CONGRESSO SOCERGS 2023

UNIÃO, ATUALIZAÇÃO E NETWORKING

Simpósio SGCCV/SOCERGS

INDICAÇÃO DE CIRURGIA DE AORTA BASEADA EM PAINEL GENÉTICO.

A MEDICINA DE PRECISÃO NA CIRURGIA CARDIOVASCULAR ESTÁ CHEGANDO?

Renato A. K. Kalil

Professor Titular jubilado de Clínica Cirúrgica da UFCSPA

Membro Titular da Academia Sul-Rio-Grandense de Medicina

Coordenador do Núcleo de Cardiopatias Congênitas do Hospital Moinhos de Vento

Cirurgião Cardiovascular nos Hospitais Moinhos de Vento, Divina Providência e Instituto de Cardiologia

UFCSPA – Universidade Federal de Ciências da Saúde de Porto Alegre

Hospital Moinhos de Vento

Rede de Saúde Divina Providência – Hospital Divina Providência

Instituto de Cardiologia

Declaração de Potencial Conflito de Interesse

Nome do Palestrante: Renato A. K. Kalil

Título da Apresentação:

INDICAÇÃO DE CIRURGIA DE AORTA BASEADA EM PAINEL GENÉTICO.

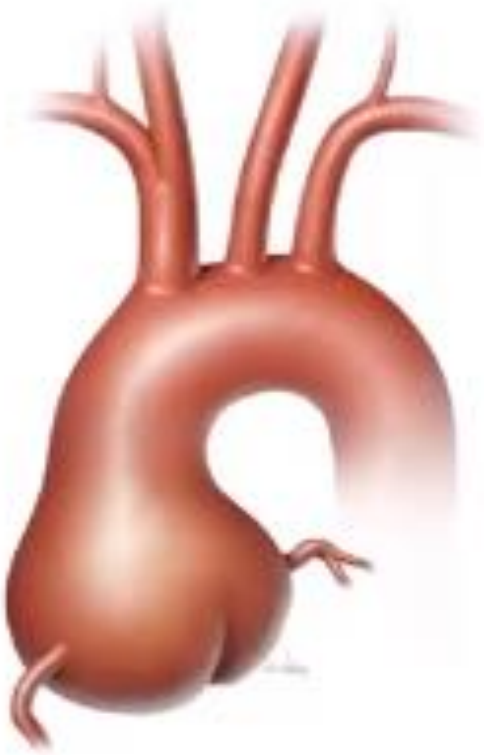
A MEDICINA DE PRECISÃO NA CIRURGIA CARDIOVASCULAR ESTÁ CHEGANDO?

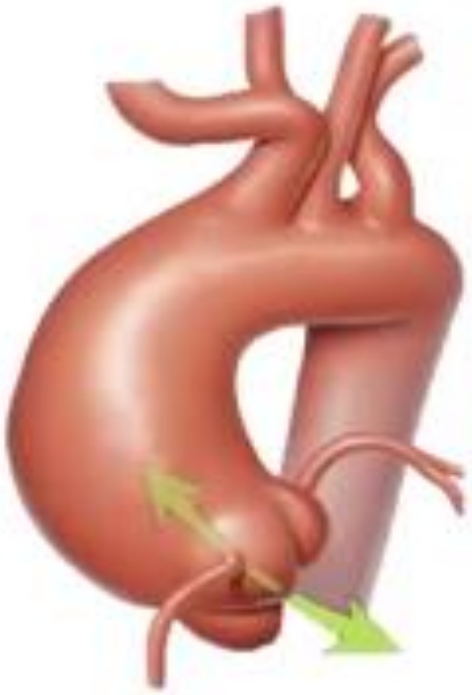
Não possuo nenhum conflito de interesse relacionado a esta apresentação

Thoracic aortic aneurysms

Marfan syndrome

Non-Marfan





CENTRAL ILLUSTRATION 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease

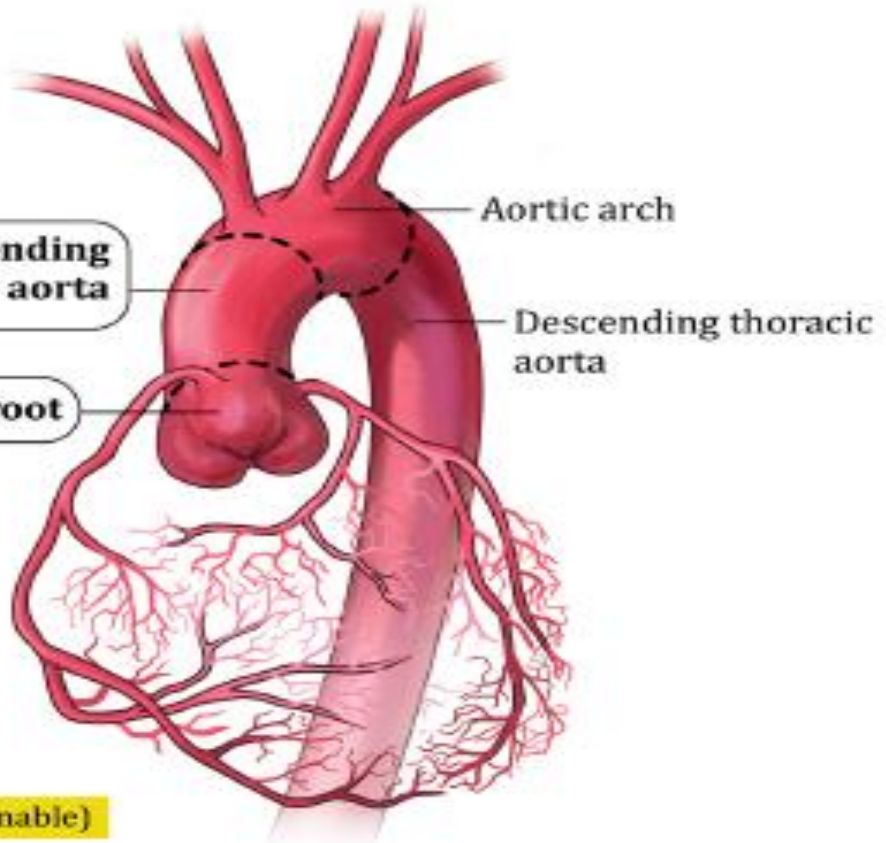
Surgical intervention thresholds for aortic root & ascending aorta in patients with…

Sporadic and BAV aneurysms*:

- 5.5 cm (COR 1)
- 5.0 cm by experienced surgeons in a Multidisciplinary Aortic Team (COR 2a)

Marfan syndrome#:

- 5.0 cm (COR 1)
- ≥4.5 cm in those with an increased risk of aortic dissection when performed by experienced surgeons in a Multidisciplinary Aortic Team (COR 2a)



COR 1 (Is recommended) COR 2a (Is reasonable)

**Surgical thresholds may be adjusted based on patient genetics, rapid aortic growth rate, cross-sectional aortic area/height ratio ≥10 cm²/m, aortic size index of ≥3.08 cm/m², or aortic height index of ≥3.21 cm/m.*

#For more on rapid aortic growth rate and patients with nonsyndromic heritable thoracic aortic aneurysms or with genetic aortopathies other than Marfan syndrome (e.g., Loeys-Dietz syndrome), please see the 2022 ACC/AHA Guideline for the Diagnosis & Management of Aortic Disease.

Erwin JP III, et al. J Am Coll Cardiol. 10.1016/j.jacc.2022.10.001

Structured Graphical Abstract

Fate of the unoperated ascending thoracic aortic aneurysm: three-decade experience from the Aortic Institute at Yale University

Key Question

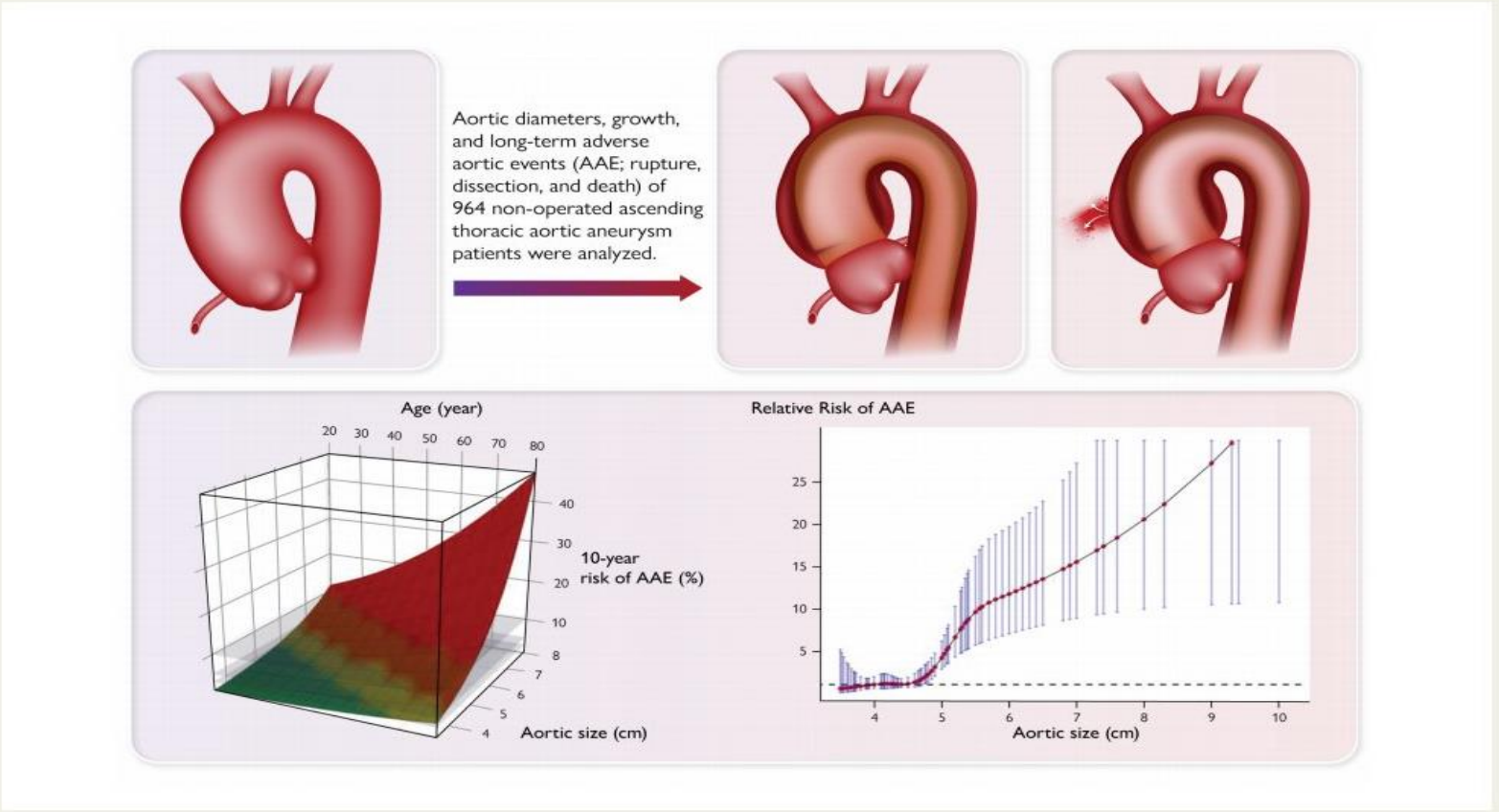
What is the natural history of ascending thoracic aortic aneurysm (ATAA), in the absence of pre-emptive surgical intervention?

