was 67% lower among male rats treated with estradiol than control male rats

Wu XF et al. Am J Surg 2009



8

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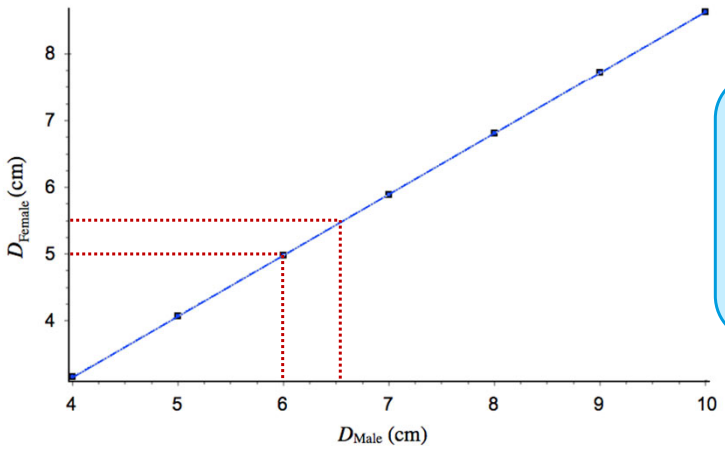
# WHY DO WOMEN WITH TAA FARE WORSE?

## RELATIVE AORTIC SIZE – ROLE OF SEX




**Consider body size when making clinical decisions about TAA in women**

Forbes T et al. *Eur J Vasc Endovasc Surg* 2010



9

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# WHAT DO GUIDELINES/ COHORTS SAY?

***ACC/AHA 2022:***
***"For male and female patients who are significantly shorter or taller than average, diameters need to be adjusted downward or upward, accordingly."***

### Aortic root

Table 2 Normal aortic root diameter by age for women with BSA of 1.7 $m^2$

| | Age (y) | | | | | |
|---|---|---|---|---|---|---|
| | 15–29 | 30–39 | 40–49 | 50–59 | 60–69 | ≥70 |
| Mean normal (cm) | 2.9 | 3.0 | 3.2 | 3.2 | 3.3 | 3.4 |
| Upper limit of normal (cm) | 3.3 | 3.4 | 3.6 | 3.6 | 3.7 | 3.9 |

Add 0.5 mm per 0.1 $m^2$ BSA above 1.7 $m^2$ or subtract 0.5 mm per 0.1 $m^2$ BSA below 1.7 $m^2$.[6]

### Ascending aorta

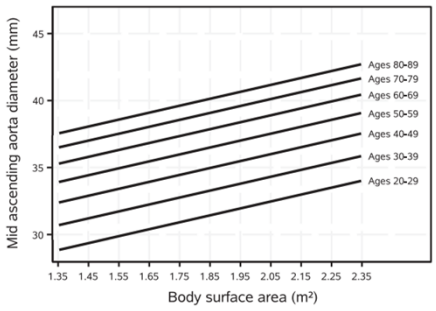


Figure 3. Nomograms with predicted 95th percentiles for mid-ascending aorta diameter by age (per decade) for women.

ACC/AHA Aorta guidelines 2022; ASE aorta guidelines 2018; Ayoub C et al. Am J Cardiol 2018



10

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# NEW IN THE 2022 GUIDELINE

## NORMALIZING AORTIC SIZE TO BODY SIZE

***"For male and female patients who are significantly shorter or taller tan average, diameters need to be adjusted downward or upward, accordingly."***

♂ Average height: 175 cm (5'9")

♀ Average height: 162 cm (5'4")

**Aortic size index (ASI):** Aortic diameter/ BSA, in cm/m$^2$
**Intervention cutoff:** ASI ≥ 3.08 cm/m$^2$ (class 2b)

**Aortic height index (AHI):** Aortic diameter/ height, in cm/m
**Intervention cutoff:** AHI ≥ 3.21 cm/m (class 2b)

**Cross-sectional area to height ratio:** Cross-sectional area/ height, in cm$^2$/m
**Intervention cutoff:** TAA > 10 cm$^2$/m for patients with height >1SD above or below mean (2a)

Isselbacher EM et al. *Circulation* 2022



11

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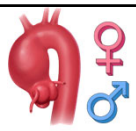
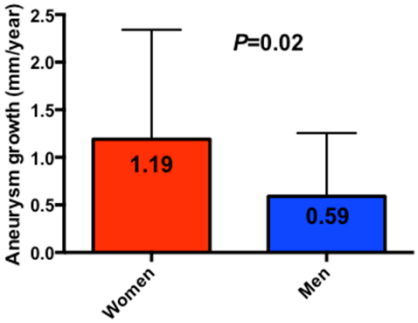
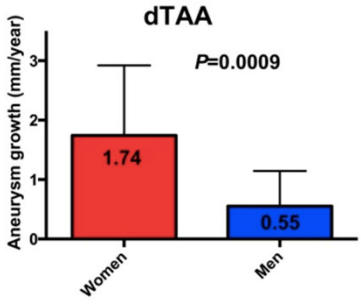
# WHY DO WOMEN WITH TAA FARE WORSE?

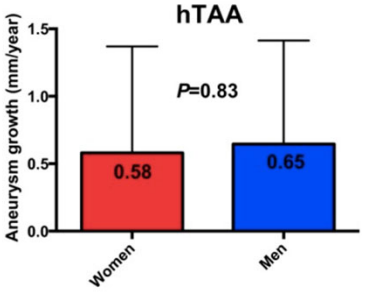
## SEX DIFFERENCES IN TAA GROWTH



n = 82, **age** 67.7±11.8 yrs, 74% **men**, 57% **dTAA**, baseline aneurysm **size**: 45.6±4.3 mm, **follow-up**: 3.1±2.8 yrs




dTAA: degenerative TAA
hTAA: heritable TAA

Statistical significance was maintained in multivariable models

**Cheung K (…) Coutinho T. *JAHA* 2017**



12

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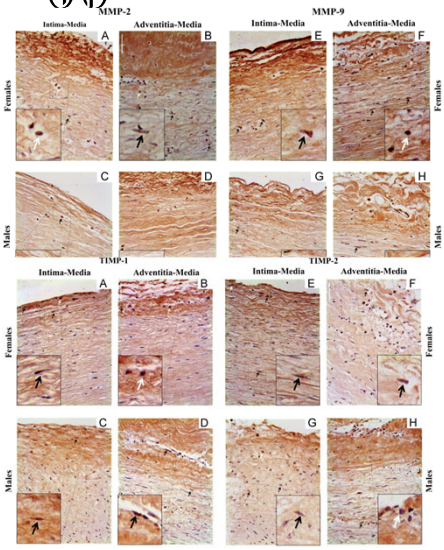
## Why do women with TAA fare worse?