Key Finding

- ATAAs enlarged slowly, with growth rates rarely over 0.2 cm/year.
- The risk of adverse aortic events in the ascending thoracic aorta rose sharply at a hinge point of 5 cm.

Take Home Message

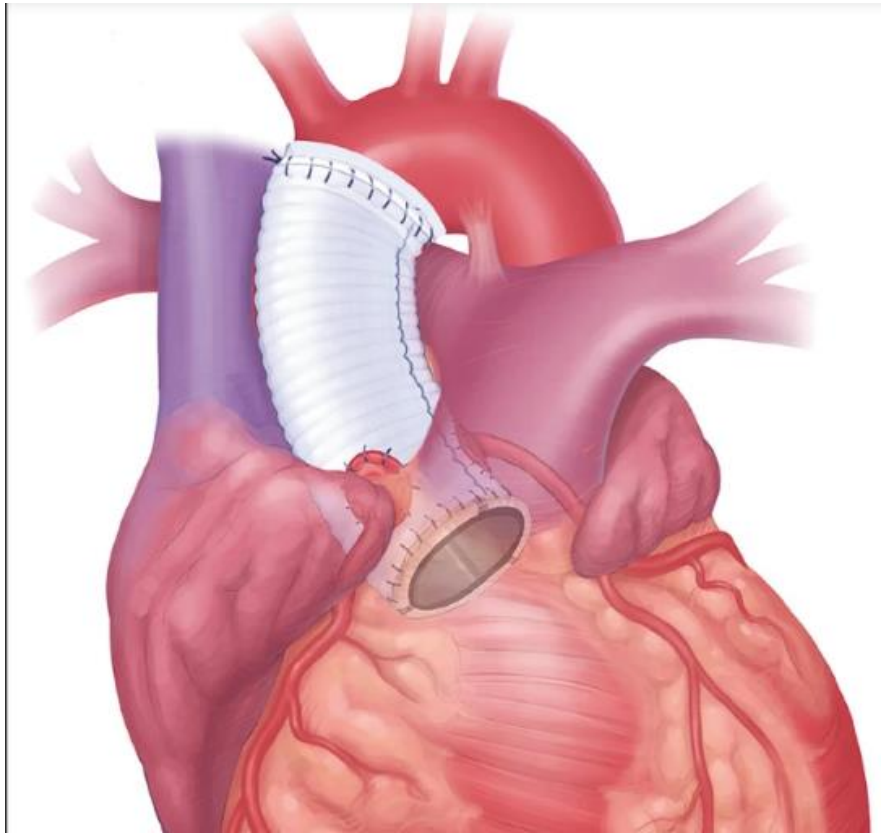
- In ATAA patients, prophylactic surgical intervention should be considered at 5 cm.
- Bona fide rapid aortic growth is a valid but unusual criterion for intervention.



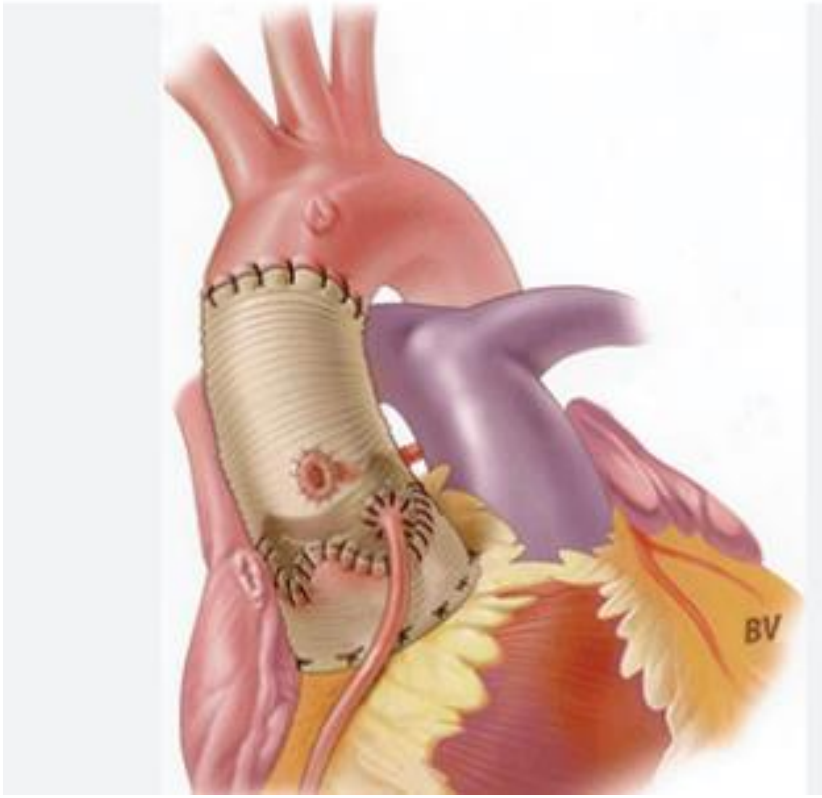
To assess the natural history of ascending aortic aneurysm, we examined the three-decade clinical outcomes of 964 non-operated patients with ascending aortic aneurysm. Note, in the 2D plot, the sharp rise in risk of adverse aortic events is at an aortic size of 5 cm. The 3D plot of risk vs. both size and age also discloses a substantial contribution of advancing age to increased risk. ATAA, ascending thoracic aortic aneurysm; AAE, adverse aortic events.

European Heart Journal (2023) **00**, 1–10
https://doi.org/10.1093/eurheartj/ehad148

TÉCNICAS CONVENCIONAIS PARA ANEURISMAS DE AORTA ASCENDENTE

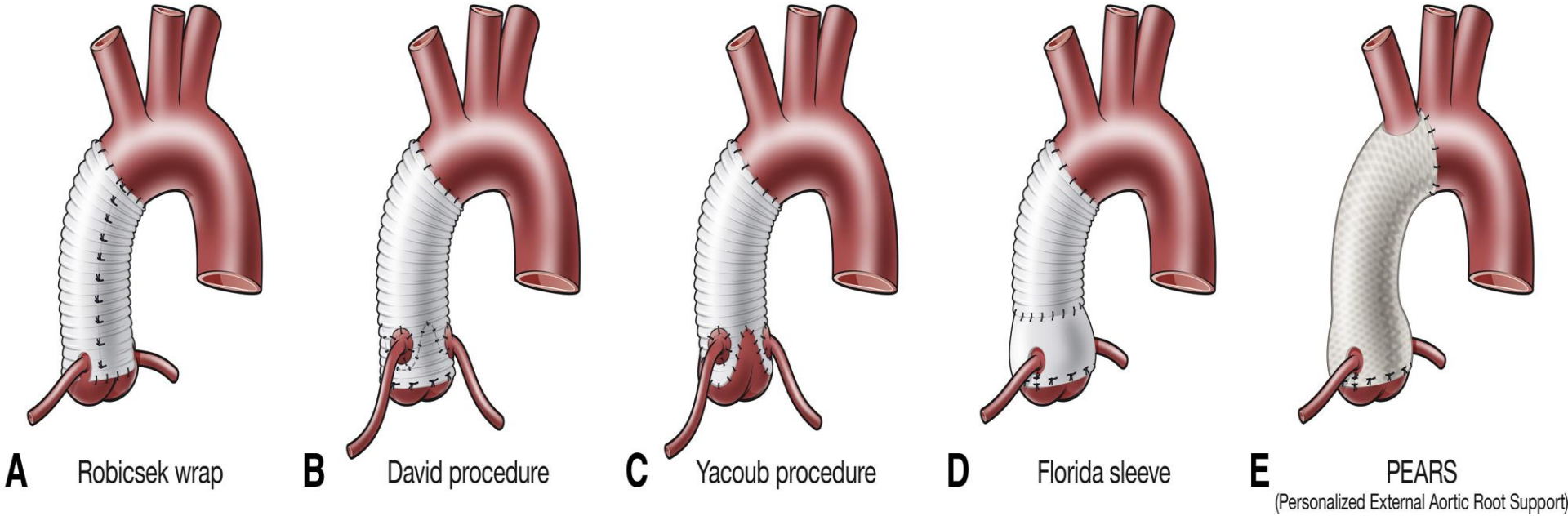


BENTALL-DeBONO



DAVID e YACOUB

Valve-sparing aortic root surgery



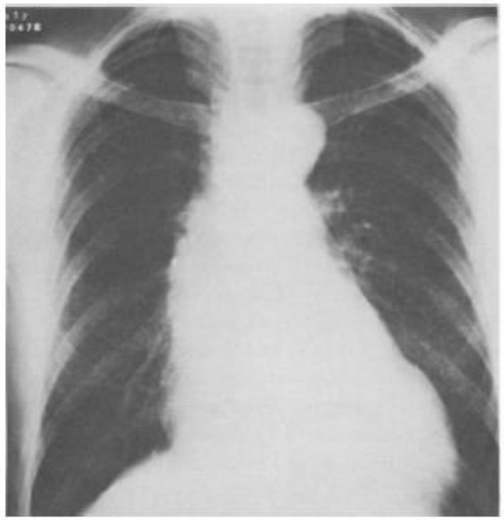
Buratto & Konstantinov
JTCVS [Congenital: Aorta: Invited Expert Technical Review| Volume 162, ISSUE 3, P955-962, September 01, 2021

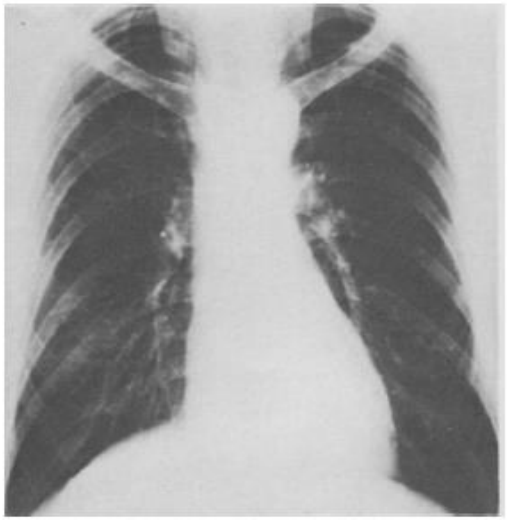
The Journal of Thoracic and Cardiovascular Surgery 2021
162955-962 DOI: (10.1016/j.jtcvs.2020.08.116)
Terms and Conditions

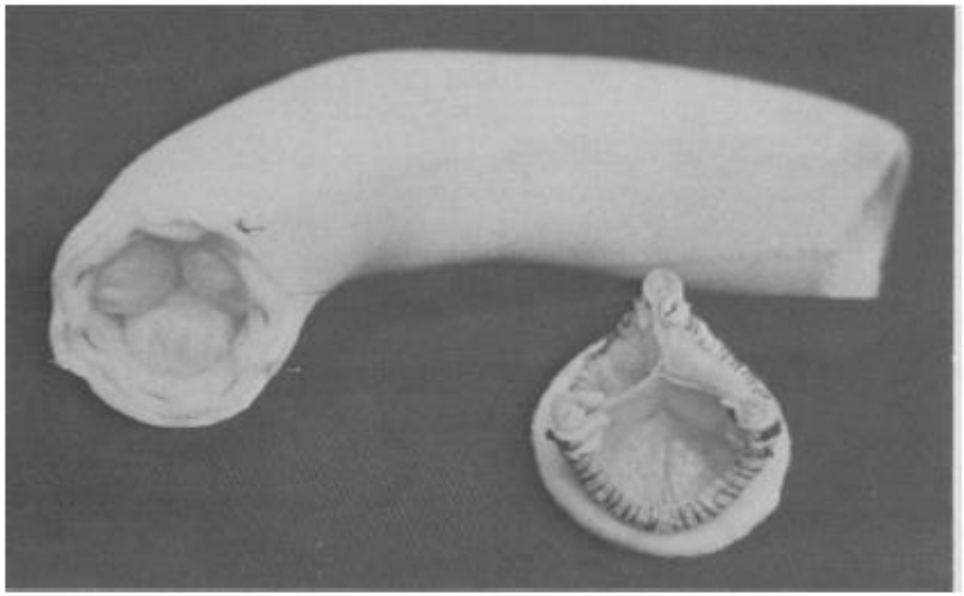
Surgical Treatment of Annuloaortic Ectasia with Composite Grafts Including Homologous Dura Mater Valves

Renato K. Kalil, M.D., Paulo C. Azambuja, M.D., Victor E. Bertoletti, M.D., Fernando A. Lucchese, M.D., Paulo R. Prates, M.D., and Ivo A. Nesralla, M.D.

N=3pts, 1976 - 1977







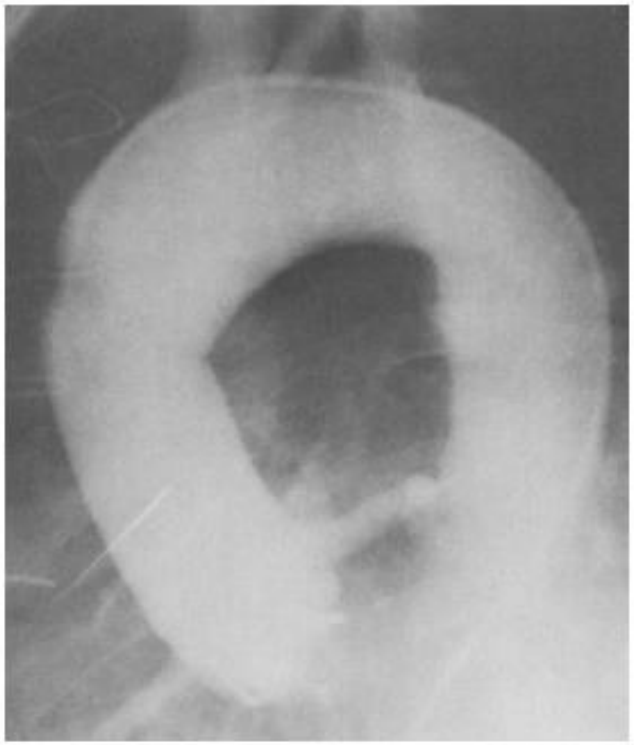


Fig 2. (Patient 3.) Postoperative aortogram. The tube graft is in the ascending aorta, both coronary arteries are well seen, and the aortic valve prosthesis is competent.

Annals of Thoracic Surgery Vol 26 No 2 August 1978

Tratamento cirúrgico para ectasia ânulo-aórtica

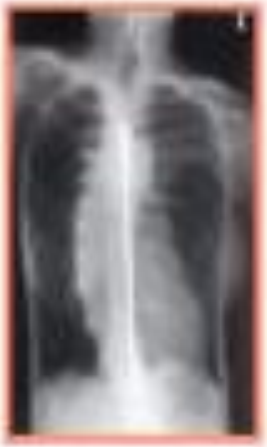
Ricardo GARCÍA-MACEDO*, Renato A. K. KALIL*, Paulo Roberto PRATES*, Fernando A. LUCCHESE, João Ricardo SANT'ANA*, Edemar M. PEREIRA*, Altamiro Reis COSTA*, Raul Feck A. LARA, Ivo A. NESRALLA*, *Porto Alegre, RS.*

RBCCV

GARCÍA-MACEDO, R.; KALIL, R. A. K.; PRATES, P.R.; LUCCHESE, F.A.; SANT'ANA, J.R.; PEREIRA, E. M.; COSTA, A.R.; LARA, R. F. A.; NESRALLA, I. A. — Tratamento cirúrgico para ectasia ânulo-aórtica. *Rev. Bras. Cir. Cardiovasc.*, **1** (1): 44-48, 1986.

RESUMO: Foram estudados 27 pacientes submetidos a implante de tubo de Dacron valvulado (segundo técnica de Bentall-De Bono), entre 1976 e 1985. Todos apresentavam ectasia ânulo-aórtica, que era devida a necrose cística da média em 23 pacientes (85,2%), dissecção crônica de aorta em 3 pacientes (11,1%) e aortite luética em 1 paciente (3,7%). A faixa etária foi de 29 a 64 anos (m = 48 anos). Três eram do sexo feminino e 24, do masculino. Foi utilizado tubo de Dacron 28 ou 30 mm em todos. As válvulas utilizadas foram: de dura-máter em 7 pacientes, de aorta heteróloga em 9 e metálica em 11 pacientes. A classe funcional era I-II em 7 pacientes e III-IV em 19 pacientes (NYHA). Houve 1 óbito (3,7%) pós-operatório imediato, por sangramento incontrolável e insuficiência renal aguda. As complicações mais freqüentes foram

Marfan Syndrome: *FBN1* Pathogenic Variants



Skeletal

Pectus deformities

Tall stature

Scoliosis

Ocular

Ectopia Lentis

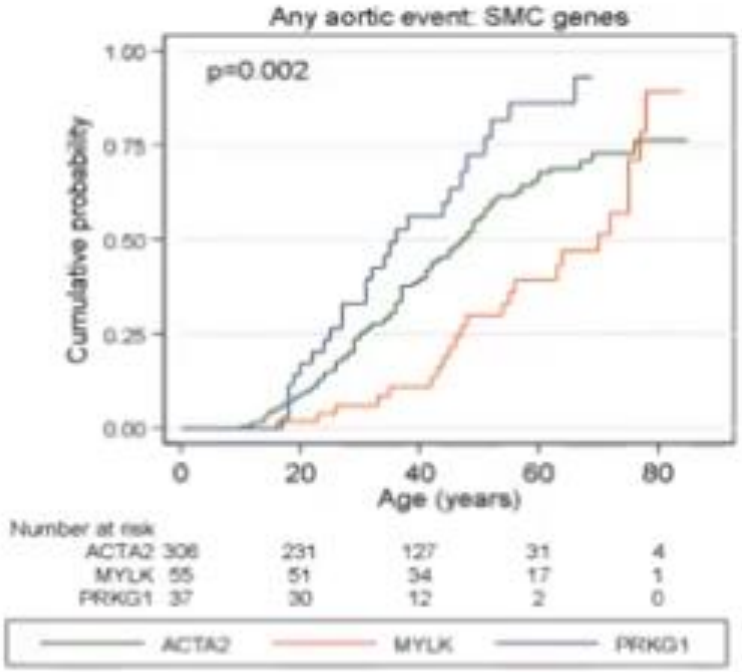
Aortic root aneurysms
Surgical repair at 5.0 cm
Low risk for ICAs and peripheral aneurysms