### More adverse matrix remodeling in female degenerative TAAs




**MMP-2 and -9 staining intensity and immunoreactivity were significantly enhanced in women**

**TIMP-1 and -2 staining intensity and immunoreactivity were significantly enhanced in men**

n=20 men and 15 women with TAA (average age 68 & 65 years, respectively)

TAA surgically resected (average size: 55 mm)

No sex differences in age or indexed TAA size

**Sokolis PS et al. *J Mechan Behav Biomed Mat* 2014**



13

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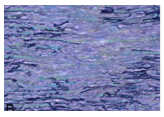
## TAA SAMPLES FROM WOMEN…

… had lower elastin and collagen content than men's TAAs



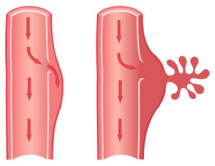
… had less distensible and weaker walls than men's TAAs

Older

↑ MMPs/TIMPs

↑ aortic wall remodeling (↓elastin and collagen fiber contents)

↑ aortic stiffness
↓aortic strength



↑ growth and rupture potential in



14

## Why do women with TAA fare worse?

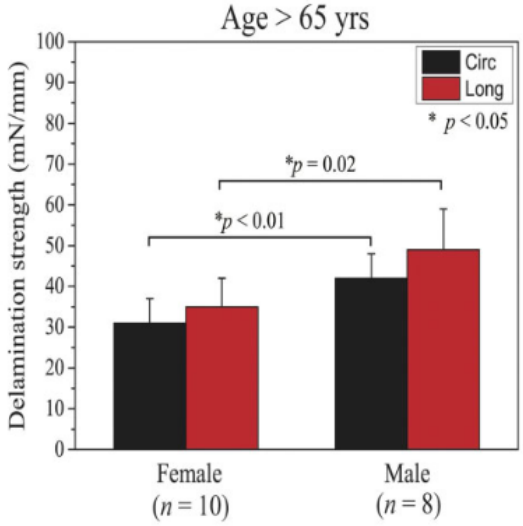
### Dissection properties differ between older males and females with TAA

n= 22 males and 19 females with ascending TAA (mean 50-52 mm)

Delamination strength of the TAA assessed

No sex differences in patients 65 y.o or younger (~75% of younger patients had BAV)

Among those >65 y.o., HTN was much more prevalent in females (80%) than males (38%)




Tong J et al. *Interact Cardiovasc Thorac Surg* 2022



15

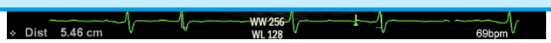
## ILLUSTRATIVE CASE

### 76 Y.O F WITH HTN, AFIB, HFPEF, REMOTE H/O BREAST CA. BSA: 1.5 M²

2012: Ascending 4.69 cm (3.13 cm/m²)



2018: Ascending 5.46 cm (3.64 cm/m²)


**TAA size > 3.08 cm/m²**

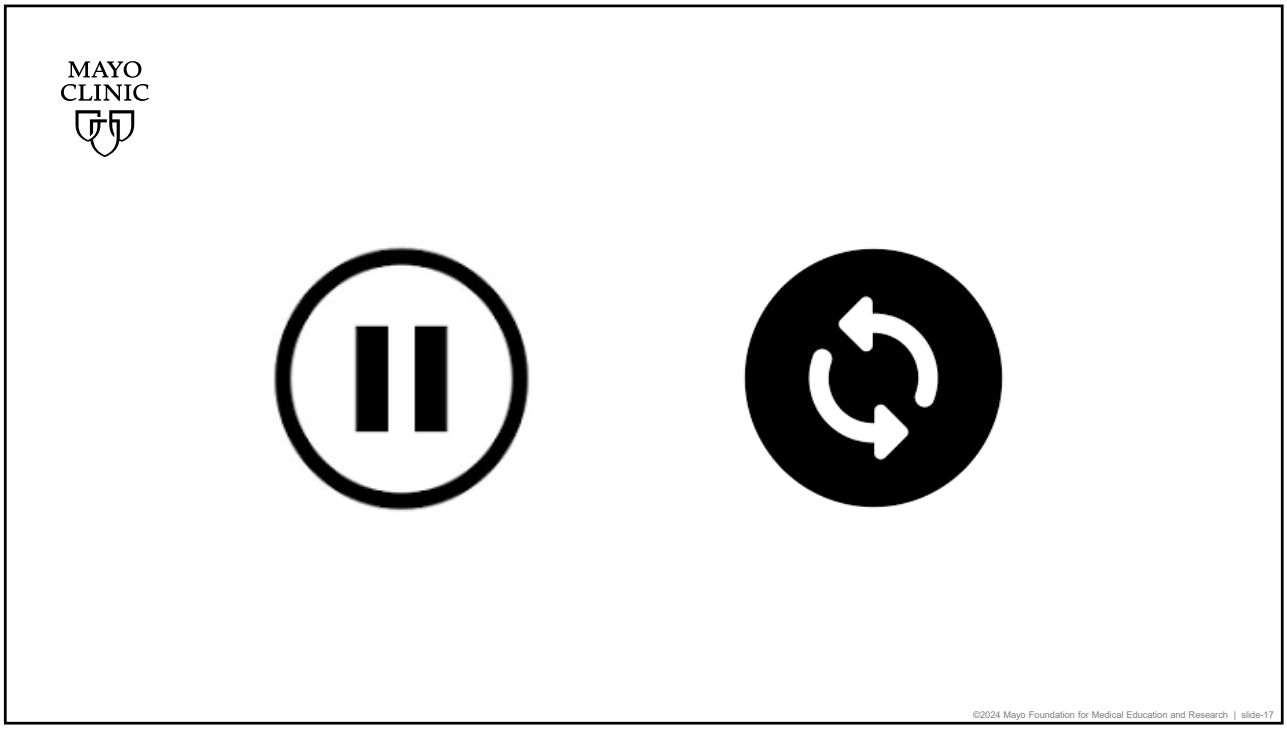
**TAA growth rate: 1.28 mm/year**

(compare to the average of 0.55 mm/year in men with TAA from Cheung K et al paper)