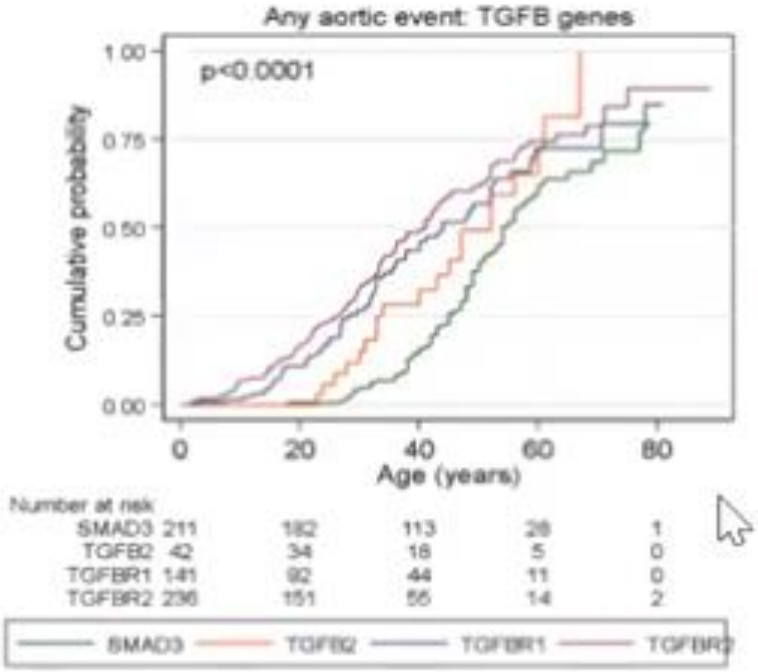
Heritable Thoracic Aortic Disease Genes

ECM	*FBN1*	fibrillin-1
	MFAP5	microfibril associated protein 2
	LOX	lysyl oxidase
	BGN	biglycan
	LTBP3	latent TGF-β binding protein
TGF-β Signaling	*TGFBR1*	TGF-β receptor type I
	TGFBR2	TGF-β receptor type II
	SMAD3	Smad3
	SMAD2	Smad2
	TGFB2	TGF-β2
	TGFB3	TGF-β3
SMC Contraction	*ACTA2*	smooth muscle α-actin
	MYH11	smooth muscle myosin heavy chain
	MYLK	myosin light chain kinase
	PRKG1	cGMP-dependent kinase I
	ARIH1	Ariadne-1 ubiquitin ligase
	MAT2A	methionine adenosyltransferases IIα
	FOXE3	forkhead transcript factor E3
Channels	*HCN4*	Hyperpolarization-activated cyclic nucleotide-gated channel 4
	KCN5A	Kv1.5 potassium channel

Cumulative Risk for an Aortic Event Based on HTAD Gene

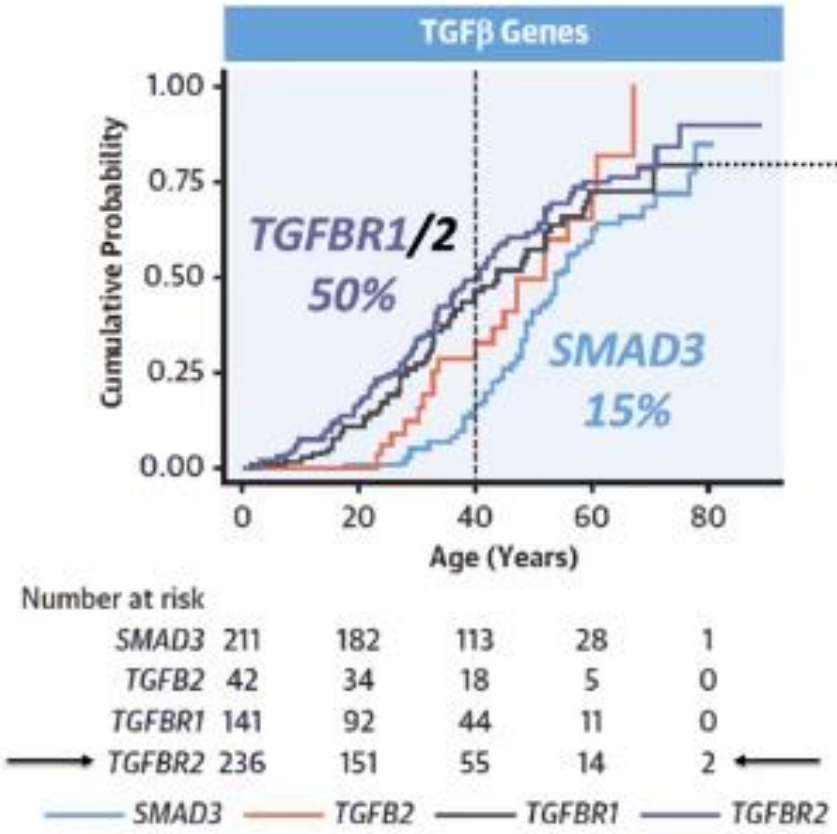
Aortic Event = Surgical repair of an aneurysm, type A, or B dissection



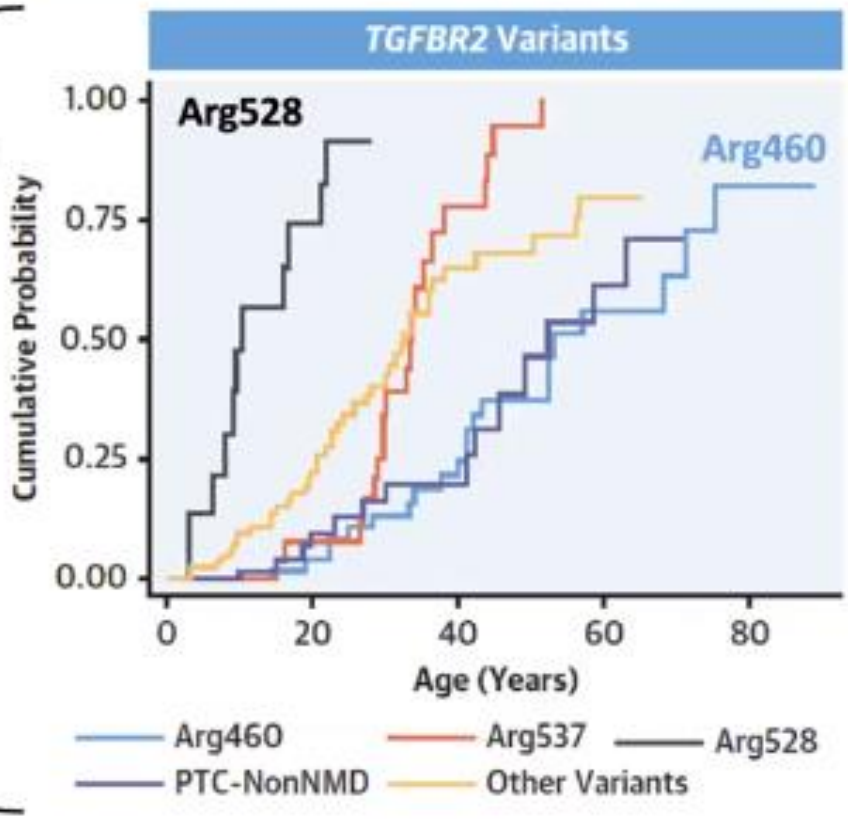


Regalado et al. *JACC* 2022 Aug 30;80(9):857-869.

Gene-Level Differences in Disease Severity



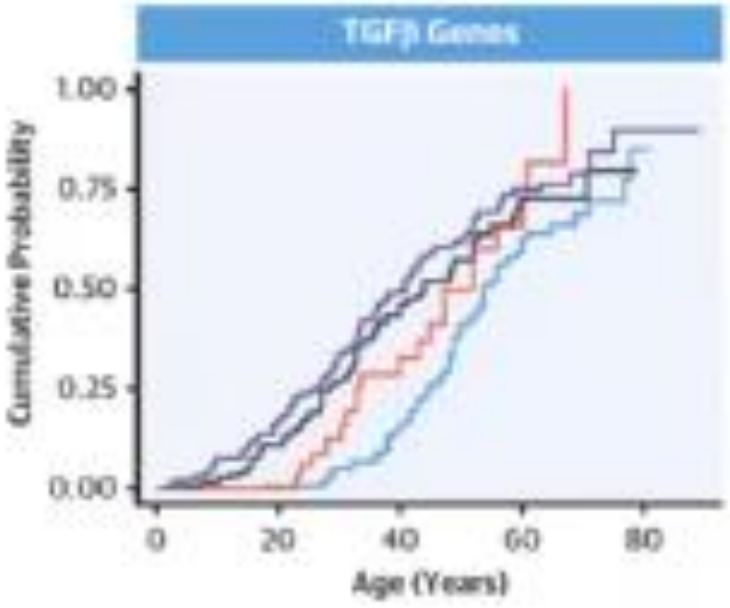
Variant-Level Differences in Disease Severity

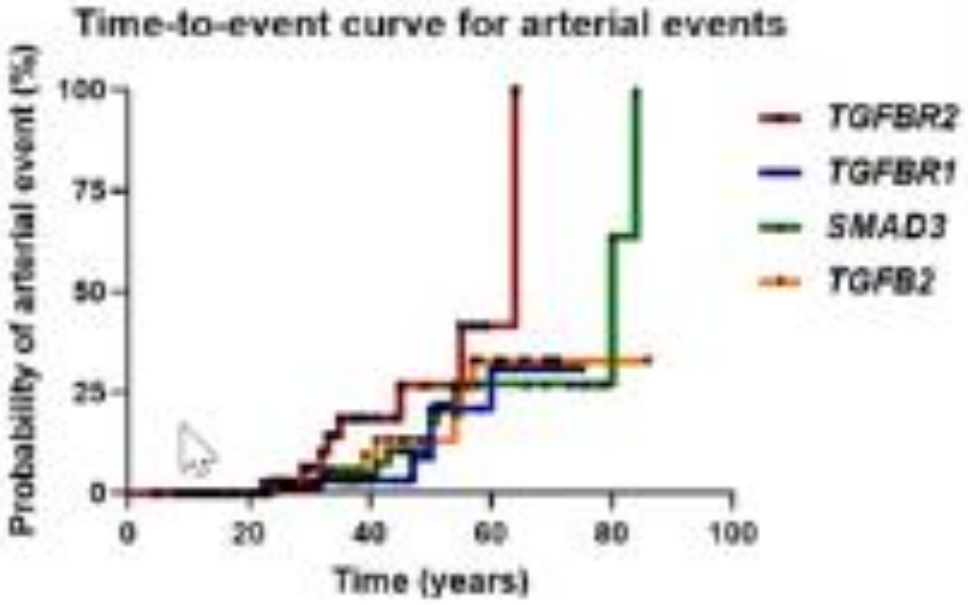


Regalado et al. *J Am Coll Card* 2022 (MAC)