3 months after last echo: Sudden death at home



16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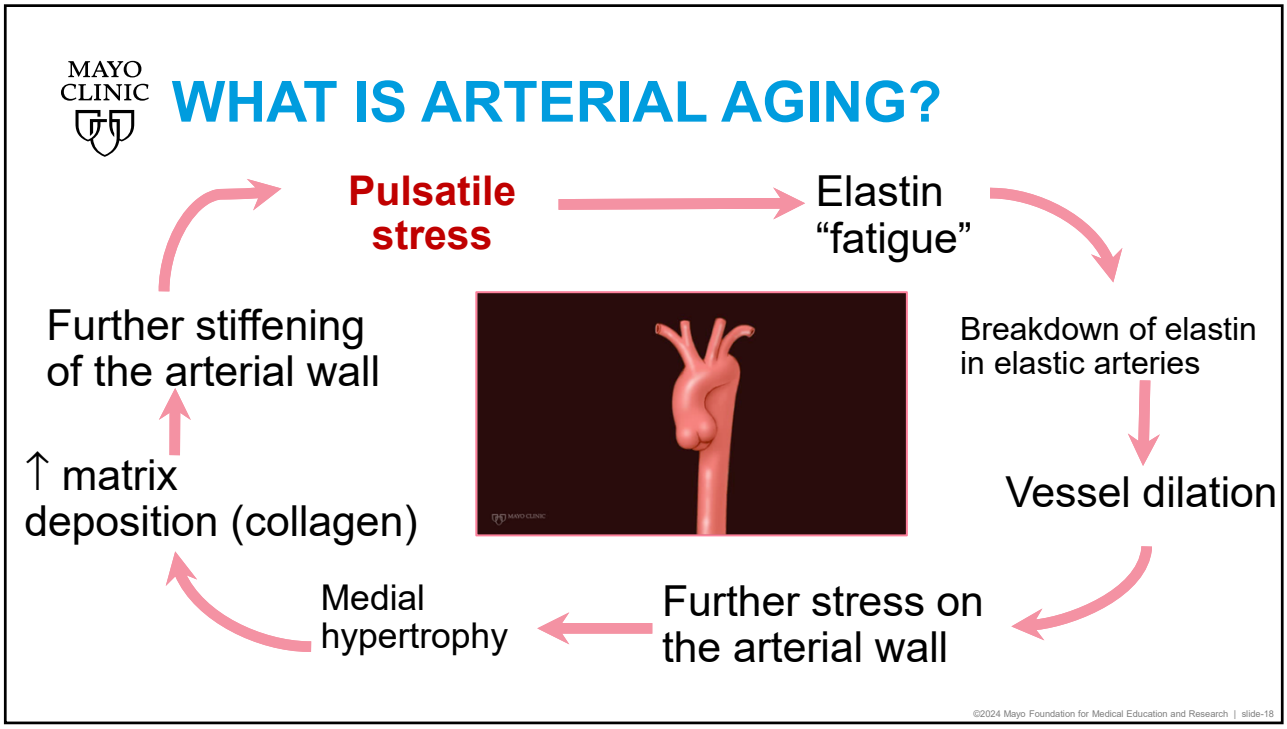
17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WHAT IS ARTERIAL AGING?
Pulsatile stress
Elastin "fatigue"
Breakdown of elastin in elastic arteries
Vessel dilation
Further stress on the arterial wall
Medial hypertrophy
↑ matrix deposition (collagen)
Further stiffening of the arterial wall
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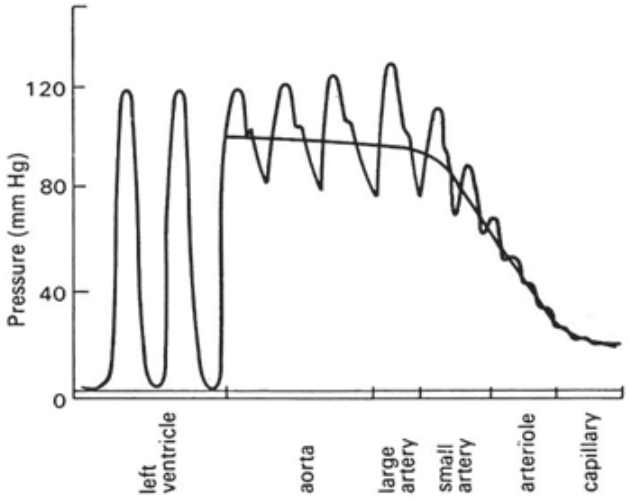
18

## ARTERIAL FUNCTION AS A WINDOW INTO THE HEALTH OF THE AORTIC WALL

**Aortic functions:**

- **Conduit**
- **Reservoir**
- **Pressure-buffer**

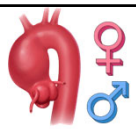
**Aortic stiffening and worsening of the pressure-buffering capabilities of the aorta are markers of worse aortic health and hallmark findings of arterial aging**

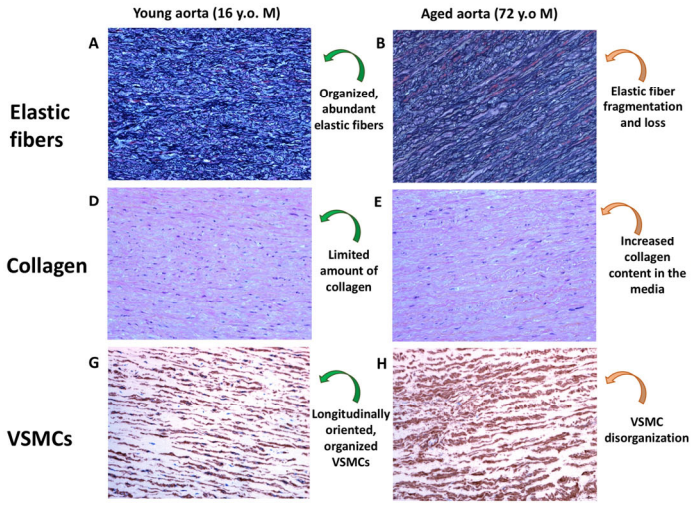





19

## HISTOLOGY OF AORTIC AGING






**Biomechanical and hemodynamic result of aortic aging:**

A stiffer aorta that has decreased ability to buffer pressure, leading to increased pulsatile arterial load

Rooprai J and Coutinho T. In: *Chirinos – Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health And Disease* 2022



20

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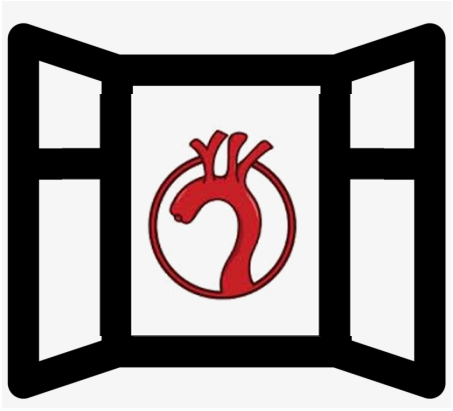
# AORTIC STIFFNESS AND PULSATILE HEMODYNAMICS



## A WINDOW TO UNDERSTAND AORTIC WALL HEALTH



21

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# ARTERIAL AGING: ARE MEN AND WOMEN DIFFERENT?