LDS Genes: Time to Arterial Event

Aneurysm repair, dissection or rupture

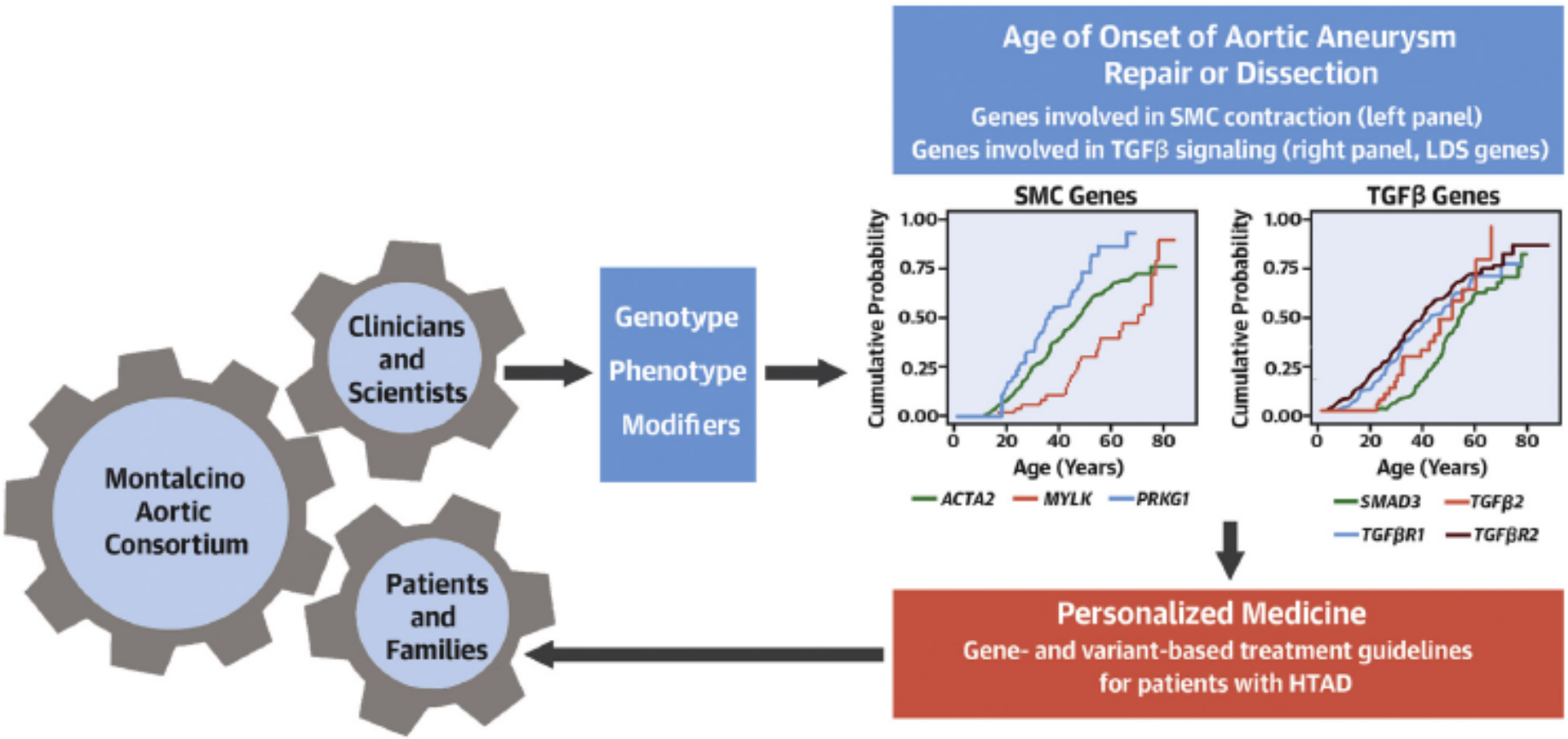




Personalized Management of Heritable Thoracic Aortic Disease: Montalcino Aortic Consortium

Dianna M. Milewicz, M.D. Ph.D.
President George H.W. Bush Chair
Director, John Ritter Research Program
McGovern Medical School
University of Texas Health Science Center at Houston

CENTRAL ILLUSTRATION Gene-Specific Thoracic Aortic Risk Models From the Montalcino Aortic Consortium

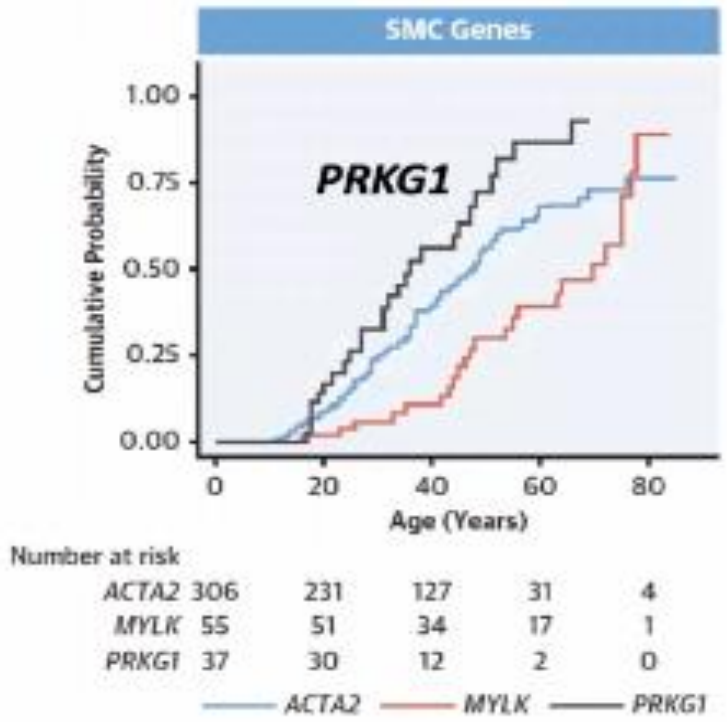


Data were collected from probands and family members with rare variants in seven genes predisposing to heritable thoracic aortic disease. Using these data, risk and type of first aortic event were stratified based on both the altered gene and recurrent variants within the genes.

Regalado ES, et al. J Am Coll Cardiol. 2022;80(9):857-869.

The international Montalcino Aortic Consortium (MAC) collects patient data to generate gene- and pathogenic variant-specific risk models to improve outcomes for individuals with heritable thoracic aortic disease (HTAD).

Prophylactic Root Replacement in Patients With High-Risk Clinical Features and Virulent Gene Variants

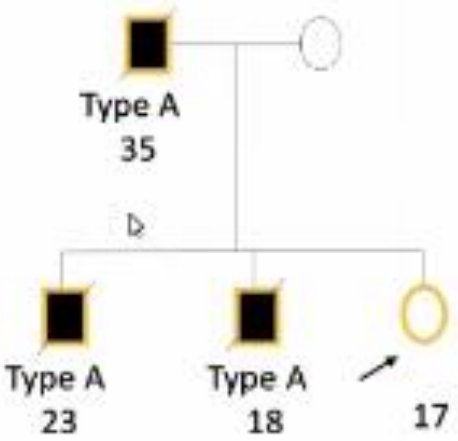


Regalado et al. *J Am Coll Card* 2022 (MAC)

https://www.aats.org/resources/gene-guided-management-of-aortic-disease

Prophylactic Root Replacement in Patients With High-Risk Clinical Features and Virulent Gene Variants

- 17-year-old woman with *PRKG1* variant and normal root diameter
- Father and two brothers died of acute type A dissections (ages 18-35 years)
- Underwent successful elective valve-sparing root replacement
  - Thin aortic wall
  - Smaller sutures (5-0)

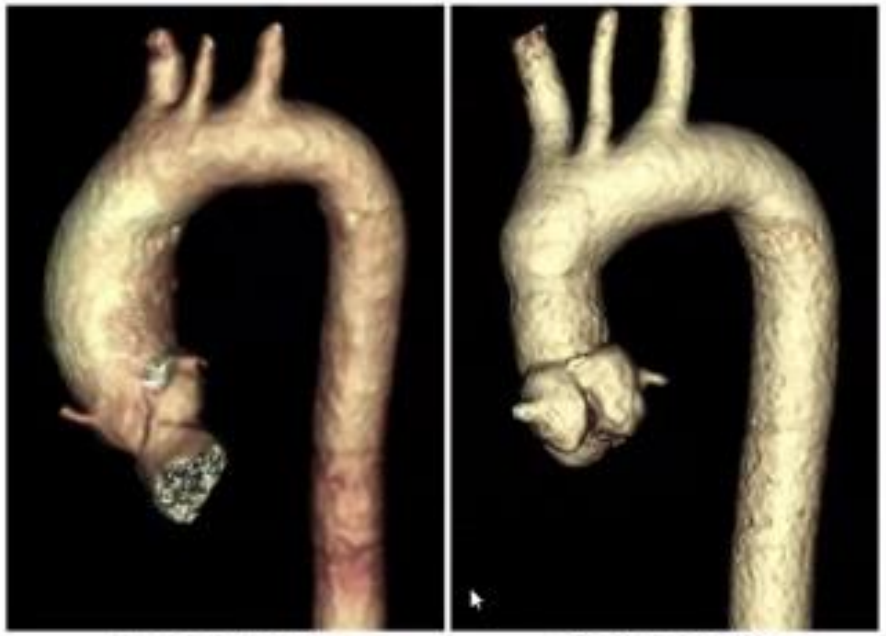


Courtesy of Dr. Dianna Milewicz (UT Houston)
Photo used with patient permission

https://www.aats.org/resources/gene-guided-management-of-aortic-disease

Prophylactic Root Replacement in Patients With High-Risk Clinical Features and Virulent Gene Variants

- 47-year-old woman with *PRKG1* variant and 3.7 cm root
- Brother with acute dissection (age 35 years)
- Niece with acute dissection (fatal, age 16 years)
- Successful valve-sparing root replacement
- Thin aortic wall (1 mm) → technical modifications for cannulation, etc.