## PULSATILE HEMODYNAMICS IN OLDER MEN AND WOMEN

n = 408 older subjects
Age ~ 75 yrs
55% women

| Variable, Units | Women | Men | *P* |
|---|---|---|---|
| Central pulse pressure, mm Hg | 75.0±22.4 | 67.1±19.5 | <0.001 |
| Peripheral pulse pressure, mm Hg | 75.8±18.7 | 69.5±16.8 | <0.001 |
| Mean arterial pressure, mm Hg | 96.0±12.3 | 92.6±12.6 | 0.007 |
| Cardiac output, ml/s | 62.0±14.1 | 65.4±15.1 | 0.023 |
| Characteristic impedance, dyne× s/cm$^5$ | 277±95 | 236±93 | <0.001 |
| CFPWV, m/s | 12.0±3.1 | 13.2±4.3 | 0.001 |
| Aortic PWV, m/s | 15.5±5.8 | 15.3±5.9 | 0.65 |
| Aortic Eh, $10^6$ dyne/cm | 8.2±7.3 | 8.6±7.2 | 0.61 |
| Augmentation index, % | 11.0±15.9 | 7.9±12.9 | 0.032 |

***Mitchell GF et al. Hypertension 2008***



22

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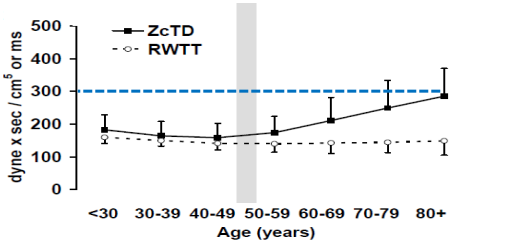
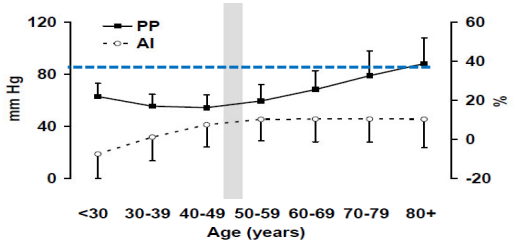
# ARTERIAL AGING: MEN VS. WOMEN

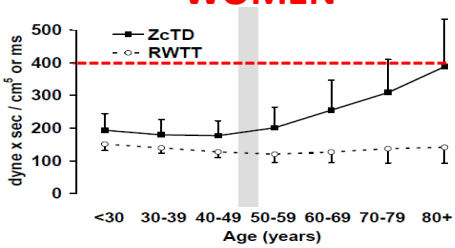
## FRAMINGHAM HEART STUDY

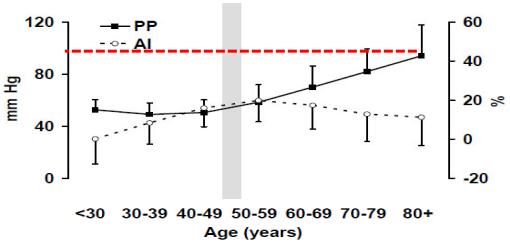
### MEN




### WOMEN




*Mitchell GF et al. Circulation 2010*



23

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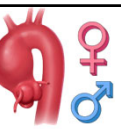
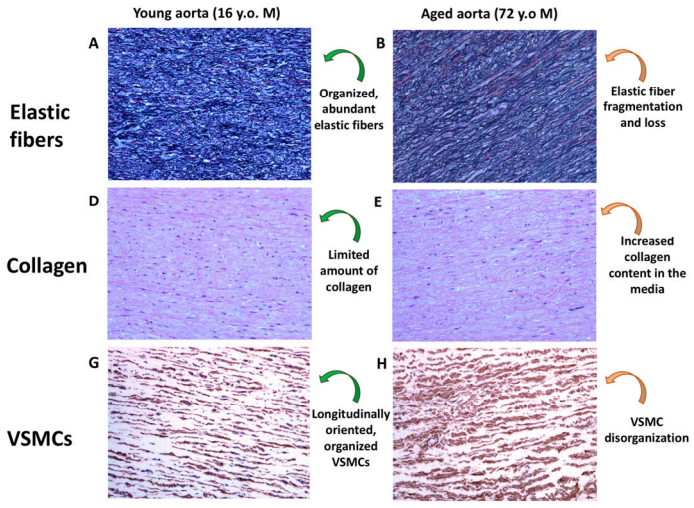
# HISTOLOGY OF AORTIC AGING






Rooprai J and Coutinho T. In: *Chirinos – Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health And Disease* 2022



24

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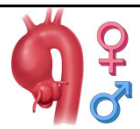
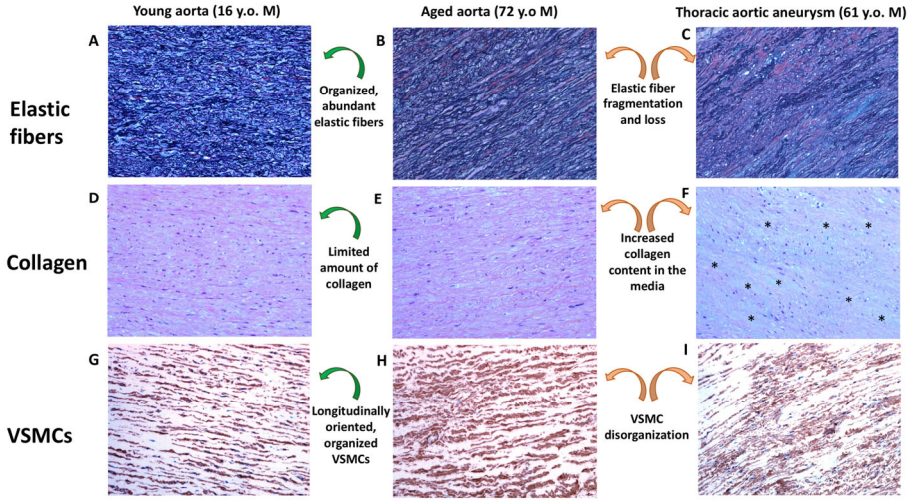
## HISTOLOGY OF AORTIC AGING






Rooprai J and Coutinho T. In: *Chirinos – Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health And Disease* 2022