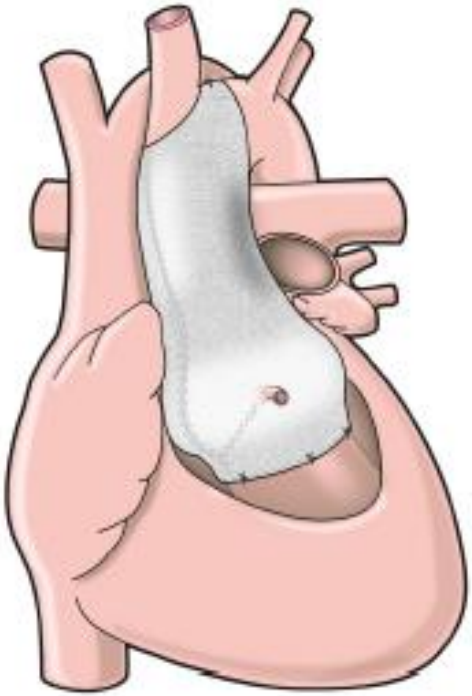
Preoperative Postoperative

Norton et al. *J Thorac Cardiovasc Surg* 2019 (U Michigan)

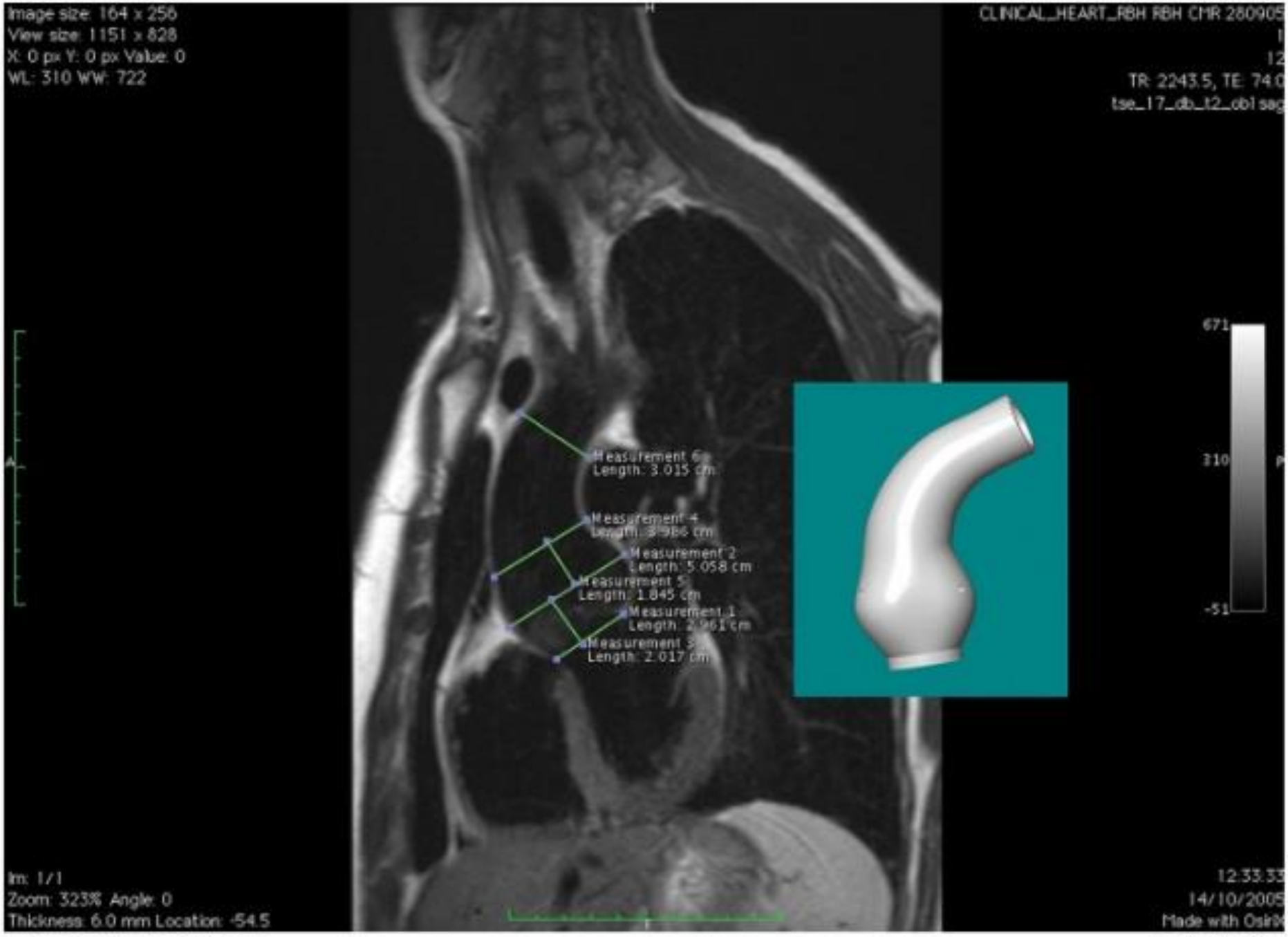
https://www.aats.org/resources/gene-guided-management-of-aortic-disease

Personalised External Aortic Root Support (PEARS)

The new approach to surgical management of the dilated aorta



Personalised External Aortic Root Support (PEARS) is now emerging as an effective pre-emptive operation to halt aortic root expansion and maintain aortic valve function in Marfan syndrome and is also applicable in treating aortic root dilatation to prevent aneurysms associated with other aetiologies[1].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WL: 310 WW: 722
CLINICAL_HEART_RBH RBH CMR 280905
TR: 2243.5, TE: 74.0
tse_17_db_t2_ob1 sag
671
310
-51
Measurement 6
Length: 3.015 cm
Measurement 4
Length: 3.986 cm
Measurement 2
Length: 5.058 cm
Measurement 5
Length: 1.845 cm
Measurement 1
Length: 2.961 cm
Measurement 3
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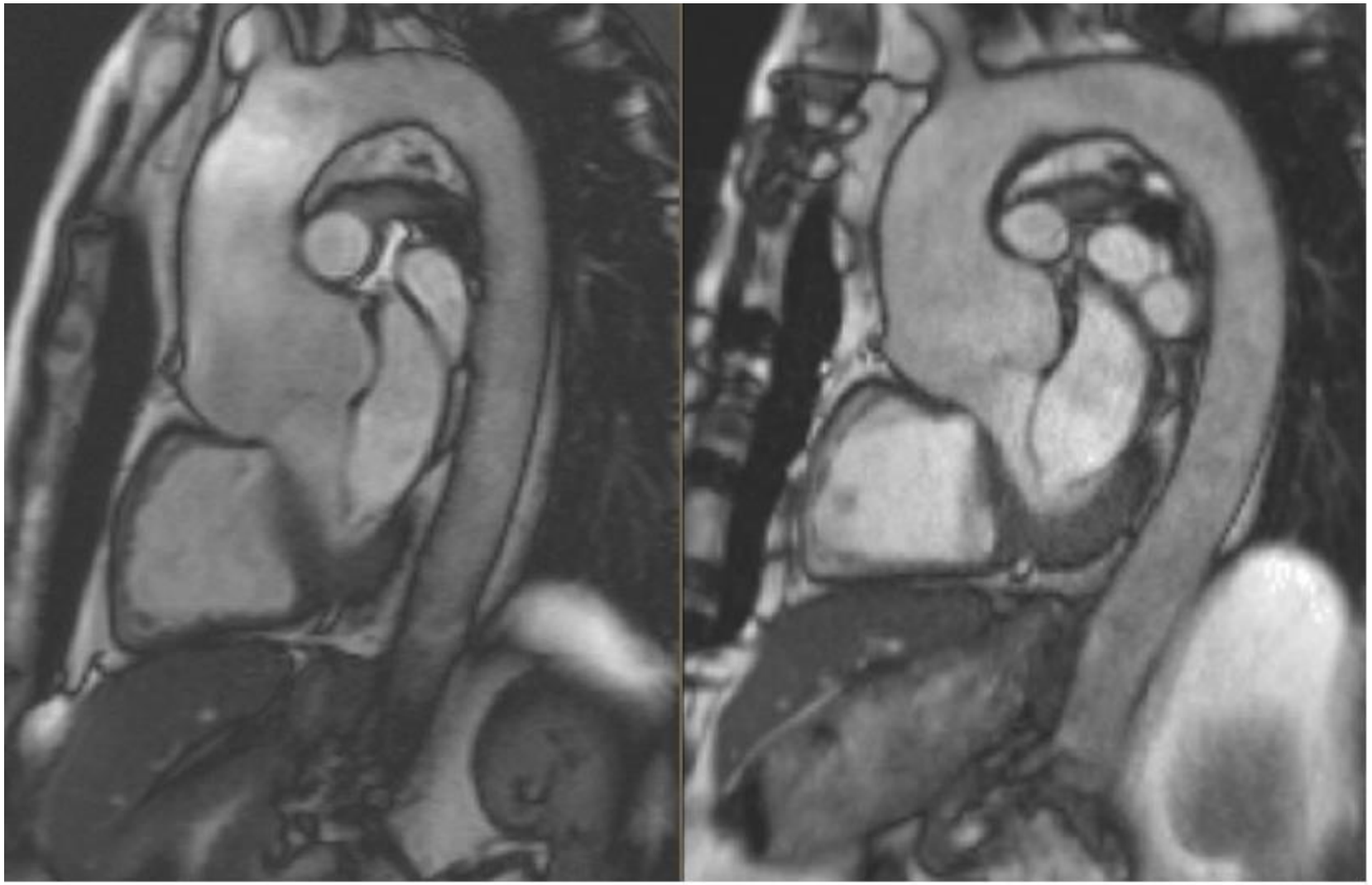