25

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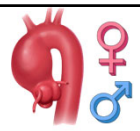
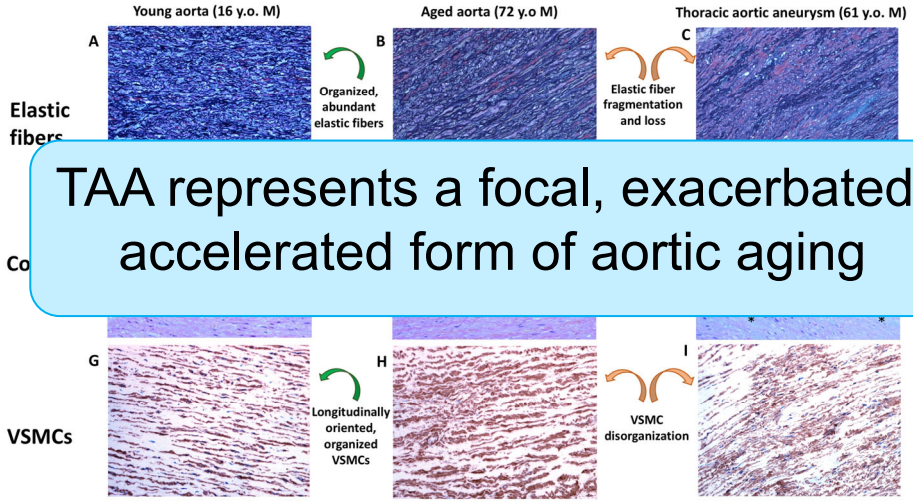
## HISTOLOGY OF AORTIC AGING






TAA represents a focal, exacerbated, accelerated form of aortic aging

Rooprai J and Coutinho T. In: *Chirinos – Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health And Disease* 2022



26

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27

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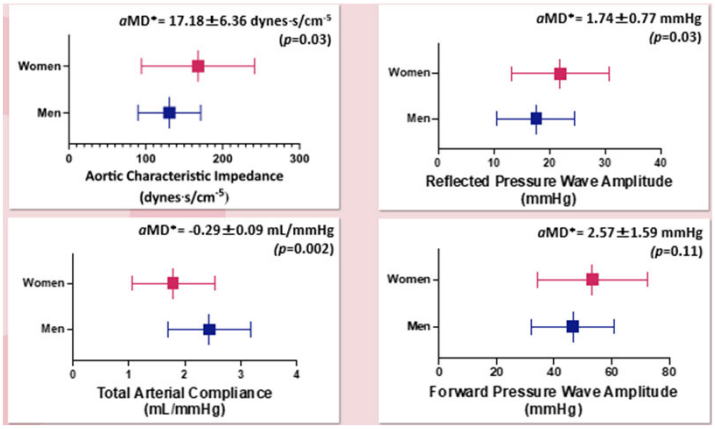
## PULSATILE HEMODYNAMICS ARE WORSE IN FEMALES THAN MALES WITH DEGENERATIVE TAA

n = 80 with dTAA, 67% men, mean age 67±10 yrs in both sexes, HTN 65% in women and 69% in men (P=0.78), MAP 91±10 mmHg both sexes, TAA size: 47±5 mm in both sexes.




Women with dTAA display greater abnormalities in pulsatile arterial load, resulting from worse aortic function, as compared to men with dTAA.

Linear regression models adjusted for age, BMI, MAP, HTN, DM, smoking.

Paquin A(…) Coutinho T. *Can J Cardiol* 2024



28

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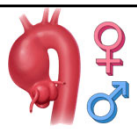
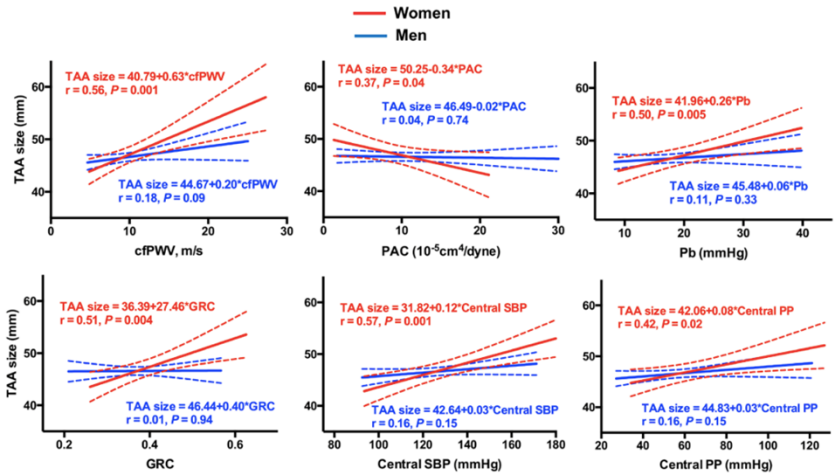
# WHY DO WOMEN WITH TAA FARE WORSE?

## ROLE OF AORTIC HEALTH AND HEMODYNAMICS






n=116, 72% men
Mean age 63 yrs
59% had degenerative TAA

Sex differences persisted after multivariable adjustment

Jue J (…) Coutinho T. *Circulation* 2019



29

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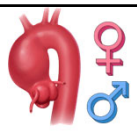
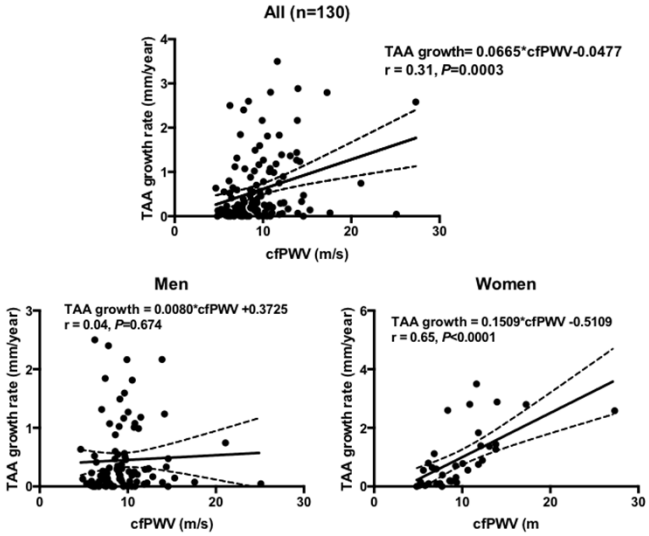
# WHY DO WOMEN WITH TAA FARE WORSE?