Patient 1: April 2004 (3 weeks pre-op) and January 2019 (15 years post-op)

PEARS Intention to Treat (NOV 2022)

Surgical conversions

Of 638 patients intended for Aortic PEARS surgery,

621 have been implanted,

5 were converted to VSRR,

1 converted to a Florida Sleeve,

4 converted to TRR,

3 converted to bio-Bentall,

2 converted to an inter position graft,

1 converted to MV replacement only. ***97.33 surgical success***

Mortality

1 patient died perioperatively

1 patient died 43 days post op

1 patient died 7 months after surgery. ***0.47 CV mortality***

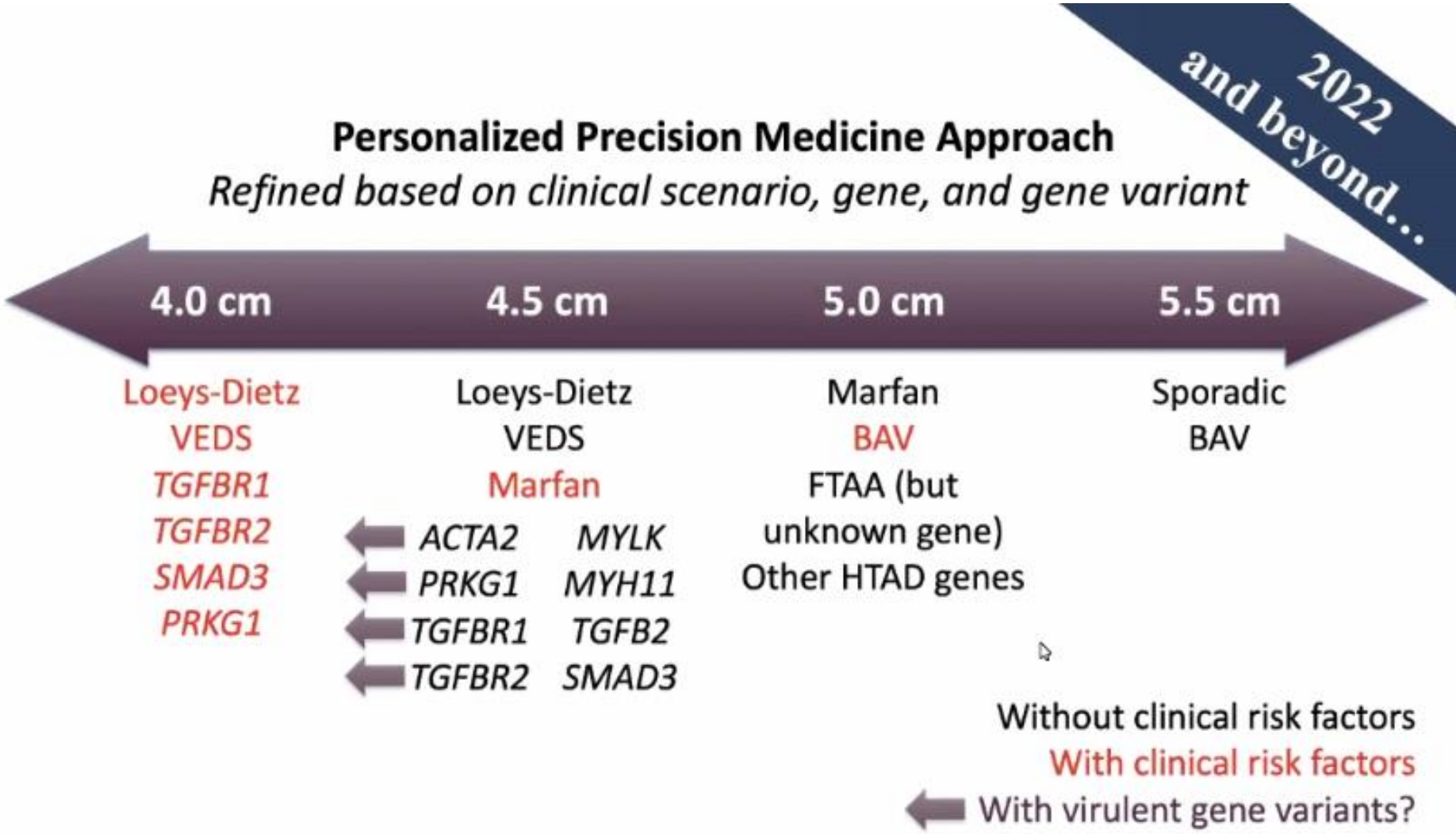
- The patient who died perioperatively (number 36) had a severe pectus escavatus
- Patient number 530 died 43 days post-operatively after a successful surgery suffering a myocardial ischaemic event a few days post op resulting in myocardial stunning. This was managed with ECMO but the patient contracted an infection and died.
- Patient number 115 died 7 months after surgery. This patient had a history of aortic valve replacement and alcoholic cardiomyopathy that had been managed by implanting an ICD. This patient had a non-flow limiting lesion in their left circumflex artery prior to surgery. Postoperatively the patient developed cardiac failure due to an occluded circumflex coronary artery, which was managed by reoperation to adjust the ExoVasc support and application of a vein graft to the circumflex artery. Twelve days later the patient had a cardiac arrest and his ICD was reactivated. The patient died 6.5 months later of congestive heart failure.

Personalized External Aortic Root Support (PEARS) Jan 2023

2. Disease types treated

PEARS surgery has been applied to aortic management associated with the following established conditions:

- Marfan syndrome – 312 (20 patients having concurrent mitral repair)
- Loeys-Dietz syndrome - 39 (1 patient having concurrent mitral repair)
- Bicuspid Aortic Valve disease – 93 (1 patient having concurrent mitral repair)
- Idiopathic aortic dilation/other – 115 (inc. Turner's Syndrome, SMAD3, MYBCP3, NOS & FAAP)
- ACTA2 mutation – 3
- Ehlers Danlos Syndrome - 1
- Tetralogy of Fallot -1
- Transposition of the great arteries repaired by an arterial switch operation - 7
- Post free-standing root Ross op. autograft dilation – 11 (1 patient having concurrent MV repair)
- Aortic valve disease treated by the Ross Procedure – 96 (1 patient having concurrent mitral repair)
- Case Report Form yet to be received – 66



*VEDS=Vascular Ehlers Danlos Syndrome
*FTAA= fortuitus thoracic aortic aneurysm

https://www.aats.org/resources/gene-guided-management-of-aortic-disease

Summary

- Diameter thresholds for aortic repair have evolved substantially

  Dichotomy → Disease-Based → Gene-Based → Mutation-Based
- Genetic variants currently inform decisions about when to operate and how to operate
- Entering a new era of a precision medicine approach to data-driven, individualized care
- Decision making will be supported by integrated multidimensional patient-specific data: clinical features, imaging, genetics