## ROLE OF AORTIC STIFFNESS






**Sex*cfPWV: *P*<0.0001**

Association of cfPWV with TAA size in women persisted in a multivariable model

Boczar KE (…) Coutinho T. *Hypertension* 2019



30

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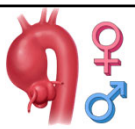
# A TALE OF TWO AORTAS



**A**

2.6 cm/m²

**76 y.o woman**
Hypertensive
Former smoker
BSA: 2.1 m²
Baseline TAA
size: 54 mm

**B**

2.6 cm/m²

**75 y.o woman**
Hypertensive
Former smoker
BSA: 2.0 m²
Baseline TAA
size: 51 mm

Boczar K, (…) Coutinho T. *Hypertension* 2021



31

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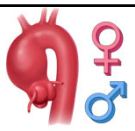
# A TALE OF TWO AORTAS



**A**

2.6 cm/m²

**76 y.o woman**
Hypertensive
Former smoker
BSA: 2.1 m²
Baseline TAA
size: 54 mm

**cfPWV: 27.3 m/s**
**$Z_c$: 275 dyne * s/cm⁵**
**PAC: 1.33 10⁵ cm⁴/dyne**
**TAC: 0.85 mL/mmHg**

**Stiffer aorta, greater pulsatile load and central BP**

**$P_f$: 98 mmHg**
**$P_b$: 39 mmHg**
**cSBP: 186 mmHg**
**cPP: 120 mmHg**

**TAA growth rate: 1.85 mm/year**

**B**

2.6 cm/m²

**75 y.o woman**
Hypertensive
Former smoker
BSA: 2.0 m²
Baseline TAA
size: 51 mm

**cfPWV: 10.6 m/s**
**$Z_c$: 96 dyne * s/cm⁵**
**PAC: 9.78 10⁵ cm⁴/dyne**
**TAC: 2.09 mL/mmHg**

**More compliant aorta, lower pulsatile load and central BP**

**$P_f$: 51 mmHg**
**$P_b$: 30 mmHg**
**cSBP: 145 mmHg**
**cPP: 80 mmHg**

**TAA growth rate: 0.61 mm/year**

Boczar K, (…) Coutinho T. *Hypertension* 2021



32

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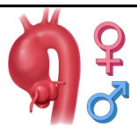
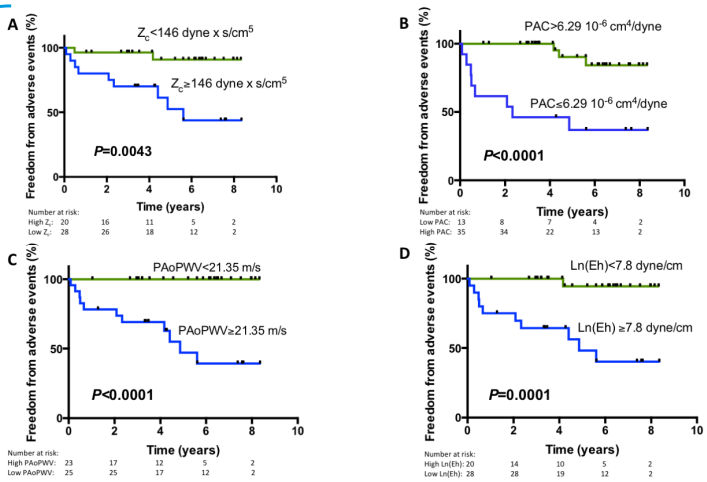
# WHY DO WOMEN WITH TAA FARE WORSE?

## ROLE OF AORTIC HEALTH AND HEMODYNAMICS



**In females only**




**n=150; 68% male**
**Follow-up: 5.5±2.3 yrs in males, 4.6±24 yrs in females**

**Composite outcome:**
**acute aortic syndromes, death or aortic surgery**
**n=37**

$Z_c$: **Aortic characteristic impedance**
PAC: **proximal aortic compliance**
PAoPWV: **Proximal aorta pulse wave velocity**
Eh: **aortic elastance-thickness product**

Crosier R (…) Coutinho T. Presented at *ESC 2023* – Amsterdam, NL



33

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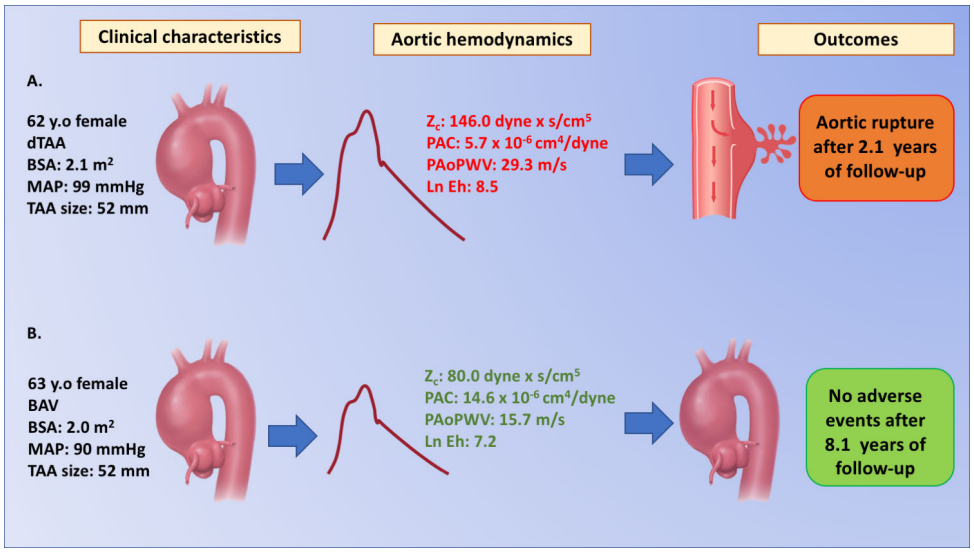
# A TALE OF TWO MORE AORTAS






34




35

## You can mathematically estimate aortic pulse wave velocity (ePWV)

**1. Patients with CV risk factors:**

**ePWV**=9.5875−0.4025×**Age**+4.56×**Age**$^2$/1000−2.621×**Age**$^2$/1000×**MAP**/100+0.3176×**Age**×**MAP**/100−1.832×**MAP**/100

**2. Patients without CV risk factors:**

**ePWV**=4.62−0.13×**Age**+0.0018×**Age**$^2$+0.0006×**Age**×**MAP**+0.0284×**MAP**

*Reference Values for Arterial Stiffness' Collaboration, 2010*
*Greve SV, et al. 2016*



36

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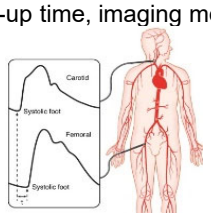
# ROLE OF ESTIMATED PWV

**n= 105 TAA patients followed prospectively for 2.9±1.0 years**
**age: 62.6±11.4 yrs, 78% men, 48% hypertensive, baseline TAA size: 46.2±3.8 mm, TAA growth rate: 0.43±0.37 mm/yr**

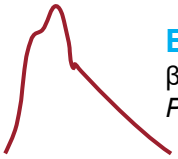
**Measured** cfPWV median (IQR): 9.15 (7.38-10.94) m/s
**Estimated** aPWV: median (IQR): 9.42 (8.12-11.36) m/s

ρ=0.72, *P*<0.0001

Multivariable linear regression for **TAA growth** adjusted for: age, sex, BSA, MAP, baseline aneurysm size, follow-up time, imaging modalities, anti-hypertensive use, and history of hypertension, diabetes and smoking




**Measured** cfPWV:
β±SE: 0.032±0.011
*P*=0.048



**Estimated** aPWV:
β±SE: 0.087±0.021
*P*<0.0001

**Addition of either cfPWV or eaPWV to the base model increased the $R^2$ from 0.39 to 0.44**

**Boczar K (…) Coutinho T. *Can J Cardiol 2022***



37

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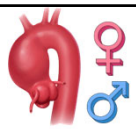
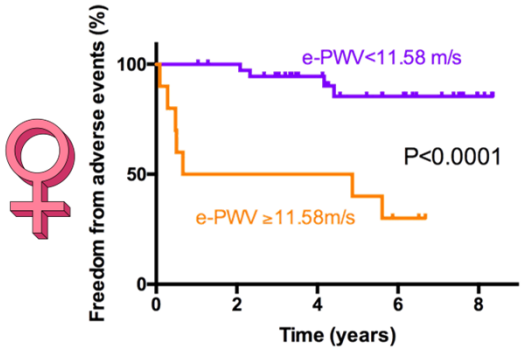
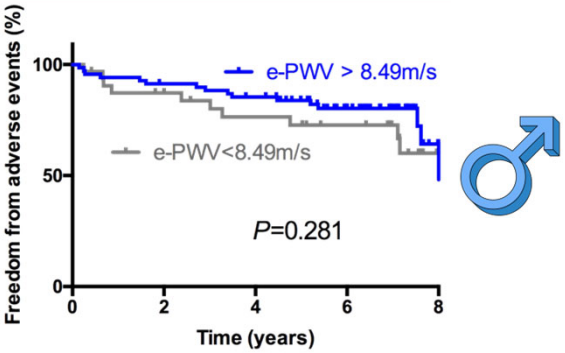
# ROLE OF ESTIMATED PWV IN THE PREDICTION OF ADVERSE OUTCOMES (ACUTE AORTIC SYNDROMES, DEATH, OR AORTIC SURGERY)



**In females only: HR (95% CI) for 1m/s ↑ in e-PWV: 3.4 (1.1-14.7), *P*=0.033**




**e-PWV 11.58 m/s:**
**73% sensitivity, 92% specificity**
**C-statistic: 0.86 (*P*=0.0002)**




**e-PWV 8.49 m/s:**
**42% sensitivity, 71% specificity**
**C-statistic: 0.525 (*P*=0.761)**

Coutinho T et al. Presented at ESC 2024



38

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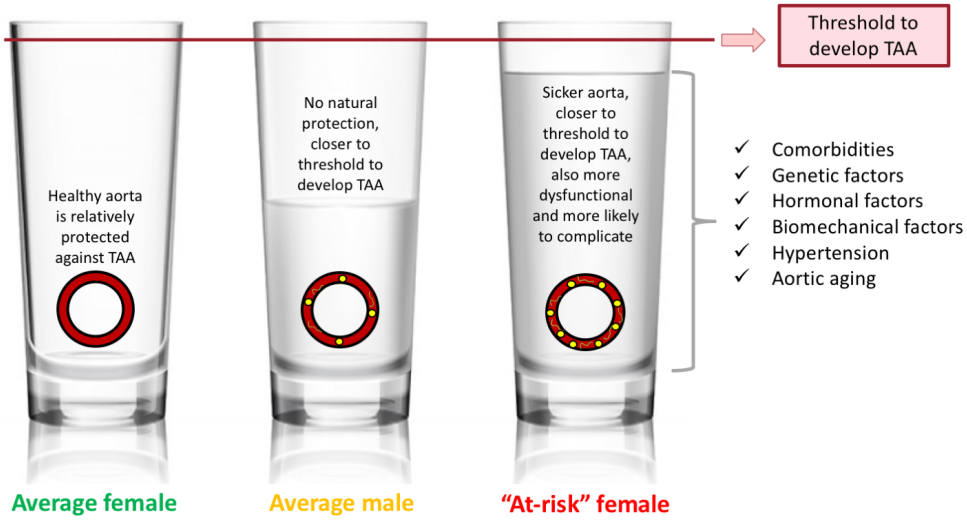
## WHEN A TAA OCCURS IN WOMEN …

### PERHAPS THE GLASS IS FULLER






39

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## TAKE-HOME POINTS

- TAAs are much more common in men, but risks of accelerated expansion, dissection, rupture, surgical complications and death are higher in women;
- The protective effects of estrogen, when removed at the onset of menopause, may play a partial role;
- More adverse aortic hemodynamics may also contribute to worse TAA disease activity and outcomes in women;

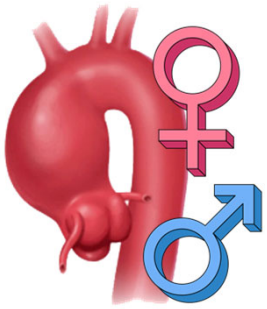
This remains an understudied area, with critical need for sex-specific fundamental, clinical and outcomes research.



40

# THANK YOU!

: coutinho.thais@mayo.edu
: @ThaisCoutinhoCV
: #NotJustAPipe



## Research funding:



41

# SPECIAL IMAGING CONSIDERATIONS IN PREGNANT WOMEN WITH TAA

- WHO Pregnancy risk category:
  - II-III (moderate): Aortic dilation < 4.5 cm in BAV, Marfan without aortopathy
  - III (significant): Aortic dilation 4.0-4.5 cm in Marfan and 4.5-5.0 cm in BAV
  - IV (extremely high): Aortic dilation >4.5 cm in Marfan and >5.0 cm in BAV