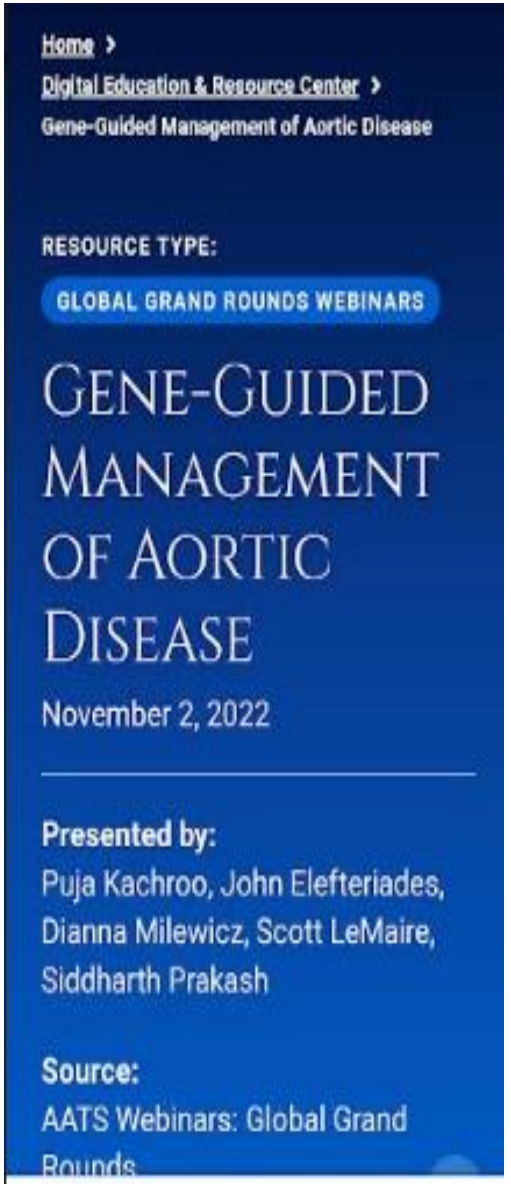


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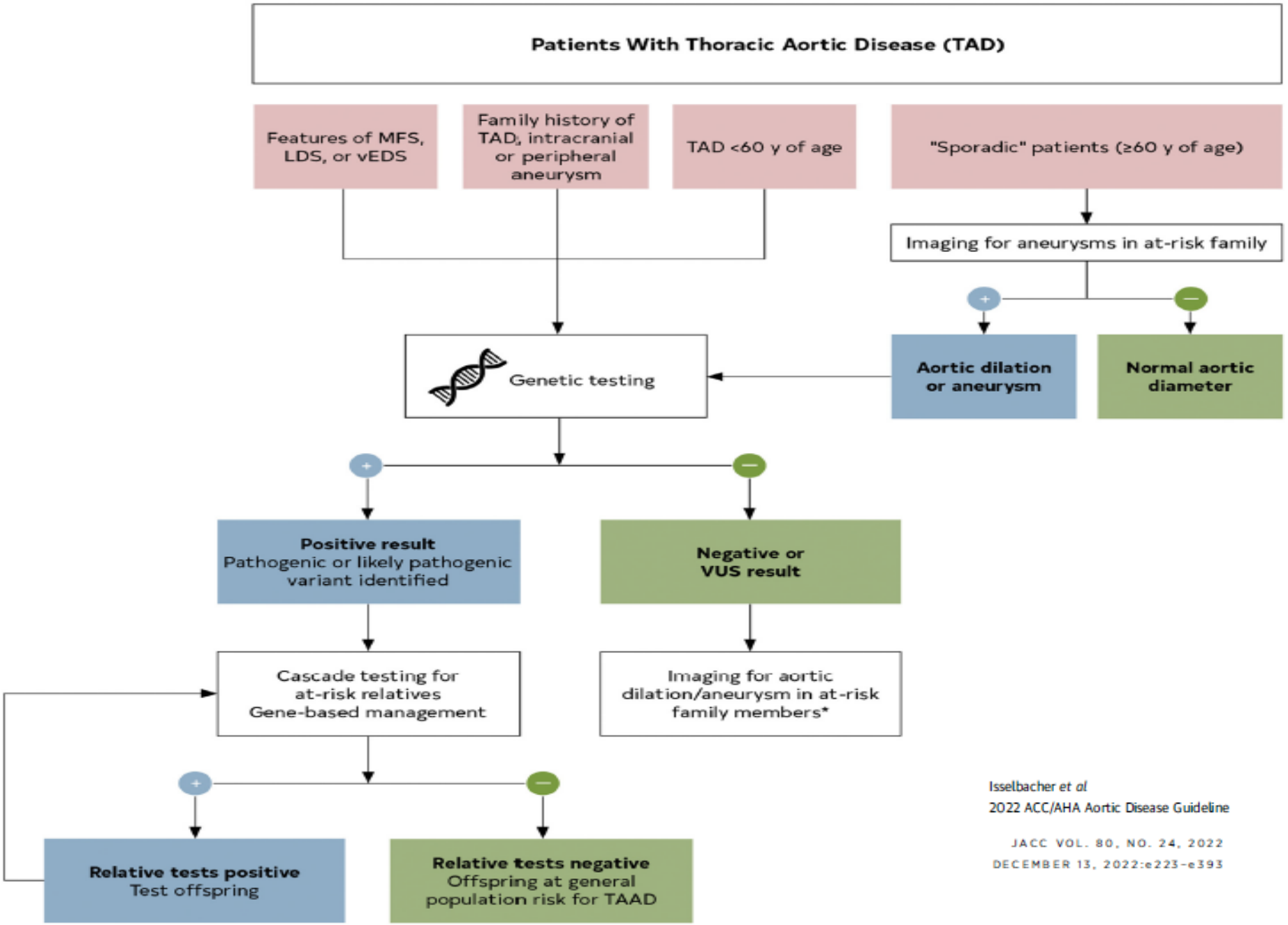
FIGURE 17 Evaluation and Genetic Testing Protocol for Patients With TAD



Isselbacher *et al*
2022 ACC/AHA Aortic Disease Guideline

JACC VOL. 80, NO. 24, 2022
DECEMBER 13, 2022:e223–e393

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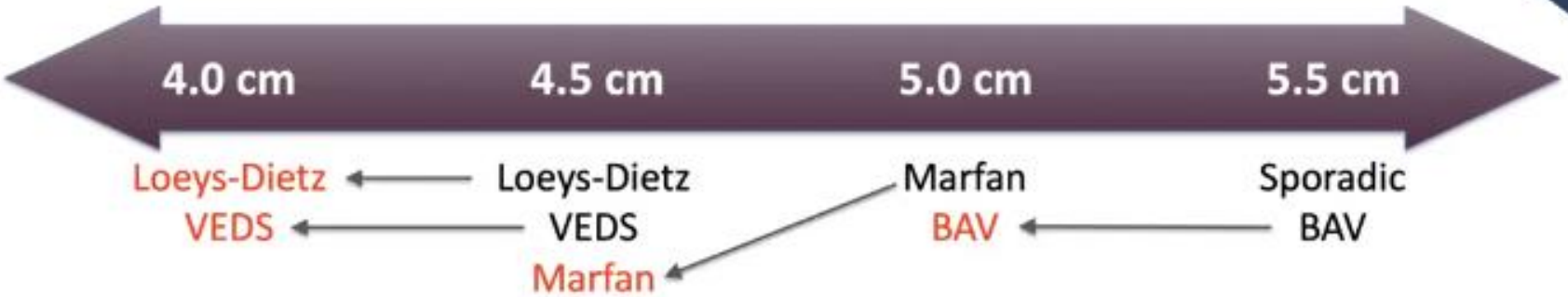
2005 - 2022

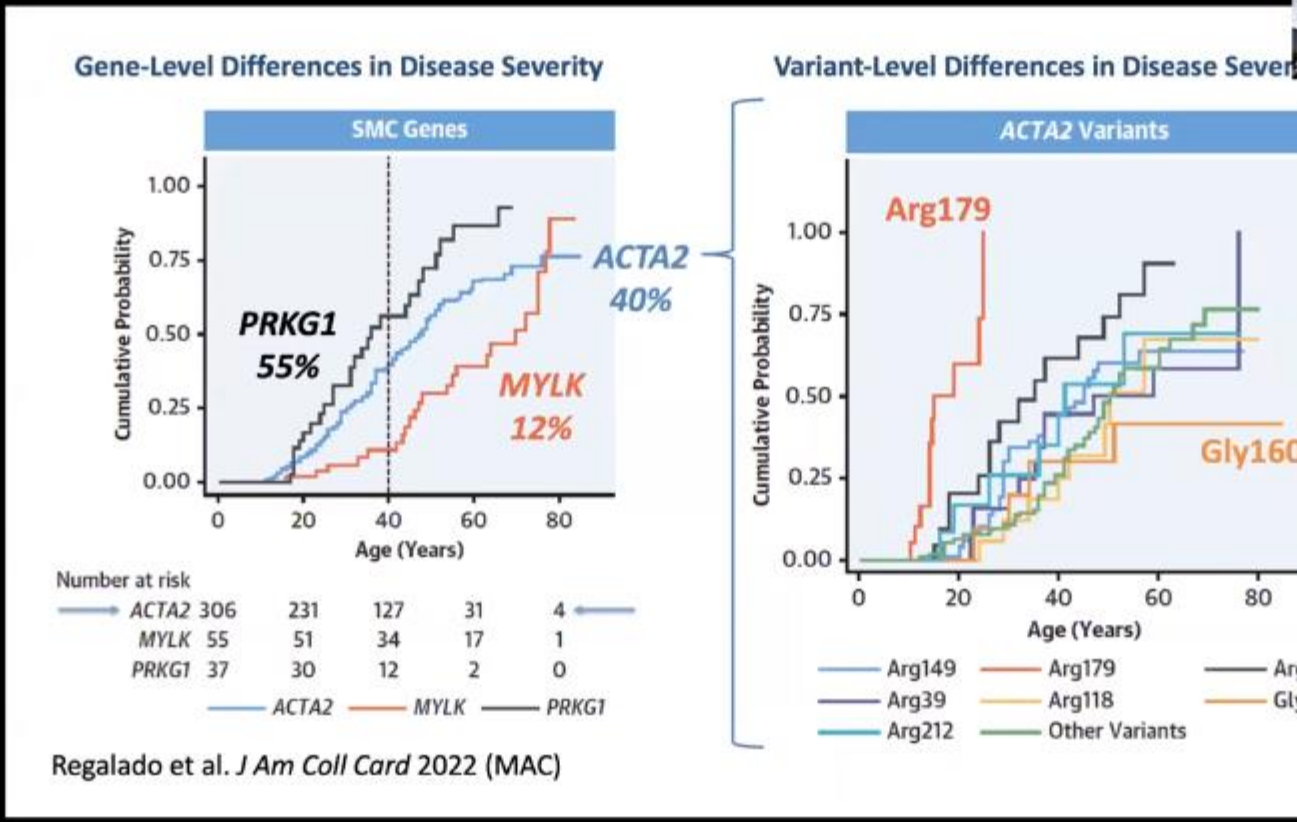


High Risk Clinical Factors

- Severe systemic features
- Family history of aortic events (young age, small diameters)
- Rapid expansion (> 0.5 cm per year)

Without clinical risk factors

With clinical risk factors



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Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease

Ellen S. Regalado, PhD,[a] Shaine A. Morris, MD, MPH,[b] Alan C. Braverman, MD,[c] Ellen M. Hostetler, BA,[a] Julie De Backer, MD, PhD,[d,e] Ruosha Li, PhD,[f] Reed E. Pyeritz, MD, PhD,[g] Anji T. Yetman, MD,[h] Elena Cervi, MD,[i] Sherene Shalhub, MD,[j] Richmond Jeremy, MB, BS, PhD,[k] Scott LeMaire, MD,[l] Maral Ouzounian, MD, PhD,[m] Arturo Evangelista, MD,[e,n] Catherine Boileau, PhD,[e,o] Guillaume Jondeau, MD, PhD,[e,o] Dianna M. Milewicz, MD, PhD[a]

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- 1028 patients with rare mutations in seven HTAD genes:
  - 3 genes related to SMC function: *ACTA2, MYLK, PRKG1*
  - 4 genes related to TGF-β signaling: *TGFBR1, TGFBR2, SMAD3, TGFB2*
- Sites: Australia, Belgium, Canada, Japan, France, Spain, UK, USA
- Cumulative probability of first aortic event: elective aneurysm repair or any aortic dis