**≤Moderate risk:** Image **q12w** during pregnancy and 6 months postpartum

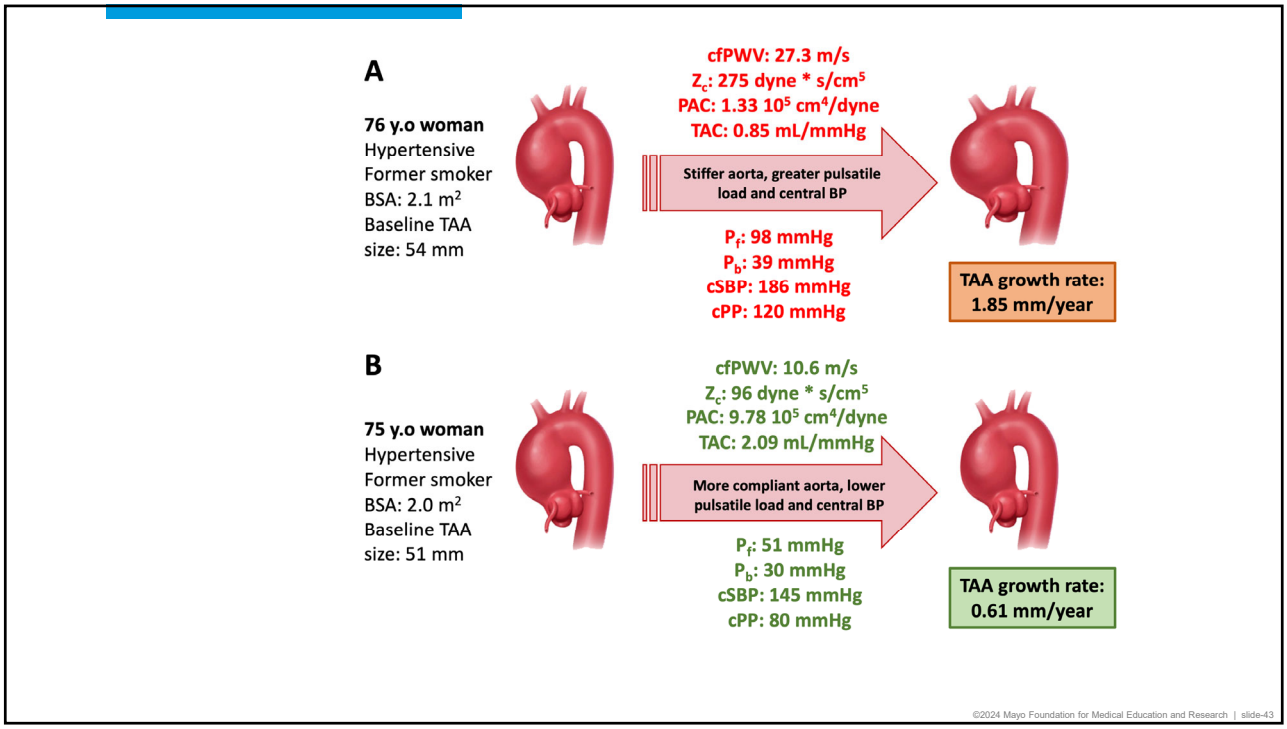
**Significant** or **extremely high risk**: Image **q4w** during pregnancy and 6 months postpartum

Imaging of choice: **TTE.** MRI without contrast can be used when needed
Prophylactic repair when aorta >4.5 cm and growing rapidly (IIa)

[42]



42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Baseline TAA size: 54 mm
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TAC: 0.85 mL/mmHg
Stiffer aorta, greater pulsatile load and central BP
Pf: 98 mmHg
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More compliant aorta, lower pulsatile load and central BP
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Pb: 30 mmHg
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cPP: 80 mmHg
TAA growth rate: 0.61 mm/year
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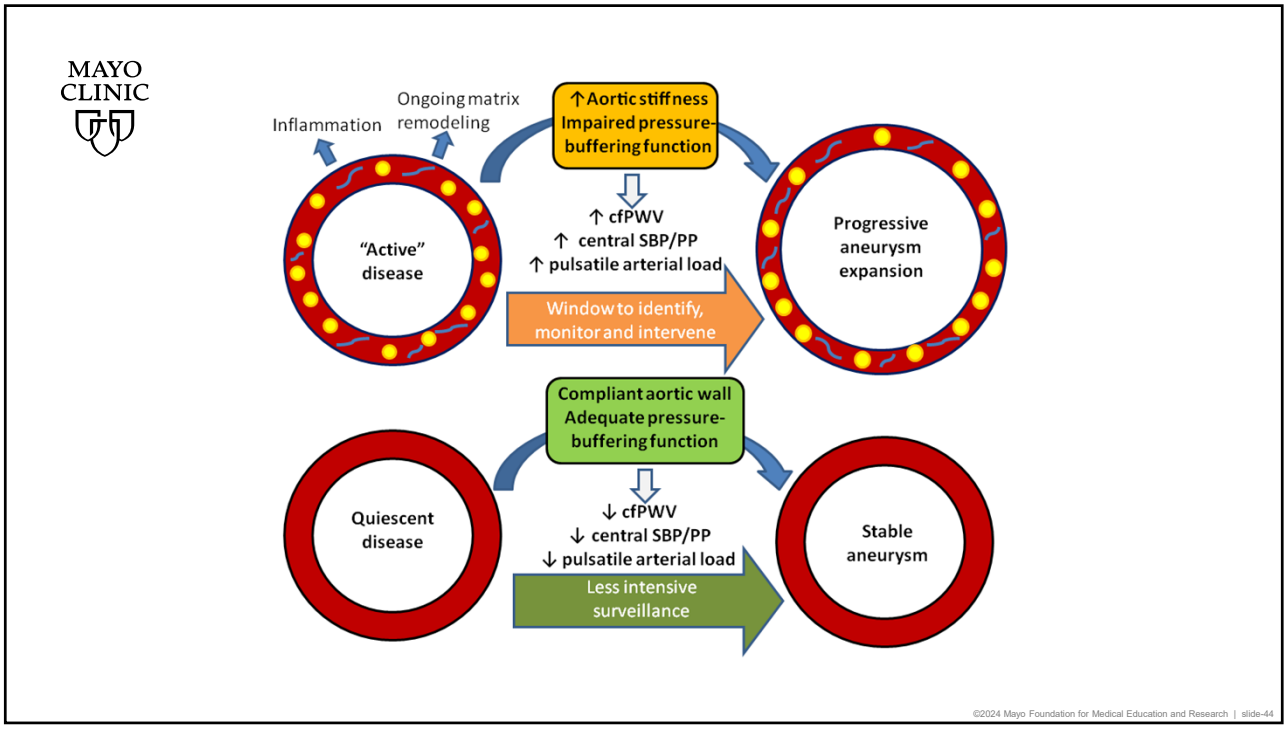
43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Inflammation
Ongoing matrix remodeling
↑ Aortic stiffness
Impaired pressure-buffering function
"Active" disease
↑ cfPWV
↑ central SBP/PP
↑ pulsatile arterial load
Window to identify, monitor and intervene
Progressive aneurysm expansion
Compliant aortic wall
Adequate pressure-buffering function
Quiescent disease
↓ cfPWV
↓ central SBP/PP
↓ pulsatile arterial load
Less intensive surveillance
Stable aneurysm
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44